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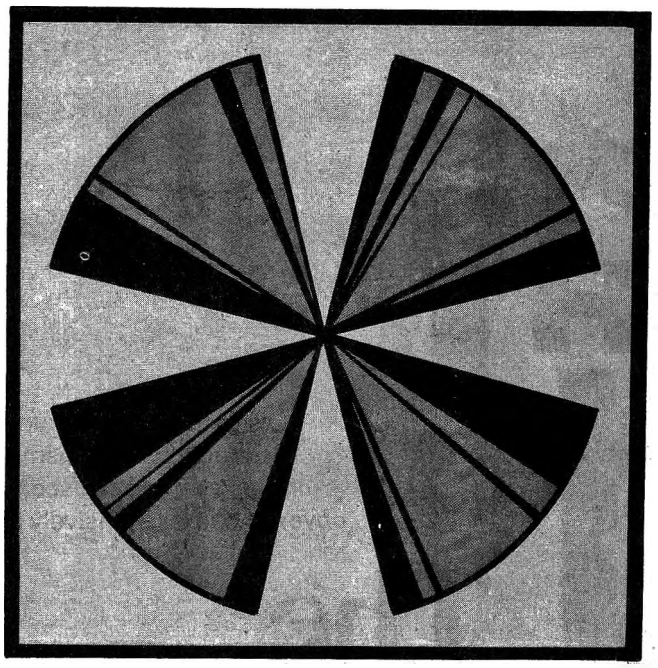

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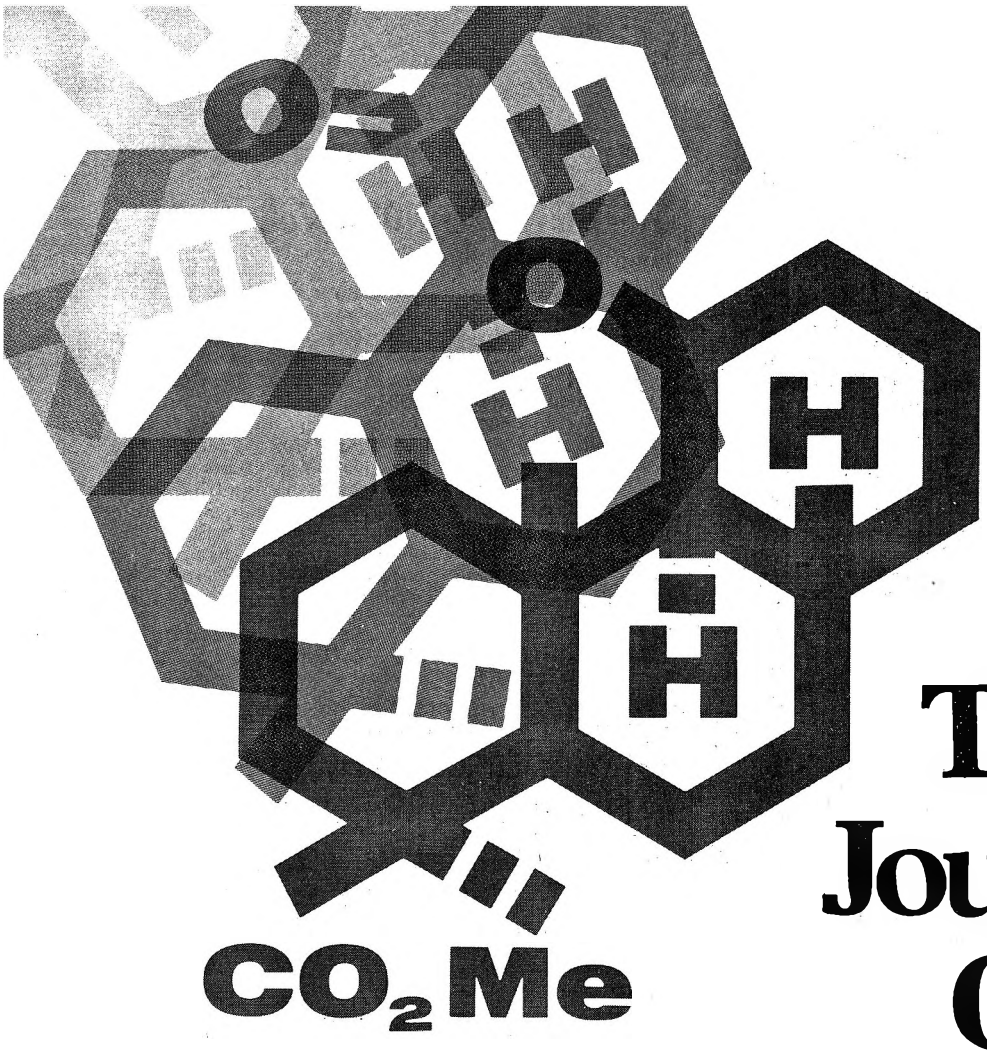

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APRIL 4, 1975

The Polar [$_{\pi}4 + _{\pi}2$] Cycloaddition Reaction. Enamines as Dipolarophiles in 1,3-Dipolar Additions[1]

Marcus K. Meilahn,[2] Bruce Cox, and Morton E. Munk*

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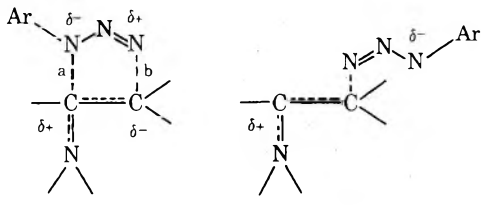
Received September 11, 1973

Hammett ρ values of −1.0, +2.1, and −0.66, respectively, were obtained for the addition of (1) phenyl azide to a series of meta- and para-substituted acetophenone piperidine enamines, (2) a series of meta- and para-substituted phenyl azides to phenylacetaldehyde piperidine enamine, and (3) *m*-nitrophenyl azide to a series of meta- and para-substituted phenylacetaldehyde piperidine enamines. Measured activation parameters and the insensitivity of reaction rate to ion-solvating power of the solvent implicate a concerted cycloaddition process. Hammett parameters and the regiochemistry of the enamine–azide reaction are consistent with a polar transition state in the electron reorganization process, in contrast to the more usually encountered isopolar transition states of 1,3-dipolar additions. Molecular orbital calculations on ground-state enamine and the observed dependence of reaction rate on the nature of the amino substituent lend support to the mechanism suggested.

One of the striking features of the 1,3-dipolar addition of organic azides to enamines is the high degree of regiospecificity observed over a broad range of azide and enamine substrates.[3,4] Without exception, that terminal nitrogen atom of the 1,3 dipole bearing the substituent is directed to the carbon atom of the dipolarophile bearing the amino group. The preferred orientation of addition could not be reversed, even partially, by manipulation of steric effects. Thus, the addition of phenyl azide to the piperidine enamine of acetophenone gives 1,5-diphenyl-5-(1-piperidino)-4,5-dihydro-1,2,3-triazole, the product of kinetic control, exclusively.[4] Control of the direction of addition appeared to be the result of electronic stabilization and therefore it was suggested that the reaction proceeds via a polar transition state (1 or 2) in the rate-determining step. An important role was attributed to electron-releasing nitrogen in delocalizing positive charge. Orientation phenomena provided no distinction between the stepwise and concerted cycloaddition.



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To further illuminate the nature of the transition state activation parameters, solvent dependence, Hammett correlations, and the stereochemistry[5] of cycloaddition have been examined. A number of pertinent kinetic studies have been published[6-8] and these will be contrasted with results reported herein.

Two reactions were chosen for initial kinetic study (Table I). In each case a first-order relationship was derived for both enamine and azide. Activation parameters for these reactions are summarized in Table I.

Table I
Activation Parameters. Addition of Phenyl Azide[a] to Piperidine Enamines in Chloroform

Enamine	E_a, kcal/mol	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$	Registry no.
Acetophenone	16 ± 1.2	15 ± 1.2	−34 ± 4.0	14990-66-0
Phenylacetaldehyde	14 ± 1.2	13 ± 1.2	−35 ± 4.0	332-15-0

[a] Registry no., 622-37-7.

Table II
Solvent Dependence. Addition of Phenyl Azide to Acetophenone Piperidine Enamine at 44.8°

Solvent	*Z* value, kcal/mol[a]	$k_2 \times 10^4$, l. mol^{-1} min^{-1}
Chloroform	63.2	9.1 ± 0.26
Acetonitrile	71.3	12.0 ± 0.5
Ethanol	79.6	7.0 ± 0.38

[a] Reference 10.

The large negative entropies of activation are indicative of highly ordered transition states[9] and provide presumptive, but not compelling, evidence favoring the concerted mechanism. The insensitivity of rate to solvent polarity (Table II) is also consistent with the concerted process, but, it should be noted, does not require a cyclic transition totally devoid of charge separation. No correlation between the solvent polarity parameter *Z* and rate is evident;[10] rather the most rapid reaction, by a modest margin, occurs in acetonitrile.[11] Huisgen[8] has reported a similar pattern of

Table III
Rate Constants for Cycloaddition in Chloroform at 44.8°

Substituent	Rate constant, $k_2 \times 10^3$ l.·mol^{-1} min^{-1}		
	Reaction 1[a,e]	Reaction 2[b,f]	Reaction 3[c,g]
p-OCH_3	1.9 ± 0.04[d]	3.8 ± 0.13	
p-CH_3	1.1 ± 0.09	4.5 ± 0.07	280 ± 5
m-CH_3	0.95 ± 0.004		
H	0.91 ± 0.026	10.0 ± 0.3	210 ± 8
m-OCH_3	0.89 ± 0.014		190 ± 3
p-Cl	0.52 ± 0.018	29.0 ± 0.6	150 ± 3
p-Br	0.50 ± 0.001	42.0 ± 0.7	150 ± 6
m-NO_2	0.17 ± 0.012	210.0 ± 8	
p-NO_2		980.0 ± 9	

[a] Addition of PhN_3 to the piperidine enamine of meta- and para-substituted acetophenones. [b] Addition of meta- and para-substituted phenyl azides to phenylacetaldehyde piperidine enamine. [c] Addition of *m*-nitrophenyl azide to the piperidine enamine of meta- and para-substituted phenylacetaldehydes. [d] Average deviation. [e] Registry no. of the piperidine enamine of substituted acetophenones are, respectively, 53927-01-8, 53927-02-9, 53927-03-0, 53927-04-1, 53927-05-2, 53927-06-3, 53927-07-4. [f] Registry no. of the substituted phenyl azides are, respectively, 2101-87-3, 2101-86-2, 3296-05-7, 2101-88-4, 1516-59-2, 1516-60-5. [g] Registry no. of the piperidine enamine of substituted phenylacetaldehydes are, respectively, 53927-08-5, 53927-09-6, 53927-10-9, 53927-11-0.

bon bearing the amino substituent, and the known superior +R quality of the pyrrolidine group relative to piperidine.[15]

In the acetophenone enamine series (reaction 1), steric inhibition of resonance may account for the reduced role of phenyl, as molecular models[16] indicate that phenyl and amino group cannot simultaneously achieve the coplanarity required for delocalization of positive charge because of severe steric crowding.

Equally good Hammett σ and σ^- correlations were derived for the addition of a series of meta- and para-substituted phenyl azides to phenylacetaldehyde piperidine enamine;[17] σ^0 values gave a somewhat less satisfactory fit. The extended form of the Hammett equation,[18] $Q_X = \alpha\sigma_I + \beta\sigma_R + h$, gave an ϵ value approaching unity (para substituents only; reaction 2, Table V) indicating a balance of inductive and resonance effects better expressed by normal Hammett σ values than σ^- values.[19] Kinetic data for the addition of para-substituted phenyl azides to cyclohexanone pyrrolidine enamine[8] (reaction 4), norbornene[6,8] (reaction 5), and cyclopentene[8] were also processed by us using the extended form of the Hammett equation (Table V) and show a gradual decline in ϵ in the order given,[19] consistent with a reduction in charge separation in the transition state.

The sign and magnitude of ρ for reaction 2 (Table IV) is suggestive of negative charge at nitrogen bearing phenyl in the transition state. This result complements that derived from reaction 1, and together they provide convincing evidence for substantial charge separation at bond a, as depicted in expression **1**.

Table IV
Hammett Relationship. Correlations with Various Substituent Constants[a]

Reaction studied[b]	Hammett ρ value (correlation coefficient)			
	σ	σ^0	σ^+	σ^-
Reaction 1	−1.0 (0.98)	−0.97 (0.96)	−0.71 (0.94)	
Reaction 2	+2.1 (0.98)	+2.2 (0.96)		+1.7 (0.98)
Reaction 3	−0.66 (0.99)	−0.63 (0.99)	−0.59 (0.95)	

[a] Substituent constants taken from C. D. Ritchie and W. F. Sager, *Prog. Phys. Org. Chem.*, **2**, 323 (1964). [b] Reactions described in Table III.

solvent insensitivity in the cycloaddition of phenyl azide to cyclopentanone piperidine enamine. A more profound rate dependence on solvent polarity is expected in cycloadditions proceeding by way of zwitterionic intermediates,[12] e.g., **2**. Finally, the conservation of the configuration of the enamine during electron reorganization lends strong support to the concertedness of cycloaddition.[5]

The Hammett relationship was chosen to assess the magnitude and distribution of charge among the centers undergoing electron reorganization. In the addition of phenyl azide to a series of meta- and para-substituted acetophenone piperidine enamines, the rate constants (Table III, reaction 1) correlate best with the original Hammett σ values[13] (Table IV).

The sign of ρ in reaction 1 is consistent with the development of positive charge in the transition state at the carbon atom bearing the substituent probe. However, the magnitude of ρ may not reflect the full extent of electron deficiency because of the presence of a second and powerful electron donor, the amino group, at that site. Evidence in support of the latter point is found in a study of the dependence of the rate of cycloaddition on the nature of the amino group (Table VI). Although piperidine and pyrrolidine are nearly equal in basicity, the acetophenone enamine of the latter amine is 34 times more reactive toward phenyl azide. In sharp contrast the piperidine enamine reacts only 4.5 times faster than the morpholine enamine in spite of the 1000-fold difference in amine basicity.[14] This behavior is explicable in terms of electron deficiency at car-

Table V
Correlation of Rate Data with the Extended Hammett Equation

Reaction	No. of data points[a]	h[b]	α[b]	β[b]	ϵ (α/β)
1[c]	5	−0.092 (80.0)	−0.99 (98.0)	−1.2 (98.0)	1.2
2[c]	6	−2.0 (99.9)	2.4 (99.0)	2.2 (99.0)	0.91
3[c]	4	−0.68 (99.9)	−0.69 (99.0)	−0.75 (99.0)	1.1
4[d,e]	4	3.9 (99.0)	2.8 (99.0)	2.3 (98.0)	0.83
5[f,e]	4	2.4 (99.0)	1.0 (95.0)	0.77 (95.0)	0.77
5[f,g]	5	0.041 (50.0)	0.98 (99.0)	0.70 (95.0)	0.71
6[h,e]	4	0.38 (80.0)	1.0 (80.0)	0.67 (50.0)	0.67

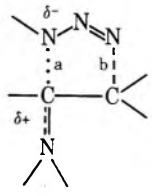
[a] Only rate constants for para-substituted derivatives used. [b] Confidence levels for the significance of h, α, and β appear in parentheses. [c] Reaction described in Table III. [d] Addition of para-substituted phenyl azides to cyclohexanone pyrrolidine enamine. [e] Data from ref 8. [f] Addition of para-substituted phenyl azides to norbornene. [g] Data from ref 6. [h] Addition of para-substituted phenyl azides to cyclopentene.

In Hammett studies related to reaction 2, Huisgen[8] obtained ρ = +2.54 in the addition of substituted phenyl azides to cyclohexanone pyrrolidine enamine, but ρ drops in magnitude to ~+0.9 with norbornene[6,8] and cyclopen-

tene.[8] The latter observation suggests less charge separation in the transition states of olefin cycloadditions.

The substituent probe was next attached to the β carbon atom of the dipolarophile to examine charge separation at bond b in the transition state **1**. An excellent fit was obtained with both σ and σ^0 values in the addition of *m*-nitrophenyl azide to a series of substituted phenylacetaldehyde piperidine enamines. The ϵ value (reaction 3, Table V) of 1.1 suggests that σ values provide a better measure of substituent effects.

The negative sign of ρ is inconsistent with the generation of negative charge at the β carbon atom as shown in transition state **1**. Rather, it is best accommodated by well-advanced bond formation at bond b, and therefore, little or no charge separation at bond b (**3**). The rate-enhancing



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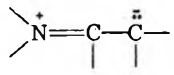
qualities of electron donors on the substituent probe at the β carbon atom are then explicable in terms of the modest stabilization of positive charge at the α carbon atom. Transmission of the electronic effect occurs through the nearly saturated β-carbon atom and this accounts for the reduced magnitude of ρ.[20]

Alternatively, the sign of ρ in reaction 3 could implicate a substituent effect more profoundly influencing the ground-state dipolarophile than transition state. If the ground-state enamine is characterized by charge separation as expressed by the polar resonance form **4**, an electron-attract-



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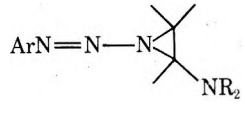
ing substituent could stabilize the enamine and retard the rate of cycloaddition. Such a ground-state controlled model of cycloaddition is not, however, consistent with the sign of ρ in reaction 1.[21] Further, the MO calculations described below suggest little contribution of resonance form **4** to the enamine ground state.

Mechanistically, the cycloaddition of aryl azides to electron-rich enamines[22] proceeds in a concerted fashion with the simultaneous, but uneven, formation of two new σ bonds.[23] Electron reorganization leads to an ordered transition state in which bond formation at b is considerably further advanced than at bond a. The resultant charge separation at bond a accounts for the observed regiospecificity even in sterically encumbered transition states.

Finally, a mechanism based on initial triazene formation (**5**), followed by rearrangement to triazoline,[24] was also re-



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jected in light of the observed conservation of enamine configuration in the cycloadduct.[5] The results of the analogous conversion of *N*-acylaziridines to oxazolines[25] would suggest inversion of configuration in the rearrangement of triazene **5**.

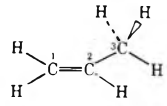
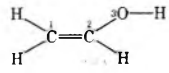
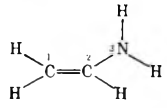
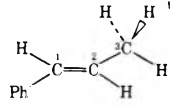
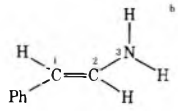
Semiempirical CNDO molecular orbital calculations[26] on a series of 1-substituted alkenes shed light on the nature of

Table VI
Dependence of Rate on Amine. Addition of Phenyl Azide to Acetophenone Enamines[a]

Amine	Basicity of amine (K)	$k_2 \times 10,^3$ l. mol^{-1} min^{-1}	Registry no.
Piperidine	1.6×10^{-3}	0.91	
Morpholine	2.4×10^{-6}	0.20	7196-01-2
Pyrrolidine	1.3×10^{-3}	31.	3433-56-5

[a] In chloroform at 44.8°.

Table VII
CNDO Molecular Parameters[a]

Compd	π electron density, q			π bond order, p	
	q_1	q_2	q_3	p_{12}	p_{23}
	1.0570	0.9809		0.9855	
	1.0888	0.9745	1.9367	0.9670	0.2539
	1.0957	0.9708	1.9336	0.9644	0.2623
	1.0577	0.9556		0.9532	
	1.1266	0.9335	1.9236	0.9246	0.2829

[a] Convergence requirements set at $E = 0.0001$, TCONV = 0.001. [b] Phenyl group in plane of carbon-carbon double bond.

ground-state enamine. Although a number of physical phenomena establish π electron delocalization in enamines,[27,28] the evidence adds little to our knowledge of the extent of charge separation in the ground state relative to an alkene as the standard of comparison. π electron density (q) and π bond order (p) were chosen as a measure of the importance of the polar resonance form **4** (Table VII).

The p_{12} values of the five compounds listed are close to unity, with propene displaying the greater degree of π bond localization as expected. Values for the first three entries follow the generally accepted order of increasing resonance effect (+R effect).[29] The π bond orders, p_{23}, reflect the same trend. These data suggest strong localization of π electrons for all compounds listed, and thus little charge separation in the ground state. This conclusion finds support in the calculated q values at C-1, which differ little for the just three compounds.

Although limited in scope, the MO calculations do appear to lend support to the proposed mechanism of cycloaddition and the assertion that substituent effects influence the transition state more profoundly than the initial state.

In reactions in which carbon develops positive charge in the transition state, both OR and NR_2 substituents at the reaction site generally accelerate the rate relative to an alkyl group, e.g., solvolysis reactions. Such is not the case in azide cycloadditions.[30] The striking discrepancy in rates of addition of aryl azides to enamines and enol ethers is likely

Table VIII
Comparative 1,3-Dipole Reactivity

Entry	Dipolarophile	1,3 Dipoles: relative rates of cycloaddition		
		PhC≡NNPh[a]	PhN_3	PhC≡NO[b]
1	PhCH=CH_2	11.8 } 3.5×	1.66[c] } 50,000×	3.71 } 22×
2	PhCH=CH(Pyr)[g]	40.9 }	83,000.[d] }	81.3 }
3	CH_2=CHC_5H_{11}-*n*	1.00	1.00[c]	1.00
4	CH_2=$CHCO_2Et$	350.	41.0[c]	25.8
5	Me_2NCH=$CHCO_2Et$	1.97		
6	(Pyr)CH=$CHCO_2Et$[f]		600.[e]	5.85

[a] Relative second-order rate constants in benzene: A. Eckell, R. Huisgen, R. Sustmann, G. Wallbillich, D. Grashey, and E. Spindler, *Chem. Ber.*, **100**, 2192 (1967). [b] Relative second-order rate constants in ether: ref 35. [c] Relative second-order rate constants: ref 8. [d] $k_2 = 5.7 \times 10^{-5}$ l. mol^{-1} sec^{-1} ($CHCl_3$, 30°) for addition of PhN_3 to phenylacetaldehyde piperidine enamine (Table IX). This value multiplied by pyrrolidine/piperidine rate factor of 35 (Table VI) for relative rate calculation. [e] Estimated by dividing $k_2 = 8 \times 10^{-6}$ l. mol^{-1} sec^{-1} for addition of *m*-nitrophenyl azide to 3-methyl-3-pyrrolidinoacrylic ethyl ester (Experimental Section) by 20 (rate ratio *m*-nitrophenyl azide/phenyl azide, Table III) and multiplying by 36 (rate ratio CH_2=$CHCO_2Et/CH_3CH$=$CHCO_2Et$, ref 8). [f] Registry no., 53927-12-1. [g] Pyr = 1-pyrrolidyl.

due to differences in the transition states.[31] It would appear that in the cycloaddition of the enol ether, electron reorganization proceeds with less charge separation, and, therefore, the transition state more closely resembles those involving alkenes where regioselectivity is more sensitive to steric influences.

The chemical phenomena described in this paper implicate a charge-separated transition state in the 1,3-dipolar addition of aryl azides to enamines. In fact, the magnitude of charge separation as revealed by the Hammett correlations appears unmatched in concerted 1,3-dipolar additions. This suggested that the azide–enamine cycloaddition stands apart, not only with regard to 1,3-dipolar additions of azides, but among 1,3-dipolar additions in general. A number of other observations, taken together, lend support to that view.

First, there is the insensitivity of the regiochemistry of cycloaddition to steric effects,[4] which has already been mentioned. Second, compared to other 1,3 dipoles with a "double bond and octet stabilization",[9] the rate of azide cycloaddition is dramatically enhanced by substitution of an electron-releasing amino group at the dipolarophile π electron system (entries 1 and 2, Table VIII). In contrast, the magnitude of rate enhancement brought about by the electron-attracting carboethoxy group is more comparable for all three 1,3 dipoles (entries 3 and 4, Table VIII). Finally, the rate data in Table VIII reveal another example of the selective and powerful rate-enhancing qualities of the amino group in azide 1,3-dipolar additions. For all three 1,3 dipoles, a powerful electron-releasing or a powerful electron-attracting substituent at the dipolarophile π electron system increases the rate. However, in the case of diphenylnitrilimine and benzonitriloxide, substitution of an amino group in a dipolarophile already bearing a carboethoxy group retards the rate of cycloaddition (entries 4–6, Table VIII). In contrast, substitution of an amino group in the β position of ethyl acrylate enhances the rate of phenyl azide addition by a factor of 15 (entries 4 and 6, Table VIII).

Where then does the azide–enamine cycloaddition fit mechanistically into the larger scheme of 1,3-dipolar additions? The reaction, while concerted in nature and consonant with the principle of conservation of orbital symmetry, apparently diverges mechanistically from the more usually encountered isopolar-like transition states.[32] It appears that the azide–enamine reaction is representative of a limiting mechanistic model of concerted 1,3-dipolar addition: the polar transition state model.

A powerful new approach to the rationalization and prediction of substituent effects on the rate and regiochemistry of 1,3-dipolar addition has been advanced by Houk[33] and by Sustmann,[34] and more recently applied advantageously by Huisgen[35] in a study of dipolarophile reactivity toward benzonitriloxide. The model proposed by Houk and Sustmann, which has as its basis perturbation MO theory, promises a more coherent insight into the nature of the reaction; however, the method neither requires consideration of, nor treats the question of charge separation in the transition state.

Experimental Section

Kinetic Method—Data in Table III. Infrared Absorbance Measurements. A Beckman Model IR 12 infrared spectrophotometer was used to determine the absorbance of the azides in all kinetic runs. The base line (I_0) was defined by a line extending from the established base lines on each side of the azide absorption in the 2100-cm^{-1} region. The maximum deflection of each azide was taken as I. The average of three scans provided the actual value of I used. The Bouguer–Beer plots (log I_0/I vs. concentration) were linear in all cases over the concentration ranges studied.

Determination of the Aromatic Azide Concentration. The absorbance, A_s, of a freshly prepared standard azide solution of known molar concentration, M_s, and the absorbance of the unknown sample, A, were determined. Substitution into eq 1 allows the calculation of the unknown molar concentration, M. The term $a_i b$ is the slope of the Bouguer–Beer plot for the azide.

$$\frac{A - A_s}{a_i b} = M - M_s \qquad (1)$$

Error Analysis. The major source of error in this method is the reproducibility of I, which varies slightly from scan to scan. The *maximum* error introduced in any single scan was estimated to be ±1.5%. Since the value of azide concentration used is the average of three scans, the magnitude of the error is reduced. The concentration of known phenyl azide solutions containing various concentrations of enamine and aminotriazoline were analyzed for phenyl azide via this method and the concentrations were determined within ±1%.

Determination of Rate. Freshly purified enamine was weighed into a volumetric flask, dissolved in the solvent, stoppered, and placed in a constant-temperature bath (±0.2°). A known amount of pure azide was placed in a small vial and placed in the constant-temperature bath along with a vial of solvent and the reaction vessel. After thermal equilibrium was established, the azide was rapidly and quantitatively transferred into the volumetric flask, diluted to volume by the addition of solvent, mixed, and transferred to the foil-encased reaction vessel. The solution was blanketed with a nitrogen atmosphere and the flask was sealed with a silicone rubber septum. Periodically 0.1 ml of the solution was removed via microliter syringe, quenched in cold solvent in a 1-ml volumetric flask, and diluted to volume. The absorbance was immediately determined on this solution. Reactions were followed to between 20

Table IX
Rate Constants Derived for Calculation of Activation Parameters (Table I)

Dipolarophile[a]	Rate constant, $k_2 \times 10^3$ l. mol^{-1} min^{-1} 30.0°	38.9°	44.8°
PhC(Pip)=CH_2[b,d]	0.26 ± 0.01	0.58 ± 0.02	0.91 ± 0.03
PhCH=CH(Pip)[c]	3.4 ± 0.1	6.9 ± 0.1	10.0 ± 0.3

[a] PhN_3 is the dipole. [b] Initial concentration in moles/liter; azide, 1.20; enamine, 2.40. [c] Initial concentration in moles/liter; azide, 1.00; enamine, 2.00. [d] Pip = *N*-piperidyl.

Table X
Initial Concentrations of Reactants in Kinetic Runs (Table III)

Reaction[a]	Azide[b]	Enamine[b]
1.	1.20	2.40
2. *p*-OCH_3, CH_3, H, Br, Cl	0.86	1.72
p-NO_2, *m*-NO_2	0.10	0.20
3.	0.10	0.20

[a] Reactions described in Table III. [b] Concentration in moles/liter.

and 40% of completion. In several cases clean second-order kinetics were followed for at least 70% of reaction. The rate constants reported are the average of multiple runs in all cases. The average deviation from the mean is also recorded.

Kinetic Method—Pyrrolidine Enamine of Ethyl Acetoacetate. To a solution of 0.175 g (0.00096 mol) of 3-methyl-3-pyrrolidinoacrylic ethyl ester in a 1-ml volumetric flask was added 0.330 g (0.0020 mol) of *m*-nitrophenyl azide. Deuteriochloroform was added to bring the volume of the solution to 1 ml. About 0.4 ml of the solution was transferred to an NMR sample tube which was sealed with a stopper. Periodically the NMR spectrum of the solution was recorded and from the integration of the region of δ 4.85–3.75, the concentration of the enamine and the adduct was determined. The rate constant in Table VIII is the average of two independent runs.

Solvents. Analytical reagent grade chloroform (Mallinckrodt Chemical Works) was used without purification in all the kinetic work with the exception of the study of solvent effects. Reagent-grade acetonitrile (Matheson Coleman and Bell) was distilled from P_2O_5 prior to use. Absolute ethanol was distilled from magnesium. The samples run in acetonitrile were quenched and diluted in acetonitrile and the samples run in absolute ethanol were quenched and diluted with chloroform.

Material Balance. 1,5-Diphenyl-5-(1-piperidino)-4,5-dihydro-1,2,3-triazole. A solution of 0.528 g (0.0044 mol) of phenyl azide and 0.834 g (0.0045 mol) of the piperidine enamine of acetophenone in chloroform (5 ml) was sealed in a flask with a nitrogen atmosphere and placed in the dark for 2 days. The solvent was removed *in vacuo* and distillation of the residue at a bath temperature of 36° (0.12 mm) afforded 0.326 g (62%) of phenyl azide as determined by GLC (20% DC550/Anakrom ABS, 170°, 15 psi). The nonvolatile material was dissolved in pentane and decolorized. Crystallization afforded 0.349 g (26%) of the crude aminotriazoline, mp 96–103° (lit.[4] mp 109–110.5°).

Duplication of the above procedure accounted for 85% of the starting material as the aminotriazoline or the unreacted phenyl azide.

Preparation of Enamines (Table XI). Enamines of ketones were prepared by the method of Stork.[15] The procedure of Mannich[36] was employed for the preparation of enamines of aldehydes. The substituted phenylacetaldehydes were prepared by rearrangement of the corresponding styrene oxide.[37] The following enamines are reported in the literature: the piperidine enamine of phenylacetaldehyde,[36] *p*-chlorophenylacetaldehyde,[38] acetophenone,[4] the pyrrolidine enamine of acetophenone,[39] the morpholne enamine of acetophenone,[40] and the pyrrolidine enamine of ethyl acetoacetate.[41]

Preparation of Azides. Phenyl azide was prepared by the method of Linsay and Allen.[42] The following substituted phenyl azides were prepared by the method of Smith and Boyer:[43] *m*-nitrophenyl azide,[44] *p*-nitrophenyl azide,[44] *p*-chlorophenyl azide,[45] *p*-bromophenyl azide,[45] *p*-methylphenyl azide,[45] *p*-methoxyphenyl azide.[46]

Table XI
New Enamines

Piperidine enamine	Physical properties[a]
Substituted Phenylacetaldehydes	
m-Methoxy	bp 136–138° (0.1 mm), n^{25}D 1.6110
p-Bromo	mp 87.5–88.5°
p-Methyl	mp 42–43°
Substituted Acetophenones	
p-Bromo	bp 99–102° (0.1 mm), n^{25}D 1.5845
m-Methoxy	bp 104–106° (0.1 mm), n^{25}D 1.5563
m-Methyl	bp 69–72° (0.1 mm), n^{25}D 1.5505
p-Methoxy	bp 92.5–94.5° (0.1 mm), n^{25}D 1.5592
m-Nitro	mp 76–77°
p-Chloro	bp 80–83° (0.06 mm), n^{25}D 1.5661
p-Methyl	bp 78° (0.1 mm), n^{25}D 1.5510

[a] Satisfactory analytical data for C, H, N (±0.35%) were provided for these compounds: Ed.

Acknowledgment. We are most grateful to Professor Robert W. Woody of Arizona State University for the valuable discussions of the MO calculations. Dr. Robert B. Hermann of the Lilly Research Laboratories, Indianapolis, Ind., also reviewed the results of our MO calculations and we wish to express our appreciation to him for his comments. Professor Marvin Charton of Pratt Institute processed our kinetic data in terms of the extended form of the Hammett equation. His efforts and the discussions that followed are acknowledged with gratitude.

Registry No.—3-Methyl-3-pyrrolidinoacrylic acid ethyl ester, 2723-42-4.

References and Notes

(1) (a) Presented in part at the 158th National Meeting of the American Chemical Society, New York, N.Y., Sept 7–12, 1969. (b) Taken in part from the Ph.D. Thesis of M.K.M., Arizona State University, 1967. (c) Supported in part by a generous grant from Parke, Davis and Co.
(2) NDEA Fellow, 1963–1966.
(3) R. Fusco, G. Bianchetti, and D. Pocar, *Gazz. Chim. Ital.*, **91**, 849 (1961).
(4) M. E. Munk and Y. K. Kim, *J. Am. Chem. Soc.*, **86**, 2213 (1964).
(5) Manuscript on the stereochemical studies in preparation. Presented in part at the 1973 Annual Meeting of the American Chemical Society, Chicago, Ill., Aug 27–31, 1973.
(6) P. Scheiner, J. H. Schomaker, S. Deming, W. J. Libbey, and G. P. Novak, *J. Am. Chem. Soc.*, **87**, 306 (1965).
(7) A. S. Bailey and J. E. White, *J. Chem. Soc. B*, 819 (1966).
(8) R. Huisgen, G. Szeimies, and L. Mobius, *Chem. Ber.*, **100**, 2494 (1967).
(9) See R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, **2**, 633 (1963), for a general discussion.
(10) E. M. Kosower, *J. Am. Chem. Soc.*, **80**, 3255 (1958).
(11) This may reflect more effective solvation of a bulky transition state with delocalized charge. See P. K. Kadaba, *Synthesis*, **2**, 71 (1973).
(12) R. Huisgen and P. Otto, *J. Am. Chem. Soc.*, **91**, 5922 (1969).
(13) A σ correlation does not suggest the absence of direct conjugation between substitution and reaction site. It is generally agreed that direct conjugation is of some importance in the ionization of benzoic acids: C. D. Ritchie and W. F. Sager, *Prog. Phys. Org. Chem.*, **2**, 329 (1964).
(14) Huisgen[8] reports a rate factor of 45 in the addition of phenyl azide to the pyrrolidine and morpholine enamines of cyclopentanone.
(15) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963).
(16) Corey–Pauling–Koltun (CPK) models.
(17) Product formation is regiospecific as in all azide–enamine cycloadditions examined.[4]
(18) (a) K. Haymizer and O. Yamamoto, *J. Mol. Spectrosc.*, **29**, 183 (1969); (b) see also M. Charton, *J. Org. Chem.*, 36, 266 (1971), and references cited therein.
(19) M. Charton, *J. Am. Chem. Soc.*, **86**, 2033 (1964), and private communication from this author. This author also suggests that an ϵ value of 1.5 best corresponds to systems where direct resonance between reaction

center and substituent takes on special importance as in σ^+ and σ^- correlations and that $\epsilon \sim 0.65$ corresponds to a σ° correlation.
(20) A. Landis and C. A. Vander Werf, *J. Am. Chem. Soc.*, **80**, 5277 (1958), report a good σ correlation in the solvolysis of para-substituted benzyldimethylcarbinyl chlorides in aqueous ethanol and a ρ value of -1.11.
(21) Implicit in this study is the assumption of similar transition states in reactions 1, 2, and 3. The high regiospecificity of each reaction, the comparable rates of cycloadditions (Table III) and activation parameters (Table I), and the observation of good Hammett correlations (a not-too-common observation in 1,3-dipolar additions) provide justification of this assumption.
(22) Enamines of basic aliphatic secondary amines.
(23) Unequal σ bond formation has been previously proposed,[6,8] but not as definitively supported.
(24) R. Huisgen, R. Sustmann, and K. Bunge, *Tetrahedron Lett.*, 3603 (1966); *Chem. Ber.*, **105**, 1324 (1972).
(25) H. W. Heine, *Angew. Chem., Int. Ed. Engl.*, **1**, 528 (1962); F. Winternitz M. Mousseron, and R. Dennilauler, *Bull. Soc. Chim. Fr.*, 382 (1956).
(26) J. Del Bene and and H. H. Jaffe, *J. Chem. Phys.*, **48**, 1807 (1968). Values for overlap integrals and other parameters described by these authors were used. Normal bond lengths and angles were assumed.
(27) G. Opitz, H. Heilman, and H. W. Schubert, *Justus Liebigs Ann. Chem.*, **623**, 112 (1959); N. J. Leonard and V. W. Gash, *J. Am. Chem. Soc.*, **76**, 2781 (1954).
(28) W. D. Gurowitz and M. A. Joseph, *J. Org. Chem.*, **32**, 3289 (1967).
(29) See J. March, "Advanced Organic Chemistry: Reactions, Mechanisms and Structure," McGraw-Hill, New York, N.Y., 1968, p 243.
(30) The relative rates of addition of phenyl azide to 1-ethoxy-, 1-morpholino-, and 1-pyrrolidinocyclopentene are 1:5300:230,000, respectively.[8] The rates of addition of phenyl azide to 1-heptene and *n*-butyl vinyl ether differ by a factor of less than 2.[8] Electron-withdrawing substituents on the aryl azide appear to magnify the rate difference; ethyl vinyl ether adds picryl azide 290 times faster than 1-pentene.[7]
(31) The MO calculations (Table VII) suggest that enamines and enol ethers possess similar ground states.
(32) Isopolar transition states are those that differ little in charge distribution from the initial states: E. M. Kosower, "An Introduction to Physical Organic Chemistry", Wiley, New York, N.Y., 1968, p 195.
(33) K. N. Houk, *J. Am. Chem. Soc.*, **94**, 8953 (1972).
(34) R. Sustmann, *Tetrahedron Lett.*, 2717 (1971); R. Sustmann and H. Trill, *Angew. Chem., Int. Ed. Engl.*, **11**, 838 (1972).
(35) K. Bast, M. Christl, R. Huisgen, and W. Mack, *Chem. Ber.*, **106**, 3312 (1973).
(36) C. Mannich and H. Davidsen, *Chem. Ber.*, 69, 2106 (1936).
(37) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **87**, 1353 (1965).
(38) F. Krohnke and I. Vogt, *Justus Liebigs Ann. Chem.*, **589**, 52 (1954).
(39) R. Dulou, E. Elkik, and A. Veillard, *Bull. Soc. Chim. Fr.*, 967 (1960).
(40) S. Hunig, K. Hubner, and E. Benzing, *Chem. Ber.*, **95**, 926 (1962).
(41) G. A. Berchtold, G. R. Harvey, and G. E. Wilson, Jr., *J. Org. Chem.*, **30**, 2642 (1965).
(42) R. O. Linsay and C. F. H. Allen, "Organics Syntheses", Collect. Vol. III, Wiley, New York, N.Y., 1955, p 710.
(43) P. A. S. Smith and J. H. Boyer, *Org. Syn.*, **31**, 14 (1951).
(44) H. H. Hodgson and W. H. H. Norriss, *J. Chem. Soc.*, 762 (1949).
(45) H. O. Spaushchus and J. M. Scott, *J. Am. Chem. Soc.*, **73**, 208 (1951).
(46) S. Maffei and L. Coda, *Gazz. Chim. Ital.*, **85**, 1300 (1955).

Cycloaddition. XVII. The Twelve Products of Photosensitized Addition of 1-Chloropropene to Cyclopentadiene

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cis- and *trans*-1-chloropropene have been added to cyclopentadiene both thermally at 200° and with β-acetonaphthone as a photosensitizer. As in other similar cases, the thermal reaction is a stereospecific Diels–Alder process. The photosensitized cycloaddition leads to mixtures of the same four 1,4 and eight 1,2 cycloadducts from both geometrical isomers of 1-chloropropene. Structures were established by a set of syntheses, identities, and correlations involving the thermal and photosensitized cycloadducts of 1,1-dichloropropene to cyclopentadiene, their dechlorination with tributyltin hydride, catalytic hydrogenation of the bicyclo[3.2.0]heptenes to the bicycloheptanes, and close comparison of NMR spectra.

In connection with our studies of cycloaddition reactions proceeding through biradical intermediates, we have studied the thermal and photosensitized cycloaddition of both *cis*- and *trans*-1-chloropropene to cyclopentadiene. This paper describes the isolation and identification of the products of those reactions.

Results

Isolation of Pure *cis*- and *trans*-1-Chloropropene. Commericial technical grade "1-chloropropene" (Columbia Organic Chemicals Co., Inc., Columbia, S.C.) as received was a mixture of about 10% 2-chloropropene, bp 23–24°, 25% *cis*-1-chloropropene, bp 31–32°, and 65% *trans*-1-chloropropene, bp 35–36°.[2]

Several workers have separated the above compounds by distillation and VPC, and established the structures of the cis and trans materials by NMR,[3] ir correlation,[4a] and dipole moment.[4b]

Isolation of pure *cis*- (98+%) and *trans*-1-chloropropene (98+%) was accomplished by distillation using a spinning band column. Because of the great difficulty of the separation, however, a mixture consisting of 15% cis and 85% trans was used for generating photoadduct mixtures for preparative VPC.

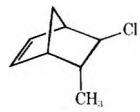
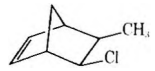
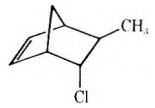
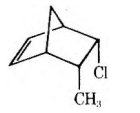
Isolation and Identification of the 1,4 Adducts. The 1,4 adducts of cyclopentadiene and *cis*- and *trans*-1-chloropropene were produced by thermal reaction of a mixture of the 1-chloropropene isomers (15:85, respectively) with cyclopentadiene at 200° in a sealed tube. VPC analysis of the product on a β,β'-oxydipropionitrile (β,β'-ODPN) column indicated the presence of four peaks of retention times greater than those of dicyclopentadiene. From pure *trans*-1-chloropropene (99+%) and cyclopentadiene, olefin was recovered unisomerized and the product mixture consisted of dicyclopentadiene and two fractions (ratio 67.5:32.5) of retention time corresponding to the first and third peaks in the chromatogram from the mixed olefin isomers and cyclopentadiene. Therefore the first and third peaks correspond to the thermal *trans*-1-chloropropene–cyclopentadiene adducts and the second and fourth peak correspond to the *cis*-1-chloropropene–cyclopentadiene adducts. Each component in the cis, trans thermal reaction was collected preparatively on β,β'-ODPN.

The assignment of the structures is based chiefly on the NMR spectra and some chemical evidence to follow. The assumptions relied upon were (a) 1,4 Diels–Alder addition with retention of configuration in common with dichloroethylene[4a] and alkylethylenes;[5] (b) that endo substituents (proton[6] or methyl[5]) are shifted upfield (shielded) relative to exo substituents; (c) that C_7 protons couple in a W pattern with endo protons.[6a,7]

The NMR peaks of the Diels–Alder addition compounds are listed in Table I with their structural assignments.

Chemical evidence that further confirms the identity of

Table I

VPC peak	Compd	NMR τ	NMR Number of H's	Mult	Assignment	J, Hz
Δ1		9.05	3	d	$CHCH_3$	7
		8.30	1	d of q	Anti C_7H	9, 2
		8.04	1	d of t	Syn C_7H	9, 1
		7.77	1	t of q	$CHCH_3$	7, 3
		7.35	1	m	Ring junction	
		7.13	1	m	Ring junction	
		6.88	1	d of d	CHCl	3, 2
		3.90	2	m	Olefin	
Δ2		8.85	3	d	$CHCH_3$	7
		8.49	1	d of qn	Anti C_7H	9, 2
		8.10	2	m	Syn C_7H, $CHCH_3$	
		7.55	1	m	Ring junction	
		7.08	1	m	Ring junction	
		6.15	1	d of d	CHCl	7, 2
		4.02	1	d of d	Olefin	6, 3
		3.75	1	d of d	Olefin	6, 3
Δ3		8.82	3	d	$CHCH_3$	7
		8.44	3	m	$CHCH_3$, C_7H's	
		7.56	1	m	Ring junction	
		6.97	1	m	Ring junction	
		6.26	1	t	CHCl	3
		3.94	1	d of d	Olefin	6, 3
		3.64	1	d of d	Olefin	6, 3
Δ4		9.13	3	d	$CHCH_3$	7
		8.68	1	d	Syn C_7H	9
		8.46	1	d of t	Anti C_7H	9, 2
		7.68	1	m	$CHCH_3$	7
		7.28	1	m	Ring junction	
		6.89	1	m	Ring junction	
		5.56	1	d of d	CHCl	8, 3
		3.85	2	m	Olefin	

the thermal 1,4 adducts is based on the known exo hydride donation preference of tri-*n*-butyltin hydride.[8]

The thermal reaction of 1,1-dichloropropene and cyclopentadiene (200°, 24 hr) yields material that on isolation gives a single peak on several VPC columns. The NMR, however, displays two methyl doublets at τ 8.99 and 8.73 in the ratio of about 60:40 and therefore the material consists of at least two separate compounds, presumably *exo*- and *endo*-5,5-dichloro-6-methyl-2-norbornene. Reduction of this mixture with 1 equiv of tri-*n*-butyltin hydride yields a mixture of compounds. VPC analysis on β,β′-ODPN indicates the results listed in Table II on the basis of the above NMR assignments.

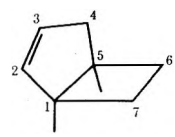
The two compounds which predominate are the two with the endo chloro structures in accord with exo hydride donation by the tin hydride. The ratio of exo donation of a hydrogen atom to endo donation in the endo methyl compounds is 9.7:1. This corresponds to a small trans/cis directive factor of 1.3 by neighboring methyl, superposed on a normal exo/endo preference of 7.4.

The thermal reaction of 1,1-dichloropropene and cyclopentadiene on the basis of the above analysis yields a 58:42 mixture of 5,5-dichloro-*endo*-6-methyl-2-norbornene and 5,5-dichloro-*exo*-6-methyl-2-norbornene. The ratio corresponds to the 60:40 ratio of the methyl doublets at π 8.99 and 8.73, with the endo material again being the more upfield of the two.

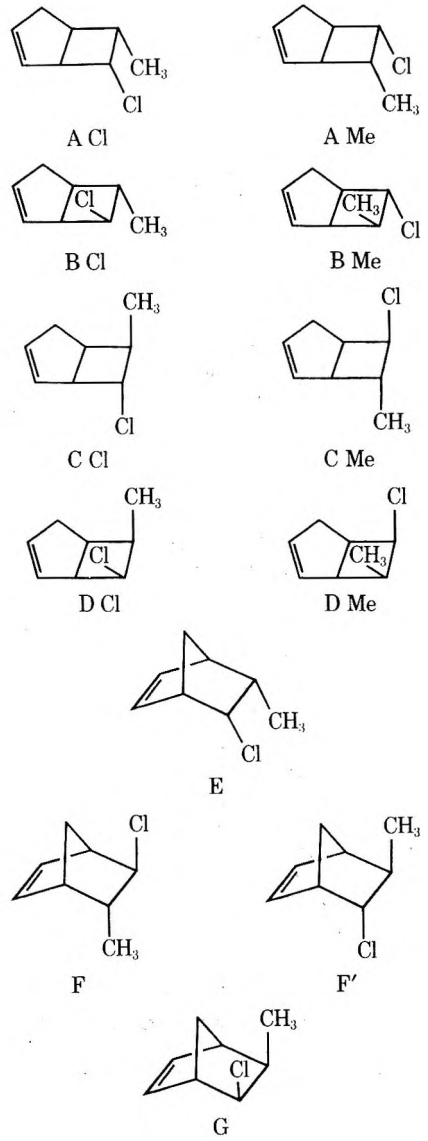
Designation of Isomers. The 12 isomeric cycloadducts obtained from photosensitized addition of the 1-chloropropenes to cyclopentadiene are resolved by β,β′-ODPN and TCEP columns into nine fractions, the order of elution being the same on both columns. In discussing the steps in the identification of the isomers, the VPC fractions will be named *hν*1 through *hν*9, with no implication as to the number of components in each fraction. In the course of the study the isomers will be matched with the possible four 1,4 cycloadducts (Table I) and the eight 1,2 cycloadducts. Since these correspond in structure and configuration to the 2-butene cycloadducts previously studied,[9,10] the structures are designated by an adaptation of the same scheme previously used (Scheme I). For example, the names A Cl or A Me refer to structure A with the chlorine and methyl, respectively, at position 7. For consistency with other papers from this laboratory we depict the bicyclo[3.2.0]hept-2-enes with the 4 ring in a horizontal plane and the 5 ring joined to it along the left side, inclined upward, with the double bond in front.

Table II
Results of Reaction of *exo*- and *endo*-5,5-Dichloro-6-methyl-2-norbornene with $(n\text{-Bu})_3SnH$

	Δ1	Δ2	Δ3	Δ4
% reduced material	5.4	6.3	36.2	52.1



Scheme I
The 12 Photocycloadducts of 1-Chloropropene to Cyclopentadiene



Synthesis. The synthetic and correlative sequence adopted is shown in Scheme II.

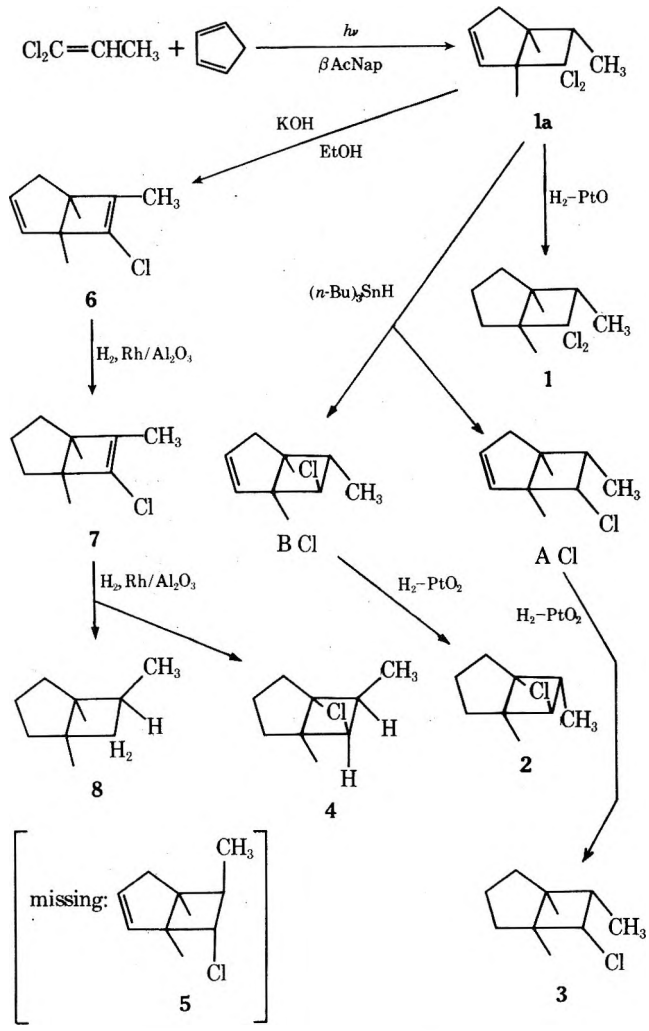
Photosensitized Cycloaddition of 1,1-Dichloropropene and Cyclopentadiene. The photoreaction of 1,1-dichloropropene and cyclopentadiene was carried out with β-acetonaphthone as sensitizer. The ratio of cross adducts to photodicyclopentadiene was about 1:6. The cyclopentadiene dimers were separated from the cross adducts by distillation with the dicyclopentadienes distilling at the lower temperature. The higher boiling fraction revealed four peaks on VPC analysis (Carbowax 20 M column).

Their relative amounts in order of increasing retention time were 61.8:27.8:1.1:9.2. Peaks 1, 2, and 4 (comprising 99% of the mixture) were each collected preparatively.

The last peak was not of cross-adduct origin, since it did not contain any olefinic hydrogens. It was tentatively identified as photodimers of 1,1-dichloropropene.

The second peak collected corresponded in retention time to the mixture of 1,4 adducts previously obtained in the thermal reaction of 1,1-dichloropropene and cyclopentadiene. The NMR indicated two doublets centered at τ 8.99 and 8.73 in the ratio of 2.6:1 and therefore a mixture of the endo and exo methyl 1,4 compounds in that ratio. This

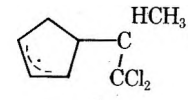
Scheme II



fraction also contained about 5% impurity from peak 1 of the photomixture.

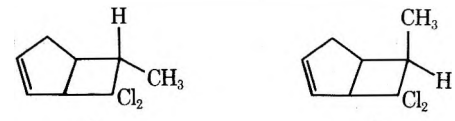
Peak 1, which comprised about 62% of the mixture and 68% of the cross adducts, appeared to be a single compound. It had a single methyl doublet centered at τ 8.82, a multiplet at τ 7–8, a broad peak at τ 6.2, and a sharp singlet at τ 4.11 in the ratio of 3:4:1:2, respectively. It was assigned the structure **1a**, 7,7-dichloro-6-*exo*-methylbicyclo-[3.2.0]hept-2-ene, for several reasons.

Accumulated experience indicates that a chlorine atom on a C=C double bond is more activating than a methyl group toward capture of a cyclopentadiene triplet, and more stabilizing to a free radical at the carbon to which the Cl is attached. There is no doubt that the prevalent biradical,[11,12] in photocycloaddition of 1,1-dichloropropene to cyclopentadiene will have the structure **9**, and the strongly



9

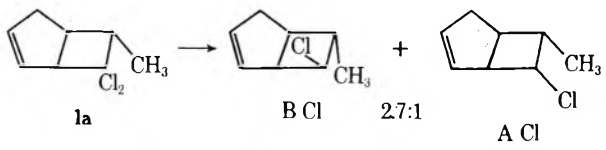
predominant *non*-1,4 adduct must therefore be either **1a** or **1b**.



1a **1b**

The far downfield position of the methyl NMR signal, τ 8.83, supports the exo assignment which would be made on the basis of experience with photosensitized cycloadditions. The assignment of structure **1a** is also uniquely compatible with the reactions of this adduct.

Compound **1a** was reduced with tri-*n*-butyltin hydride (1.1 equiv). Two monochloro materials were obtained in about 80% yield. The isomers were in the ratio of 2.7:1 and were therefore assigned structures B Cl and A Cl, respectively. The well-known exo preference for hydrogen atom donation by tri-*n*-butyltin hydride to a free radical is the basis of the assignment.[13]



1a B Cl 2.7:1 A Cl

The mass spectra of both B Cl and A Cl indicated the correct molecular weights and the nmr indicated the correct hydrogen ratios. The methyl resonances were shifted only slightly upfield from **1a** to τ 8.85 and 8.84, respectively. The downfield hydrogen at the ring junction shifted upfield in both cases to τ 6.42 and 6.70, respectively, as would be expected on removing an electronegative substituent. There appeared in each a new signal attributable to a chloromethinyl hydrogen which is split by two adjacent hydrogens. Both B Cl and A Cl can be hydrogenated quantitatively over Adams catalyst in ethyl acetate solvent, to compounds **2** and **3**, respectively. The mass spectra of **2** and **3** indicated the correct molecular weights and the NMR spectra indicate no olefin resonances, a chloromethinyl hydrogen and a ring junction hydrogen (α to the chlorine), and a doublet methyl group, as well as eight indistinguishable saturated hydrogens.

Compound **1a** can also be hydrogenated and the product **1** has a molecular weight indicating the addition of two hydrogens. The NMR shows a doublet methyl group at τ 8.78 and a single broad hydrogen at τ 6.75. When **1** is reduced with 1 equiv of tri-*n*-butyltin hydride, **2** and **3** are produced in the ratio of 4.7:1. The increased stereoselectivity is to be expected since the endo side of **1** is now more hindered than the endo side of **1a**. This further confirms the endo–exo relationship to the chlorines in compounds B Cl and A Cl.

Compound **1a**, the dichloro-exo-methyl adduct, was dehydrohalogenated in KOH–ethanol to the diene **6** in about 70% yield. The mass spectrum of **6** indicated a molecular weight of 140, corresponding to loss of HCl from **1a**. The NMR showed two distinct olefinic hydrogens at τ 4.15 and 4.3, two distinct ring-junction hydrogens at τ 6.7 and 6.85, two allylic hydrogens at τ 7.3, and an olefinic methyl signal at τ 8.23. The methyl signal appeared to be a triplet coupled to two hydrogens with a coupling constant of about 1 Hz.

In ethyl acetate over platinum oxide **6** was hydrogenated to a single material with a molecular weight of 110 and an NMR spectrum whose only distinctive feature was an upfield methyl doublet at τ 9.17. Since it is known that Pt in polar solvents can hydrogenolyze vinylic chlorines, this reduced material is probably **8**, 6-*endo*-methylbicyclo[3.2.0]heptane.[14]

Hydrogenation of **6** in hexane with 5% Rh/Al_2O_3 under about 3 atm produced three materials, all separable by VPC. Besides 55% of **7** and 5% of **8** there was 40% of a product assigned the structure **4**, 6-*endo*-chloro-7-*endo*-methylbicyclo[3.2.0]heptane, on the basis of exo hydrogenation, a molecular weight of 144 with one chlorine, an NMR spectrum with an upfield methyl doublet (τ 9.07), and a downfield chloromethinyl hydrogen at τ 5.25.

The above sequence constitutes a chemical proof of the configuration of the methyl group in **1a**. Since **2** and **3** represent the possible configurations about the chloromethinyl carbon with the unchanged fixed methyl configuration of **1**, and **4** has the endo methyl configuration (exo hydrogenation) with a specific chloro configuration, and since **2** and **3** are distinct from **4**, their methyl configurations must be different from that of **4** and hence they must have an exo-methyl configuration. Thus **1a** must have an exo-methyl configuration in accord with its assignment and the assignments of the structures based on it.

With the four possible 1,4 adducts, Δ1–4, the two 1,2 adducts, B Cl and A Cl, and the three hydrogenated 1,2 adducts, **2**, **3**, and **4**, it became possible to isolate and identify the compounds produced in the photoreaction of 1-chloropropene and cyclopentadiene.

Isolation of Photoadducts. The photosensitized reaction of a mixture of 1-chloropropene isomers and cyclopentadiene at about 0–10° produced a mixture of cyclopentadiene photodimers and cross-adducts. As has been mentioned, analysis of the mixture on a β,β′-ODPN column or TCEP column indicated nine peaks, *hν*1–9, in addition to photodimers of cyclopentadiene, which had shorter retention times than the cross-adducts. Fractions *hν*1–6 were collected preparatively on a 20 ft × 0.25 in. column of 20% β,β′-ODPN on 60/80 mesh Chromosorb P at about 95°. The fractions *hν*7–9 were collected on a 20 ft × 0.25 in. column, 20% TCEP on 60/80 mesh Chromosorb P at about 120°. The latter peaks were very small and of very long retention times. The eventual analysis was performed at higher temperature on a TCEP column and it was shown by injection of the collected samples from the β,β′-ODPN collections that the relative retention times as well as separations were identical on the two columns.

The peak *hν*3 could be separated into two closely overlapping peaks only on a 0.125 in. analytical TCEP column. On all 0.25 in. and preparative columns the best that could be obtained was a somewhat unsymmetrical peak, and hence in the collected material no appreciable separation of *hν*3 was obtained.

From the NMR spectra of the collected materials it was immediately obvious that some peaks were pure compounds and others were mixtures. The criterion used in the above analysis was the appearance of a single methyl doublet and a single chloromethinyl hydrogen. By this criterion *hν*1, *hν*2, and *hν*6–9 were all single-component peaks. The peak *hν*1 was pure Δ1(F), peak *hν*6 was pure B-Cl, and peak *hν*7 was pure Δ4(E). In addition the peaks *hν*3–5 also contained as one of their components some of the compounds previously synthesized. The peak *hν*3 consisted of A-Cl as the major component with one other minor component. The peak *hν*4 contained an unknown material as the major component and Δ2(G) as the only other component. The peak *hν*5 contained Δ3(F′) and one other component.

Hydrogenation reduces the eight possible 1,2 adducts to four, of which three have been independently synthesized. In addition, given compounds A Cl and B Cl, it is immediately possible to assign their double bond isomers by finding the other compounds that hydrogenate to **2** and **3**.

Hydrogenation of *hν*5 gives two overlapping peaks on TCEP. Each was collected on the 0.25 in. TCEP column. The first peak consisted of nearly pure **2** (impurity being the second peak) and the second peak was the hydrogenation product of Δ3(F′). Since *hν*5 consisted of Δ3 and an unknown adduct, the unknown material must have been C Me, 6-*endo*-chloro-7-*exo*-methylbicyclo[3.2.0]hept-2-ene.

Table III
Identities of the Hydrogenated VPC Peaks[a]

VPC peak	Product
$h\nu 2$	5
$h\nu 3$	3
$h\nu 4$	5 + dihydro-G
$h\nu 5$	2 + dihydro-F
$h\nu 8$	4
$h\nu 9$	4

[a] Platinum oxide, 1 atm hydrogen, 25°, in ethyl acetate.

$h\nu 3$ was hydrogenated to give pure 3 with no other compounds present as judged by VPC or NMR. The other minor component therefore must be A Me, the double bond isomer of A Cl, 6-*exo*-chloro-7-*exo*-methylbicyclo-[3.2.0]hept-2-ene.

When the pure materials $h\nu 8$ and $h\nu 9$ are hydrogenated they yield the identical product 4 and are therefore the two possible olefin isomers from which 4 can be derived, namely D Cl and D Me, whose structural assignments will be discussed.

The only remaining unidentified materials are $h\nu 2$ (a pure compound) and $h\nu 4$, which contains as a minor component Δ2(G) plus an unidentified material. When $h\nu 2$ is hydrogenated it yields a single material, **5**. The peak $h\nu 4$ gives on hydrogenation two peaks on TCEP in the approximate ratio 3:1. The larger peak was collected and shown to be identical with **5**, the hydrogenation product from $h\nu 2$. The second peak had the same retention time as the hydrogenation product of Δ2 since Δ2 was a component of the original mixture.

The above is summarized in Table III.

NMR Assignments. The position of the ring-junction hydrogen in the NMR that is both allylic and α to the chloromethinyl group offers a means of differentiating between two double-bond isomers in this series of compounds. Allylic character and proximity to –CHCl– have deshielding effects that are approximately additive. Within any two double bond isomers the shielding or deshielding effects of exo and endo adjacent chlorines or methyl will be fixed, since the configurations of the chlorine and methyl are identical. Within isomeric pairs there are four kinds of ring-junction hydrogens. They are (a) α to methylmethinyl group and nonallylic; (b) α to chloromethinyl group and nonallylic; (c) allylic and α to methylmethinyl group; (d) allylic and α to chloromethinyl group.

The deshielding one would expect for the above ring-junction hydrogens (for a fixed endo,exo chlorine–methyl series) would be d > c ≅ b > a. Hence it is possible to assign the allylic α chloromethinyl hydrogen given the NMR spectra of the two isomers, since it is simply the most downfield hydrogen, other than the chloromethinyl hydrogen, from which it can be easily differentiated. For example, B Cl has its most downfield saturated hydrogen other than the chloromethinyl hydrogen at τ 6.42. The most downfield ring-junction hydrogen in B Me is at τ 6.8, a difference of 0.38 ppm.

The compounds $h\nu 8$ and $h\nu 9$ are double bond isomers since they both hydrogenate to 4. The compound $h\nu 9$ has its most downfield ring-junction hydrogen at τ 6.3, clearly differentiated from the other saturated hydrogens. The compound $h\nu 8$ has an indistinguishable collection of hydrogens at τ 6.6–7.7, two of which are its ring-junction hydrogens and both of which are considerably more shielded than τ 6.3. Therefore $h\nu 9$ has a hydrogen which is both allylic and α to a chloromethinyl group. On this basis it can be assigned structure D Cl, 7-*endo*-chloro-6-*endo*-methylbicyclo[3.2.0]hept-2-ene, and $h\nu 8$ can be assigned structure D Me, 6-*endo*-chloro-7-*endo*-methylbicyclo[3.2.0]hept-2-ene.

Table IV
NMR Characterization of Hydrogenation Products 2–5

Compd	Position of chloromethinyl hydrogen, τ	No. cis adjacent alkyl groups and ring
5	6.62	2
3	6.00	1
2	5.99	1
4	5.25	0

Table V
Identities of the Components of the VPC Peaks on TCEP Produced in the Photosensitized Cycloaddition of Cyclopentadiene and *cis*- and *trans*-1-Chloropropene

VPC peak	Identity
$h\nu 1$	F
$h\nu 2$	CCl
$h\nu 3$	ACl + AMe
$h\nu 4$	G + BMe
$h\nu 5$	F′ + CMe
$h\nu 6$	BCl
$h\nu 7$	E
$h\nu 8$	DMe
$h\nu 9$	DCl

The assignment of structure **5** to the hydrogenation product from $h\nu 2$ was made for several reasons. First, it was not identical with **4**, the diendo compound, and did not correspond to either **2** or **3**, the exo-methyl possibilities. Second, its upfield methyl doublet (τ 9.03) is closer to that of **4** (τ 9.07) than that of **2** or **3** (τ 8.84 and 8.81). Hence, since it must have an endo methyl group and it is not **4**, it must be **5**. Also, since a methyl group is shielding relative to a hydrogen and endo hydrogens are more shielded than exo hydrogens, the chloromethinyl hydrogen of **5** should be the most shielded of all the chloromethinyl hydrogens, the effects being additive, in the series **2**, **3**, **4**, and **5**. In Table IV are listed the positions of the chloromethinyl hydrogens in the NMR for the above compounds; also listed are the number of cis adjacent alkyl groups in each case.

The position of the ring-junction hydrogen in the nmr that is both allylic and α to the chloromethinyl group again permits the assignment of structure to the two compounds that hydrogenate to **5**. The most downfield ring-junction hydrogen is $h\nu 2$ at τ 6.6, and it is clearly differentiable from the other allylic hydrogens. On the other hand, in the major component of $h\nu 4$ the corresponding hydrogens are more upfield (above τ 6.7) and not clearly differentiable. Therefore $h\nu 2$ has the structure C Cl, 7-*exo*-chloro-6-*endo*-methylbicyclo[3.2.0]hept-2-ene, and the 1,2 component of $h\nu 4$ has the structure B Me, 6-*exo*-chloro-7-*endo*-methylbicyclo[3.2.0]hept-2-ene.

In Table V are listed the final assignments for $h\nu 1$–9, and in Table VI are listed the nmr peaks of the 1,2 adducts.

Experimental Section

Thermal Reaction of Cyclopentadiene and a Mixture of *cis*- and *trans*-1-Chloropropene. The olefin mixture (85.4% trans, 14.6% cis, 7.2 g, 0.094 mol) and freshly distilled cyclopentadiene (3.85 g, 0.058 mol) was degassed and sealed in a thick-walled tube. The tube was heated in a tube oven to 200° for 24 hr and then let cool for 7 hr. The tube was opened and some of the material was

Table VI

Compd	NMR, τ	H's	Mult[a]	Assignment	J, Hz
DCl	8.96	3	d	Methyl	7
	7.60	2	m	Methylene	
	7.10	2	m	Bridge-methinyl	
	6.3	1	m	Bridge-αCHCl-allyl	
	5.3	1	t	CHCl	8
	4.2	2	m	Olefinic	
DMe	9.06	3	d	Methyl	7
	6.5–7.9	5	m	Bridge-allylic-methinyl	
	5.25	1	t	CHCl	8
	4.3	2	m	Olefinic	
BCl	8.85	3	d	Methyl	7
	7.2–8.0	4	m	Bridge-allylic-methinyl	
	6.4	1	m	Bridge-αCHCl-allyl	
	6.0	1	t	CHCl	8
	4.15	2	s (br)	Olefinic	
CMe	8.8		d	Methyl	7
	6.7–7.9		m	Bridge-allylic-methinyl	
	5.85		t	CHCl	8
	4.2		s (br)	Olefinic	
ACl	8.85	3	d	Methyl	7
	7.2–8.0	4	m	Bridge-allylic-methinyl	
	6.7	1	m	Bridge-αCHCl-allyl	
	5.85	1	d of d	CHCl	2, 8
	4.2	2	s (br)	Olefinic	
AMe	8.8		d	Methyl	7
	7.2–8.0		m	Bridge-allylic-methinyl	
	5.9		m	CHCl	
	4.2		m	Olefinic	
CCl	8.98	3	d	Methyl	7
	6.9–7.7	4	m	Bridge-allylic-methinyl	
	6.6	2	m	Bridge-αCHCl-allyl	
	6.5		d of d	CHCl	8, 6
	4.2	2	m	Olefinic	
BMe	8.95		d	Methyl	7
	6.8–8.0		m	Bridge-allylic-methinyl	
	6.5		d of d	CHCl	6, 4
	4.2		s	Olefinic	

[a] s = singlet, d = doublet, t = triplet, m = multiplet, br = broad.

analyzed on a 0.25 in. × 16 ft 20% TCP column in order to ascertain the purity of the recovered olefin. It was found to be the same as the initial mixture. The olefin was distilled off and the residue was bulb-to-bulb distilled. Analysis and collection of the material was performed on a 0.25 in. × 20 ft 20% β,β′-ODPN column at 90°, flow rate about 80 cm³/min. The retention times of the four compounds were 69.4, 74.6, 101.4, and 132.2 min.

Thermal Reaction of *trans*-1-Chloropropene and Cyclopentadiene. The reaction was conducted as described above with 4.0 g (0.06 mol) of cyclopentadiene and 5.0 g (0.065 mol) of *trans*-1-chloropropene (99.25% by VPC). The reaction was carried out at 180° for 24 hr. The tube was opened and 4.8 g of olefin was recovered which was still about 99+% pure by VPC. VPC analysis of the product after bulb-to-bulb distillation indicated largely dicyclopentadiene but there were two significant peaks with retention times of 68.3 and 99.8 min in the ratio 67.5:32.5.

Photosensitized Cycloaddition of 1-Chloropropene and Cyclopentadiene. The mixture of 1-chloropropenes (85% trans, 15% cis, 185 g, 2.42 mol), cyclopentadiene (4 g, 0.061 mol), and β-acetonaphthone (2 g, 0.012 mol) was irradiated at about 10° in a water bath by means of a water-jacketed 450-W Hanovia lamp. The solution was stirred by nitrogen bubbling through. Every 4 hr another 4 g (0.061 mol) of cyclopentadiene was added (for a total of 20 g, 0.3 mol) and the total irradiation time was 20 hr. The excess olefin was distilled off and the residue was bulb-to-bulb distilled, yielding about 27 g of material. VPC on β,β′-ODPN indicated about 75% dicyclopentadiene and 25% material consisting of six major peaks (78°, 75 cm³/min, on 0.25 in. 20% β,β′-ODPN, 25 ft) of retention times of 97.2, 106, 119.6, 130, 146.2, and 157.6 min, and three minor peaks of longer retention time. The six major peaks were collected preparatively on β,β′-ODPN, and the three minor peaks were collected on TCEP.

Thermal Reaction of 1,1-Dichloropropene and Cyclopentadiene. A solution of 1,1-dichloropropene (11.1 g, 0.1 mol) and cyclopentadiene (3.3 g, 0.05 mol) with some hydroquinone (0.2 g) was sealed in a thick-walled glass tube after degassing and heated to 200° for 24 hr. The tube was then cooled and opened, the excess olefin was removed on the rotovac, and the residue was bulb-to-bulb distilled at about 0.005 mm. VPC on Carbowax indicated mostly dicyclopentadiene, but there was also a peak of longer retention time that was collected. The VPC retention time was identical with that of the second peak in the photoreaction of the two above components and displayed two methyl doublets in the ratio of 60:40 at τ 8.99 and 8.73, respectively.

Photoreaction of 1,1-Dichloropropene and Cyclopentadiene. Synthesis of 7,7-Dichloro-6-*exo*-methylbicyclo[3.2.0]hept-2-ene (1a). A solution of β-acetonaphthone (4 g, 0.024 mol) in 1,1-dichloropropene (300 g, 2.7 mol) was irradiated with a 450-W Hanovia high-pressure lamp under N_2 with stirring at about 15–20°. To this solution was added, at about 4-hr intervals, 10-g (0.15 mol) portions of freshly distilled cyclopentadiene to a total of about 40 g (0.6 mol) over the course of about 16 hr, and the irradiation was continued overnight to bring the total irradiation time to about 22 hr. The excess dichloropropene was distilled off and the residue (about 40 g) was distilled under vacuum (18 mm) through a 12-in. Vigreux column. The DCPD came off first at about 66–75° followed by the cross adducts at 88–89° (6 g, 0.03 mol). VPC of the undistilled material on Carbowax indicated a DCPD/cross adduct ratio of about 6:1. The distilled material indicated four peaks on Carbowax 20M (10%, 0.125 in., 150°, 40 psi,

flow 2.6) of retention times of 30, 33.5, 40, and 42.5 min. The first, second, and fourth peaks were collected preparatively. Exact mass for 1a: theory, 176.0159; found, 176.0146.

Reaction of $(n\text{-Bu})_3$Sn, and Compound 1a. Synthesis of *exo*-6-Methyl-*endo*-7-chlorobicyclo[3.2.0]hept-2-ene (B Cl) and *exo*-6-Methyl-*exo*-7-chlorobicyclo[3.2.0]hept-2-ene (A Cl). A mixture of tri-*n*-butyltin hydride (0.429 g, 0.00147 mol) and 1a (0.237 g, 0.00134 mol) in hexane was refluxed overnight under argon with stirring. The material was bulb-to-bulb distilled (0.005 mm). Evaporation and isolation gave a mixture of isomers by vpc (0.170 g, 0.0012 mol, 89%), **3a:2a** 27:73. The mixture also contained about 5% starting material and about 15% of a material of short retention time, seemingly hydrocarbon. The mixture was separated on β,β'ODPN preparatively, to give pure **2a** and pure **3a**, of identical retention time with $h\nu$3 and $h\nu$6, respectively. Exact mass for **2a**: theory, 142.0549; found, 142.0546. Exact mass for **3a**: found, 142.0552.

Reaction of Thermal Dichloropropene–Cyclopentadiene Adducts with $(n\text{-Bu})_3$SnH. Formation of 1,4-Chloropropene Adducts. A mixture of the two thermal adducts from the dichloropropene–cyclopentadiene reaction in the ratio 60:40 endo:exo (0.156 g, 0.00089 mol), tri-*n*-butyltin hydride (0.290 g, 0.001 mol), and hexane was refluxed overnight under argon with stirring and then the material was bulb-to-bulb distilled at about 0.005 mm, giving the product mixture (0.124 g, 0.00088 mol, 99%). The analysis was performed on β,β'-ODPN.

6-Methyl-7-chlorobicyclo[3.2.0]hepta-2,6-diene (6). A solution of 1a (0.5 g, 0.00282 mol) in 5 ml of EtOH with 2.0 g of KOH was refluxed for about 2 days until VPC indicated replacement of the starting material by a product of short retention time (15 min, 150°, 20M 10%, 0.125 in.). Dilution with about 50 ml of water, extraction with ether, drying the ether, and its evaporation yielded the product 6 (0.281 g, 0.002 mol, 71%). Collection on a preparative column gave pure material. Exact mass: theory, 140.0393; found, 140.0398.

Hydrogenation of 2a. Formation of *exo*-6-Methyl-*endo*-7-chlorobicyclo[3.2.0]heptane (2). A solution of **2a** (0.05 g, 0.00035 mol) with PtO_2 (0.001 g) in about 0.5 ml of ether was hydrogenated at room temperature and 1 atm for 24 hr, during which 9 ml of H_2 was absorbed, and the reaction then stopped. By VPC, starting material (retention time 40 min, β,β'-ODPN, 75°, 35 psi) had disappeared to be replaced by product (retention time 30.4 min). Evaporation of the ether after bulb-to-bulb distillation gave product 2 (0.035 g, 0.00025 mol, 70%) whose nmr displayed no vinyl hydrogens. Exact mass: theory, 144.0705; found, 144.0701.

Hydrogenation of 3a. Formation of *exo*-6-Methyl-*exo*-7-chlorobicyclo[3.2.0]heptane (3). A solution of **3a** (0.037 g, 0.00026 mol) and PtO_2 (0.002 g) in CH_2Cl_2 was hydrogenated at 1 atm of H_2 with stirring for 24 hr. The reaction could not be followed by VPC, since starting material and product had the same retention time. However, after 24 hr the material had taken up about 6.5 ml of hydrogen (about 100%) and stopped. The material was bulb-to-bulb distilled and the methylene chloride evaporated. The nmr of the product (0.027 g, 0.00018 mol, 75%) had no vinylic hydrogen signals. Exact mass: theory, 144.0705; found, 144.0711.

Hydrogenation of $h\nu$4. Formation of *endo*-6-Methyl-*exo*-7-chlorobicyclo[3.2.0]heptane (5). A solution of $h\nu$4 (0.0377 g, 0.00027 mol) was hydrogenated over PtO_2 (0.001 g) in ether in the usual manner. Starting material (retention time 36 min, β,β'-ODPN, 75°, 35 psi) was replaced by two peaks in the ratio of 68:32 (retention times 34.8 and 43.2 min). The largest component, **5**, was collected (0.012 g) and its time-averaged nmr spectrum taken by use of the HA-100 spectrometer for 3 hr. Exact mass: theory, 144.0705; found, 144.0709.

Hydrogenation of $h\nu$5. Formation of 2. A solution of 0.096 g of $h\nu$5 in ether was hydrogenated over PtO_2 (0.003 g) in the usual manner with the uptake of about 17 ml of hydrogen. Starting material was replaced by two peaks on TCEP (retention times 61.1 and 63.5 min). Isolation by filtration and evaporation gave product (0.085 g, 0.00059 mol, 87%). Vpc separation and collection indicated **2** as the first peak and the hydrogenation product of the 1,4-*endo*-chloro-*exo*-methyl adduct (dihydro-F′) as the second peak.

Hydrogenation of $h\nu$2. Formation of 5. A solution of $h\nu$2 (exact mass: theory, 142.0549; found, 142.0547; 0.011 g, 0.000078 mol) and PtO_2 (0.001 g) in CCl_4 was hydrogenated in the usual manner, taking up about 2 ml of H_2, at which point the reaction stopped. The material was bulb-to-bulb distilled and isolated as CCl_4 solution. It was identified as **5** by NMR and ir.

Hydrogenation of $h\nu$3. Formation of 3. The photopeak $h\nu$3 (0.055 g, 0.00039 mol), which contained A Cl and another 1,2 product by NMR to the extent of about 15%, was hydrogenated over PtO_2 (0.003 g) in ether, taking up about 10 ml of hydrogen over the course of about 24 hr. Bulb-to-bulb distillation and evaporation of the ether gave a product (0.048 g, 0.00034 mol, 87%) whose NMR and ir indicated it to be a single material, **3**.

Hydrogenation of 6. Formation of 6-Methyl-7-chlorobicyclo[3.2.0]hept-6-ene (7). The diene 6 (0.025 g, 0.00018 mol) was hydrogenated over PtO_2 (0.001 g) in about 0.5 ml of CCl_4. After about 8 hr the material had taken up about 3 ml of hydrogen and the uptake halted. Vpc on β,β'-ODPN indicated disappearance of starting material (retention time 20 min) and the appearance of a new peak (retention time 10 min), compound **7**. Exact mass: theory, 142.0549; found, 142.0556.

Hydrogenation of 6. Formation of *endo*-6-Methylbicyclo[3.2.0]heptane (8). The diene 6 (0.05 g, 0.00036 mol) was hydrogenated over PtO_2 (0.001 g) in about 0.5 ml of ethyl acetate with chlorobenzene as internal standard. After 2 hr the material had taken up about 11 ml of hydrogen (115% of theory) and then the uptake halted. VPC on Apiezon J (15%, 16 ft, 135°, 100 cm^3/min) indicated complete disappearance of starting material (retention time 20 min) and appearance of a new peak (retention time 3.0 min) in about 95% yield based on chlorobenzene. The material was collected on the column (0.011 g, 28%). Exact mass: theory, 110.1096; foud, 110.1092.

Hydrogenation of 6. Formation of *en do*-6-Methyl-*endo*-7-chlorobicyclo[3.2.0]heptane (4). The reaction was followed on β,β'-ODPN (90°, 0.125 in. × 16 ft, 40 psi, flow rate 2.5). The diene 6 (0.1012 g, 0.00072 mol) in about 3–5 ml of hexane was hydrogenated in the Parr hydrogenator at 40 psi hydrogen over 5% Rh/Al_2O_3 (0.03 g). The starting material (retention time 19 min) had disappeared after 30 min, to be replaced by a compound of retention time 9.6 min previously demonstrated to be **8**. Sampling at 1-hr intervals indicated the appearance of a material of short retention time (2.9 min), **8**, and one of long retention time (34 min) at the expense of **8**. The reaction stopped with the composition listed in the discussion of results and could be forced to go no further. Centrifugation to remove catalyst, evaporation to remove solvent, and preparative VPC to remove impurities yielded pure 4 (0.016 g, 0.00011 mol, 32%). Exact mass: theory, 144.0705; found, 144.0708.

Hydrogenation of *endo*-6-Methyl-*endo*-7-chlorobicyclo-[3.2.0]hept-2-ene (D Cl). The olefin, D Cl (exact mass: theory, 142.0549; found, 142.0554) isolated by preparative VPC as $h\nu$9 (0.027 g, 0.00019 mol) and PtO_2 (0.002 g) in about 0.2 ml of CCl_4 was hydrogenated under 1 atm of hydrogen. The material took up 4.5 ml (95%) in 4 hr and ceased further uptake. Isolation by bulb-to-bulb distillation and evaporation of solvent yielded **4** (0.024 g, 89%) identified by ir and NMR.

Hydrogenation of *endo*-6-Chloro-*endo*-7-methylbicyclo-[3.2.0]hept-2-ene (D Me). The olefin, D Me (exact mass: theory, 142.0549; found, 142.0545) isolated by preparative vpc of $h\nu$8 (0.0114 g, 0.00008 mol) and PtO_2 (0.001 g) in about 0.1 ml of CCl_4 was hydrogenated under 1 atm hydrogen. The hydrogen uptake ceased after 5 hr. Isolation by bulb-to-bulb distillation as CCl_4 solution was effected and the material was identified as 4 on the basis of ir and NMR spectra.

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Registry No.—1a, 53835-12-4; **2**, 53835-13-5; **3**, 53861-67-9; **4**, 53861-68-0; **6**, 53835-14-6; 7, 53835-15-7; **8**, 13837-08-6; A Cl, 53835-16-8; A Me, 53835-17-9; B Cl, 53861-69-1; B Me, 53861-70-4; C Cl, 53861-71-5; C Me, 53861-72-6; D Cl, 53861-73-7; D Me, 53861-74-8; E, 53835-18-0; F, 53861-75-9; F′, 53861-76-0; G, 53835-19-1; cyclopentadiene, 542-92-7; *cis*-1-chloropropene, 16136-84-8; *trans*-1-chloropropene, 16136-85-9; 1,1-dichloropropene, 563-58-6; $(n\text{-Bu})_3$SnH, 688-73-3.

References and Notes

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(2) S. I. Miller, *J. Org. Chem.*, **26**, 2619 (1961).
(3) (a) H. Kasiwagi and J. Niwa, *Bull. Chem. Soc. Jpn.*, **36**, 405 (1963); (b) G. S. Reddy and J. H. Goldstein, *J. Am. Chem. Soc.*, **83**, 2045 (1961); (c) M. DeWoif and J. P. Baldeschwieler, *J. Mol. Spectrosc.*, **13**, 344 (1964).
(4) (a) H. L. Spell, *Anal. Chem.*, **31**, 1442 (1959); (b) W. H. King and H. A. Smith, *J. Am. Chem. Soc.*, **72**, 3459 (1950).

(5) (a) S. J. Cristol, W. K. Seifert, and S. B. Soloway, *J. Am. Chem. Soc.*, **82**, 2351 (1960); (b) K. W. Wiberg and W. J. Bartley, *ibid.*, **82**, 6375 (1960); (c) see also P. D. Bartlett and K. E. Schueller, *ibid.*, **90**, 6071 (1968).
(6) (a) P. M. Subramanian, M. T. Emerson, and N. A. LeBel, *J. Org. Chem.*, **30**, 2624 (1965); (b) W. D. Kumler, J. N. Shoolery, and F. V. Brutcher, Jr., *J. Am. Chem. Soc.*, **80**, 2533 (1958); (c) R. R. Fraser, *Can. J. Chem.*, **40**, 78 (1962); (d) T. J. Flautt and W. F. Erman, *J. Am. Chem. Soc.*, **85**, 3212 (1963).
(7) K. B. Wiberg, B. R. Lowry, and N. J. Nist, *J. Am. Chem. Soc.*, **84**, 1594 (1962).
(8) D. Seyferth, H. Yamayaki, and D. L. Alleston, *J. Org. Chem.*, **28**, 703 (1963).
(9) B. D. Kramer and P. D. Bartlett, *J. Am. Chem. Soc.*, **94**, 3934 (1972).
(10) P. D. Bartlett, 23rd International Congress of Pure and Applied Chemistry, Vol. 4, Butterworths, London, 1971, p 281.
(11) G. S. Hammond, N. J. Turro, and H. Fischer, *J. Am. Chem. Soc.*, **83**, 4674 (1961).
(12) N. J. Turro and P. D. Bartlett, *J. Org. Chem.*, **30**, 1849 (1965).
(13) D. Seyferth, A. Yamazaki, and D. L. Alliston, *J. Org. Chem.*, **28**, 703 (1963).
(14) G. E. Ham and W. P. Coker, *J. Org. Chem.*, **29**, 194 (1964).

Cycloaddition. XVIII. Isomer Distributions in the Photosensitized Addition of 1-Chloropropene to Cyclopentadiene

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cis- and *trans*-1-chloropropene have been added to cyclopentadiene with β-acetonaphthone as a photosensitizer at 30.5 and −24.8°. The relative total amounts of cis and trans photocycloadducts are about the same from *cis*- and *trans*-1-chloropropene, but the composition with respect to individual isomers is different in the two products by amounts outside the experimental error. These differences are smaller than in the similar case of the 1,2-dichloroethylenes and, as in that case, are greater at the lower temperature than at the higher. The observed regioselectivities and relative reactivities of olefins toward excited cyclopentadiene triplet are consistent with direct formation of a triplet biradical, whose time of spin inversion to singlet is appreciably shortened by the presence of chlorine within the biradical.

One of the clearest models of cycloaddition through a biradical intermediate is the reaction initiated by a photosensitizer. Triplet excitation energy is transferred rapidly from the sensitizer to that one of the unsaturated reactants having the lower lying triplet. Attack of this triplet on the second reactant produces a biradical with its electron spins unpaired, longer lived than a singlet biradical. Undergoing extensive intramolecular rotational equilibration, this biradical leads to product distributions characteristically different from those of concerted cycloadditions[2] from excited singlet state participants. Cyclopentadiene, sensitized by aromatic ketones, gives photocycloadducts to 1,2-dichloroethylene,[3,4,7,8] 2-butene,[5,7] and 1,2-dichloro-1,2-difluoroethylene,[6,7] which are mixtures of all seven possible cis-fused 1,2 and bridged 1,4 cycloadducts with extensive loss of configuration.

The comparison of the photocycloadditions of 2-butene and 1,2-dichloroethylene[7] revealed a striking difference. Six of the seven products are classifiable as belonging to the erythro or threo series,[10] this configurative feature being established at the moment of formation of the biradical. (The trans 5,6-disubstituted norbornenes are of ambiguous origin, since they can be formed from both erythro and threo biradicals.) *cis*- and *trans*-2-butene lead to identical ratios of the three erythro products, and to identical ratios of the threo products, although the ratio of total erythro to total threo depends upon the configuration of the starting material. This indicates that the internal rotations of each biradical on which the relative amounts of its products depend have reached statistical equilibrium before the spin inversion which triggers cyclization of the biradical. In the dichloroethylene products, however, although the ratio of total cis products to total trans products is largely independent of the configuration of the starting material, the actual isomer distribution within the threo series and within the erythro series shows large variation between cis and trans dichloroethylenes. The product pattern suggested that the sp^2–sp^3 rotation that equilibrates the relative configurations of the two chlorine atoms was still proceeding rapidly, but that the sp^3–sp^3 rotation about the newly formed bond in the biradical must be proceeding less completely. It has recently been established[9] that this ethane-like rotation approaches equilibration at higher temperatures, so that the dichloroethylene photocycloaddition at 80–100° is comparable in degree of equilibration to the 2-butene cycloaddition at −15°.

In the difference between the cases of 2-butene and of 1,2-dichloroethylene several factors may be involved. Since the steric requirements of the chlorine atom and the methyl group are comparable, it seems likely that the difference is more a matter of rate of spin inversion, converting triplet into singlet biradical (concerted or unconcerted with bond formation) than of the rate of intramolecular rotation in the biradical. Chlorine is not a heavy enough nucleus to cause spectacular effects on rates of spin inversion, but a finite influence of this kind is to be expected and could easily produce the marginal effect observed where ring closure just begins to compete with internal rotation. Other possible differences in the systems being compared include persistence of an exciplex in the formation of the biradical, secondary interaction between chlorine and hydrogen in the biradical, "cogwheel" facilitation of rotation past a methyl group as compared to a chlorine atom, and possible donor–acceptor character in the reaction between cyclopentadiene triplet and dichloroethylene providing a possible bypass to the conservation of spin multiplicity. Since the similarities between the butene and dichloroethylene systems are greater than the differences, the last-named factor cannot be very important. The fact that the product compositions are independent of sensitizer over a considerable range of excitation energy[3] makes competition between cyclopentadiene and a dichloroethylene–diene complex as energy acceptor seem unlikely.

Several of the possible influences mentioned here would depend in their operation on whether the chlorine atom, or the methyl group, were at the radical site or at the site of

Table I
VPC Retention Times for Hydrogenated Photoadducts[a]

Compd[b]	Retention time, min
2	59.2
Dihydro-F′	61.8
3 + 5 + dihydro-F	69.7
Dihydro-G	86.9
Dihydro-E	99.3
4	116.2

[a] 25 ft × 0.125 in. TCEP on Chromosorb P 60/80 mesh column at 90° with 5 cm³/min flow rate. [b] For structures see ref 11.

initial bond formation. It was therefore considered of interest to study the photosensitized cycloaddition of cyclopentadiene and 1-chloropropene. Biradicals in this system would resemble those from 2-butene at one point and those from dichloroethylene at the other. If the degree of stereochemical equilibration depended on the regioorientation of the biradical, it would speak for one of the more unsymmetrically operating of the effects.

Results

The photosensitized cycloaddition of a mixture of *cis*- and *trans*-1-chloropropene to cyclopentadiene was shown to produce the 12 photocycloadducts listed in Scheme I.[11]

The names A Cl or A Me refer to structure A with chlorine and methyl respectively at position 7.

The identification of all the adducts[11] does not complete the problem of determining their relative amounts. It is only from quantitative information that one can evaluate the contributions of the various factors that determine the rate of the biradicals produced in photosensitized reactions. From the separations of the photoadducts on a 25 ft × 0.125 in. column of 20% TCEP on acid-washed Chromosorb P, 60/80 mesh, it was possible to get the relative amounts of fractions $h\nu$1–9 (components listed in Table V of ref 11). On a 30 ft × 0.125 in. TCEP Chromosorb P 80/100 mesh column it proved possible to get the relative amounts of A Cl and A Me, since $h\nu$3 separated sufficiently to give a measurable shoulder. Simultaneous injection of $h\nu$3 and synthetic A Cl indicated that the shorter retention time material was A Cl. The analysis of $h\nu$3 was performed by cutting out the peaks on the chart paper and weighing them. The reproducibility of the analysis for A Cl and A Me proved to be of the order of ±1.0% of the reported value from one injection to the next.

It was therefore possible to get ten numbers by direct analysis of the original photomixture. Many other columns were tried in an effort to get additional separations. The complex nature of the mixture (the cyclopentadiene photodimers overlapped with adducts on many columns) as well as the basic similarity of structures, polarities, and volatilities of the adducts made the effort fruitless.

The key proved to be products of hydrogenation of the photoadduct mixture. The peaks $h\nu$4 and $h\nu$5 each separated into two pure compounds upon hydrogenation. The products of the hydrogenation of $h\nu$4 and $h\nu$5 did not overlap, and hence it was possible, in conjunction with the analysis of the unhydrogenated photomixture, to get a complete analysis of the entire photoadduct mixture. VPC analysis on the 25-ft TCEP column of the mixture obtained by hydrogenating the mixed photoadducts in ethyl acetate over platinum oxide under 1 atm of hydrogen revealed six peaks. Collection, in conjunction with simultaneous injection, indicated the results listed in Table I.

Table II
Product Distribution from Photosensitized Cycloaddition of Cyclopentadiene with *cis*-1-Chloropropene, β-Acetonaphthone as Sensitizer

Compd		30.5°	−24.8°
F	(trans-1,4)	11.8	10.3
C Cl	(erythro, trans-1,2)	7.1	4.8
A Cl	(threo-cis-1,2)	16.9	19.5
A Me	(threo-cis-1,2)	3.4	2.4
B Me	(threo-trans-1,2)	16.2	16.9
G	(exo-cis-1,4)	8.3	10.0
C Me	(erythro-trans-1,2)	12.8	14.2
F′	(trans-1,4)	7.7	8.0
B Cl	(threo-trans-1,2)	11.9	11.2
E	(endo-cis-1,4)	1.5	0.9
D Me	(erythro-cis-1,2)	0.3	0.3
D Cl	(erythro-cis-1,2)	2.1	1.5
Cyclopentadiene photodimers		565.	940.

The hydrogenation was shown to be quantitative by using dodecane as an internal standard. The above results therefore allow for a complete analysis of all 12 components of the photoadduct mixture. The procedure consists of (a) analysis of the isolated photoadducts $h\nu$1–9 on the 25 ft × 0.125 in. TCEP column; (b) analysis of A Cl and A Me on the 30 ft × 0.125 in. TCEP column; (c) hydrogenation of the isolated adduct mixture; (d) analysis of the hydrogenated photoadducts on the 25 ft × 0.125 in. TCEP column.

From d the amounts of hydrogenated G and hydrogenated F′ (dihydro-G and dihydro-F′) are directly measurable. The amount of dihydro-G when subtracted from the amount of $h\nu$4 gives the amount of B Me. The amount of dihydro-F′ when subtracted from the amount of $h\nu$5 gives C Me. Cross checking of the results, for instance, by taking the amount of 2 (obtained from the analysis of hydrogenation products) and subtracting the amount of B Cl ($h\nu$6) to obtain the amount of B Me indicated agreement within a run to about ±0.5–1% of the reported values.

All the quantitative analyses were performed using an F & M 7620 dual-column flame ionization chromatograph with nitrogen as carrier gas. The integrations were performed with an F & M 3370 digital integrator except as previously indicated. The detector was assumed to be equally sensitive to the various isomeric adducts. The products were shown to be stable to the photolytic conditions under which they were formed.

No reproducible quantitative results could be obtained in the case of *cis*-1-chloropropene and cyclopentadiene when irradiated at −78°. The amount of cross adducts from the cis isomer was less than 5% of the amount of photocyclopentadiene dimers.

The results of the photosensitized cycloadditions are given in Tables II and III. The experiments were all performed in degassed, sealed Pyrex tubes containing samples of either *cis*- or *trans*-1-chloropropene, freshly distilled cyclopentadiene, and 2-acetonaphthone in the approximate molar ratio of 100:10:1, respectively. The chloro olefins were of >98% purity.

Discussion

In broad terms, the photosensitized cycloaddition of 1-chloropropene to cyclopentadiene resembles that of 1,2-dichloroethylene[3,7] in yielding nonidentical product distributions from cis and trans starting materials. Also in simi-

Table III
Product Distribution from Photosensitized Cycloaddition of Cyclopentadiene with *trans*-1-Chloropropene, β-Acetonaphthone as Sensitizer

Compd		30.5°	-24.8°	-78.0°
F	(trans-1,4)	16.9	21.0	29.8
C Cl	(erythro, trans-1,2)	11.3	4.8	1.33
A Cl	(threo-cis-1,2)	19.9	21.4	23.2
A Me	(threo-cis-1,2)	4.1	3.1	1.3
B Me	(threo-trans-1,2)	9.1	5.3	3.8
G	(exo-cis-1,4)	4.3	2.4	1.4
C Me	(erythro-trans-1,2)	9.1	7.6	4.6
F′	(trans-1,4)	11.3	23.5	28.8
B Cl	(threo-trans-1,2)	10.7	8.0	3.7
E	(endo-cis-1,4)	1.5	1.4	1.2
D Me	(erythro-cis-1,2)	0.4	0.3	0.1
D Cl	(erythro-cis-1,2)	1.4	1.2	0.8
Cyclopentadiene photodimers		240.	289.	390.

Table IV
Structural and Stereochemical Distribution of Photocycloadducts of Tables II and III

	30.5°		-24.8°	
	From cis	From trans	From cis	From trans
Total cis	30.4	31.6	34.6	28.0
Total 1,2	70.7	66.0	70.8	51.7
Total 1,2 with $\cdot CHCH_3$	32.7	22.7	33.8	16.3
Total 1,2 with $\cdot CHCl$	38.0	43.3	37.0	35.4
Total erythro-1,2	22.3	22.2	20.8	13.9
Total threo-1,2	48.4	43.8	50.0	37.8
trans-1,4 (F + F′)	19.5	28.2	18.3	44.5
endo-cis-1,4 (E)	1.5	1.5	0.9	1.4
exo-cis-1,4 (G)	8.3	4.3	10.0	2.4
Total erythro-1,2 Me	13.1	9.5	14.5	7.9
Total threo-1,2 Me	19.6	13.2	19.3	8.4
Total erythro-1,2 Cl	9.2	12.7	6.3	6.0
Total threo-1,2 Cl	28.8	30.6	30.7	29.4

larity to the case of dichloroethylene, the total *cis/trans ratio* of the products near room temperature shows no significant dependence on the configuration of the starting material. The differences between the products from the cis and trans isomers, which are more marked at the lower temperatures, appear in a greater regioselectivity of the cyclopentadiene triplet toward the trans than the cis isomer, and in the distribution between 1,2- and 1,4-addition products. Thus the generalization that the sp^2–sp^3 rotation in the biradical is fast relative to spin inversion applies to this case also. There is a scattered incidence of cis–trans pairs formed with slight net inversion (PQ < 1),[12,13] but since these instances in the 1,2-addition products are almost exactly balanced by net retentions in the 1,4 products, they are probably associated with fractionations in the ring closing step. Exploring this point in great detail is hindered by the impossibility of determining what fraction of the 1,4 cycloadducts originate from the Me and the Cl biradicals, and how the trans 1,4 adducts are apportioned between erythro and threo series.

The 1,2 cycloadducts, however, are readily recognizable both as to the regio series (Cl or Me) and as to the diastereomeric series (erythro and threo)[10] to which they belong. Table IV summarizes such information about the product distributions at 30.5 and −24.8°. In general the dependence on configuration of starting material is greater than with 2-butene, but less than with 1,2-dichloroethylene.[3,5,7] There is, however, no tendency for the Cl product distribution to resemble specifically those from dichloroethylene, or those from 2-butene; rather, the results are consistent with the idea that the presence of a single chlorine atom in the triplet biradical gives it a lifetime with respect to spin inversion that is intermediate between those of biradicals with two chlorine atoms and with none.

If an intramolecular heavy atom effect is the correct explanation of the difference between the lifetimes of triplet biradicals that do and do not contain chlorine, it is surely a marginal effect. Experiments with two halogen-containing solvents (1,1,2-trichloro-1,2,2-trifluoroethane and bromobenzene) showed no significant effect of the solvent on the product compositions of the cycloadducts of cyclopentadiene with *cis*- and *trans*-2-butene. However, it should be noted that the spin inversion with which we are here concerned is that of an odd electron at one end of a rapidly rotating biradical in which the environment of the electron and its interaction with its mate are constantly changing. In the large heavy atom solvent effects on the dimerization of acenaphthylene,[14] intersystem crossing occurs in the rigid excited singlet of acenaphthylene crossing to triplet *before* the formation of any biradical. Even the time scales of these two cases are quite different so that the lack of solvent effects in the present case probably does not constitute a test of an intramolecular heavy atom effect in a biradical.

Because of the competition for cyclopentadiene triplet by the olefin and ground-state cyclopentadiene, it is possible to evaluate the competitive rate constants from an accurate determination of the relative amounts of reactants and products. The rate constants of reaction of cyclopentadiene triplet with a series of alkenes can thus be determined in terms of its rate constant toward cyclopentadiene as a standard.

In the competing reactions (D = diene, O = olefin, D_2 = dimer, A = adduct, D* = excited diene)

$$D^* + D \xrightarrow{k_d} D_2$$

$$D^* + O \xrightarrow{k_a} A$$

$$-d(D)/dt = 2k_d(D^*)(D) + k_a(D^*)(O)$$

$$-d(O)/dt = k_a(D^*)(O)$$

$$\frac{d(D)}{d(O)} = 2\frac{k_d}{k_a}\frac{(D)}{(O)} + 1 \qquad (1)$$

If (D)/(O) = x and (O) = y, then

$$\frac{dy}{y} = \frac{dx}{\left(2\frac{k_d}{k_a} - 1\right)x + 1} \qquad (2)$$

If k is defined as $2(k_d/k_a) - 1$, the integral equation is

$$\ln\frac{y_0}{y} = \frac{1}{k}\ln\frac{kx_0 + 1}{kx + 1} \qquad (3)$$

which can be applied to the initial and final amounts of material in a preparative reaction. When, as in most of the present cases, irradiation is conducted to the complete consumption of cyclopentadiene, the final x vanishes and the equation becomes

$$\ln\frac{y_0}{y} = \frac{1}{k}\ln(kx_0 + 1) \qquad (4)$$

Table V
Relative Reactivities toward Cyclopentadiene Triplets (Total Cycloadducts)

Alkene, x_0 = 0.10	R[a] 30.5°	R[a] -24.8°	$10^4 k_a/k_d$ from eq 4 30.5°	$10^4 k_a/k_d$ from eq 4 -24.8°	Ref
cis-1-Chloropropene	5.65	9.40	42	22.5	This work
Cl orientation[c]			22.5	11.8	This work
Me orientation[c]			19.5	10.7	This work
trans-1-Chloropropene	2.40	2.89	121	96	This work
Cl orientation			79.4	66	This work
Me orientation			41.6	30	This work
cis-1,2-Dichloroethylene	1.47[b]	2.29	230[b]	128	3
trans-1,2-Dichloroethylene	0.39[b]	0.45	1081[b]	909	3
2-Butene	33[b]		(5[b])		5

[a] R = (cyclopentadiene dimers)/(cross adducts). [b] At 25°. [c] Assuming that the distribution of 1,2 cycloadducts indicates the regioselectivity in formation of the total biradical.

When y is in great excess, the approximation

$$\ln \frac{y_0}{y} \approx \frac{A}{y_0}$$

becomes a good one, and eq 3 becomes equivalent to that previously used[15] in cycloadditions of 1,1-dichloro-2,2-difluoroethylene. By means of eq 4 the relative rate constants of Table V have been determined. A trans olefin captures cyclopentadiene triplet at 30.5° 2.9 times as fast as its cis isomer in the case of 1-chloropropene, and 4.7 times as fast in the case of 1,2-dichloroethylene at 25°. At −24.8° these factors become 4.3 and 7.1, respectively.

The k_a/k_d of 2-butene in Table V is of low accuracy because the dimers were only estimated retrospectively by difference from the initial diene and the measured yield of cross adduct. The value is included for qualitative comparison only.

Comparison of the rates in Table V suggests that at the site of first bond formation methyl is more deactivating than chlorine by factors of about 7 and 5, respectively, in the trans and cis alkenes, while chlorine at the radical site is more activating than methyl by corresponding factors of 13 and 6. The results are consistent with the rate of photosensitized cycloaddition being chiefly determined by local factors stabilizing a free radical and hindering the formation of a covalent bond. There are no signs of these factors being greatly modified by energy uptake by a complex nor by the entrance of an exciplex into the reaction sequence under the conditions of these reactions.

Experimental Section

Materials for Quantitative Photosensitized Cycloadditions. Eastman dicyclopentadiene was cracked thermally to give cyclopentadiene. The cyclopentadiene to be used in a run was redistilled shortly before use. Eastman White Label β-acetonaphthone was recrystallized from hexane. Pure *trans*-1-chloropropene (98+%) was obtained by distillation of practical 1-chloropropene through a 23-in. Nester-Faust spinning band column with a reflux ratio of 50–100:1, bp 37.5–38.0°. Pure *cis*-1-chloropropene (98+%) was obtained by redistillation of the 31–34° fraction from the isolation of trans olefin through the 23-in. Nester-Faust column. Pure cis olefin was obtained at 32.5–33.0° with a reflux ratio of about 100:1. The VPC analysis of these olefin mixtures was performed on either a 15 ft × 0.25 in., 15% tricresyl phosphate on Chromosorb P 60/80 mesh column or a 25 ft × 0.125 in., 20% 1,2,3-tris(cyanoethoxy)propane on acid-washed Chromosorb P 60/80 mesh column.

Irradiations. The olefin (5.0 g, 0.066 mol), freshly distilled cyclopentadiene (0.45 g, 0.0066 mol), and β-acetonaphthone (0.11 g, 0.00066 mol) were weighed into 15 × 125 mm Pyrex test tubes with constricted necks. The tubes were degassed four times and sealed under vacuum. A 550-W Hanovia mercury lamp was used for all irradiations. For the runs at 0° and above the tubes were fastened to a Pyrex well and immersed in a water bath. The water bath was kept at the desired temperature by passing cold methanol from a Lauda Kryomat Model TK30 through cooling coils. Water circulated through the Pyrex well. The runs at −24.8° were performed by placing the sealed tubes in a Pyrex flask containing enough dimethyl ether to cover the tubes. The well containing the lamp was placed next to the flask. The dimethyl ether was refluxed using the well as a heat source and a Dry Ice condenser. A stream of dry nitrogen was blown on the face of the flask adjacent to the lamp to prevent the condensation of moisture. The experiments at −78° were performed by immersing the sealed tubes in a Dry Ice–methanol bath contained in an unsilvered dewar. The Pyrex well containing the lamp was then placed adjacent to the side of the dewar next to which the tubes were suspended.

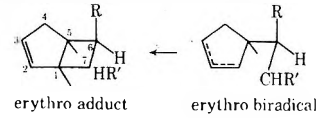
Product Analysis. An F & M 7620 dual column gas chromatograph with a flame ionization detector was used. The tubes were opened and the olefin was examined for isomerization. In no case was the product olefin analysis different from that of starting olefin within experimental error. The olefin was distilled off and the residue was bulb-to-bulb distilled at 0.001 mm into a liquid nitrogen cooled receiver. The peaks $h\nu$1–9 were analyzed on a 25 ft × 0.125 in. 20% TCEP on Chromosorb P 60/80 mesh column at 90° and 5 cm³/min He flow rate. The relative amounts of A Cl and A Me were determined on a 30 ft × 0.125 in. 20% TCEP on Chromosorb P 80/100 mesh column at 90° and less than 1 cm³/min flow rate. To about 0.03 g of this photomixture was added 2 mg of PtO_2 and about 0.5 ml of ethyl acetate. The hydrogenation was carried out under 1 atm of hydrogen for about 4 hr (uptake generally halted after 0.5 hr). The ethyl acetate solution was then decanted (after centrifugation) and analyzed directly in the 25 ft TCEP column for the hydrogenation products of Δ2 and Δ3. All integrations were performed using an F & M 3370 digital integrator except those for the relative amounts of A Cl and A Me. These were obtained by Xeroxing the VPC trace and cutting out the peaks corresponding to A Cl and A Me and weighing them.

Acknowledgments. We thank the National Institutes of Health and the National Science Foundation for grants, and the National Institutes of Health for a graduate fellowship to L.A.H.

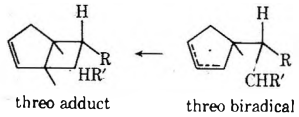
Registry No.—A Cl, 53835-16-8; A Me, 53835-17-9; B Cl, 53861-69-1; B Me, 53861-70-4; C Cl, 53861-71-5; C Me, 53861-72-6; D Cl, 53861-73-7; D Me, 53861-74-8; E, 53835-18-0; F, 53861-75-9; F′, 53861-76-0; G, 53835-19-1; cyclopentadiene, 542-92-7; *cis*-1-chloropropene, 16136-84-8; *trans*-1-chloropropene, 16136-85-9.

References and Notes

(1) To whom correspondence should be addressed: Department of Chemistry, Texas Christian University, Fort Worth, Tex. 76129.
(2) (a) O. L. Chapman and R. D. Lura, *J. Am. Chem. Soc.*, **92**, 6352 (1970); (b) H. Yamazaki and R. J. Cvetanovic, ibid., **91**, 520 (1969).
(3) P. D. Bartlett, R. Helgeson, and O. A. Wersel, *Pure Appl. Chem.*, **16**, 187 (1968).
(4) P. D. Bartlett, L. M. Stephenson, and R. Wheland, *J. Am. Chem. Soc.*, **93**, 6518 (1971).
(5) B. D. Kramer and P. D. Bartlett, *J. Am. Chem. Soc.*, **94**, 3934 (1972).
(6) R. Wheland, Thesis, Harvard University, 1970, p 62.
(7) P. D. Bartlett, 23rd International Congress of Pure and Applied Chemistry, Vol. 4, Butterworths, London, 1971, p 281.
(8) The exo-cis 1,4-cycloadduct, undetected at first in the photosensitized cycloaddition product of dichloroethylene to cyclopentadiene, has been found.[9]
(9) U. P. Singh, manuscript in preparation.
(10) For consistency with the other papers from this laboratory we depict the bicyclo[3.2.0]hept-2-enes with the 4 ring in a horizontal plane and the 5 ring joined to it along the left side, inclined upward with the double bond



erythro adduct erythro biradical



to the front. The erythro, threo designations apply to the relative configurations at C_5 and C_6 in the allylic biradical, which are permanently established when the first bond is formed. The radical ends are regarded as corresponding substituents.

(11) L. A. Hull and P. D. Bartlett, *J. Org. Chem.*, **40**, 824 (1975).
(12) L. K. Montgomery, K. E. Schueller, and P. D. Bartlett, *J. Am. Chem. Soc.*, **86**, 622 (1964).
(13) P. D. Bartlett, *Acc. Chem. Res.*, submitted for publication.
(14) D. O. Cowan and R. L. Drisko, *J. Am. Chem. Soc.*, **89**, 3068 (1967).
(15) P. D. Bartlett and L. K. Montgomery, *J. Am. Chem. Soc.*, **86**, 629 (1964).

Synthesis and Solvolytic Studies of Tetracyclo[4.2.0.0^{2,5}.0^{4,7}]octan-3-yl (Secocubane) Derivatives

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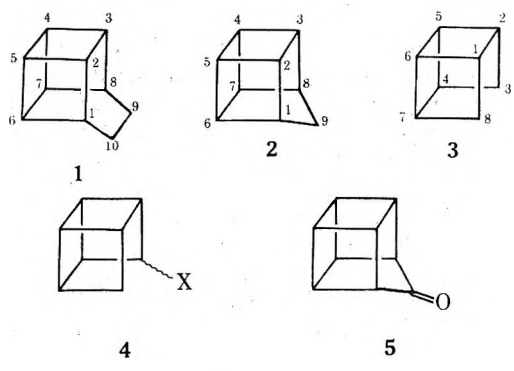
An efficient synthesis of pentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]nonan-9-one (**5**, homocubanone) has been devised and its conversion to a variety of tetracyclo[4.2.0.0^{2,5}.0^{4,7}]octan-3-yl (secocubane) derivatives is described. Baeyer–Villiger oxidation of *exo*-secocubyl methyl ketone (**14**) gave the corresponding acetate **15**, which was reduced to exo alcohol **16**. Similar oxidation of *endo*-secocubyl methyl ketone (**13**) gave acetate **18** and trifluoroacetate **19**, shown to have the rearranged *exo*-tetracyclo[4.2.0.0^{2,4}.0^{3,8}]octan-5-yl structure. *exo*-Secocubyl mesylate (**17**) solvolyzed in acetic acid with a rate of $k = 1.27 \times 10^{-4}$ sec^{-1} at 75°, and gave one product, acetate **18**. The results obtained in this investigation are compared with the reactivity of *exo*- and *endo*-bicyclo[2.2.0]hex-2-yl derivatives and explained in terms of controlling steric, geometric, and conformational factors.

The study of strained polycyclic small-ring compounds has become widespread in recent years.[1] In particular, the use of the cubane "cage" compound series pentacyclo[4.4.0.0^{2,5}.0^{3,8}.0^{4,7}]decyl (bishomocubyl), pentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}] (homocubyl), and cubane itself has facilitated the study of strain–reactivity relationships. Investigations with derivatives of these cage compounds have given insight into the nature of transition metal catalyzed rearrangements of strained systems,[2] and solvolysis studies of bishomocubyl (**1**)[3] and homocubyl (**2**)[4] derivatives have offered exceptional opportunities for the investigation of transition states, intermediates, and strain release factors in carbonium ion rearrangements.

A natural extension to the studies of cubane-related cage compounds is the tetracyclo[4.2.0.0^{2,5}.0^{4,7}]octyl (secocubane) system (**3**). These solvolytic studies of secocuban-3-yl derivatives (**4**) offer exceptional opportunities for the study of the geometrical and stereochemical requirements of carbonium ion rearrangements in strained systems. The pucker[5,6] of the side cyclobutane rings in the rigid secocubyl cage causes a large stereochemical difference in the rearrangement routes open to the exo and endo isomers of **4**. Furthermore, one would anticipate significant differences in exo vs. endo reactivities in the secocubyl series.

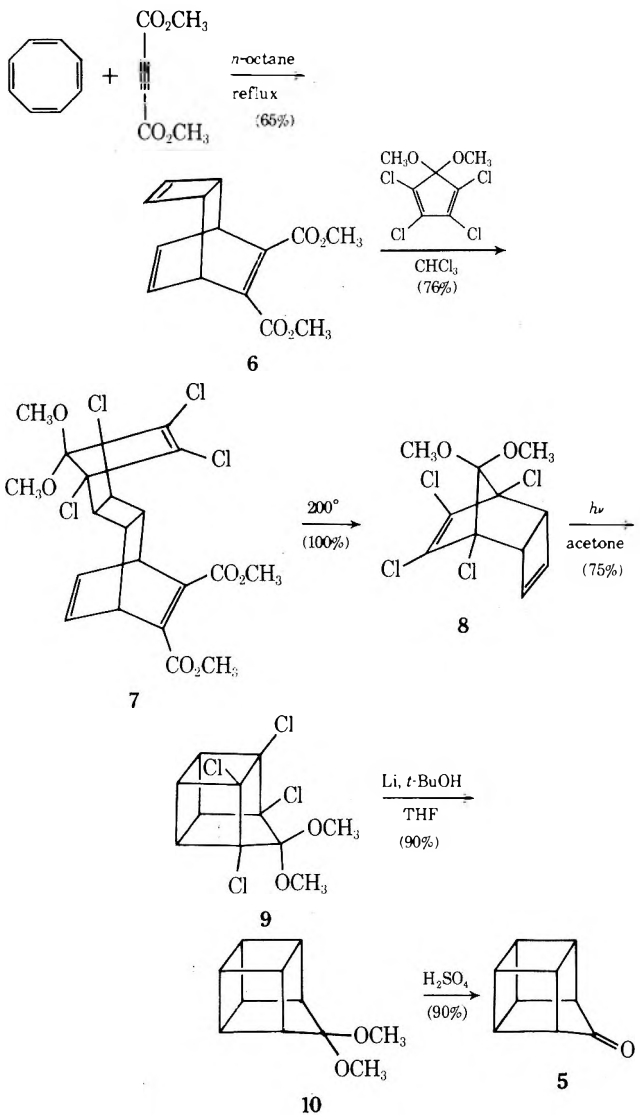


The discovery of the intramolecular [2 + 2] photocycloaddition reaction has lead to the development of synthetic routes to a variety of polycyclic cage compounds.[7] However, the difficulties which make these compounds such a synthetic challenge often hamper further studies. The multistep, low-yield synthetic routes to homocubanes[8] and secocubanes[9] limit the quantities of material available for solvolytic and other chemical investigations. We now wish to describe the development of a convenient and efficient synthesis of homocubanone (**5**) which makes large quantities of ketone available for use as a synthetic intermediate. We also wish to report, in detail, on the conversion of **5** to monofunctionalized secocuban-3-yl derivatives, and the studies undertaken of the solvolytic reactivity of the secocubane compounds.

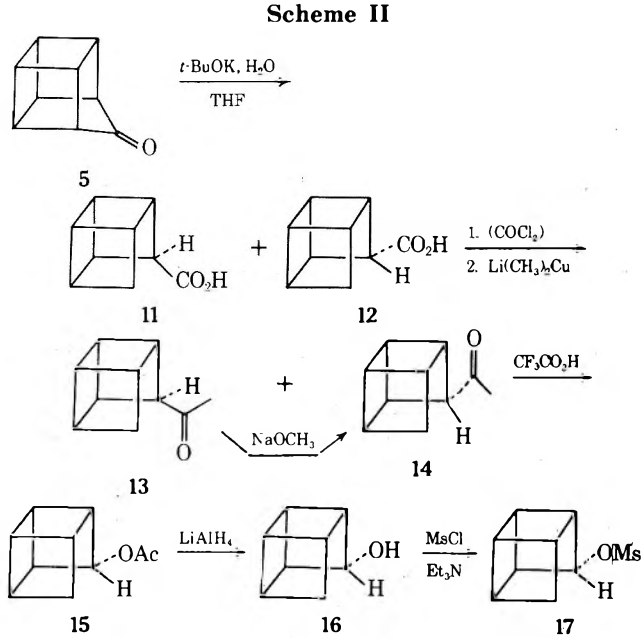
Synthesis. The synthesis of homocubanone was accomplished by the series of reactions outlined in Scheme I. The synthesis of tetrachlorohomocubanone ketal **9** was first reported by Warrener and coworkers;[10] however, no experimental details were given and no attempt was made to optimize the yield. In the present study, it has been found that a 65% yield of **6** could be obtained when the reactants were refluxed in *n*-octane (bp 125°) for 6 days.[11,12] Dechlorination of **9** with lithium metal and *tert*-butyl alcohol in tetrahydrofuran[13] gave homocubanone dimethyl ketal (**10**) in 90% yield. Ketal **10** was hydrolyzed to homocubanone (**5**) with 5% aqueous sulfuric acid. The sequence illustrated in Scheme I represents a 30% overall yield synthesis of **5** from cyclooctatetraene, and is capable of providing 20–30-g quantities of material for further synthetic efforts.

Conversion of **5** to the secocubane system was achieved via nonenolizable ketone cleavage.[14] Thus, when **5** was added to a stirred suspension of potassium *tert*-butoxide and water in tetrahydrofuran, and the mixture was heated at 50° for 6 hr, an 85% yield of a mixture of *endo*-and *exo*-secocubane-3-carboxylic acids (**11** and **12**) in a 9:1 ratio was obtained. The NMR spectrum of the mixture of **11** and **12** contained broad singlet resonances at δ 2.3 for **11** and 2.5 for **12** (in a ratio of 9:1) for the methylene protons and a broad multiplet at δ 3.0–3.7 for the remaining cage protons of both isomers. The upfield shift of the methylene protons of endo isomer **11** is consistent with the results found for

Scheme I



Scheme II



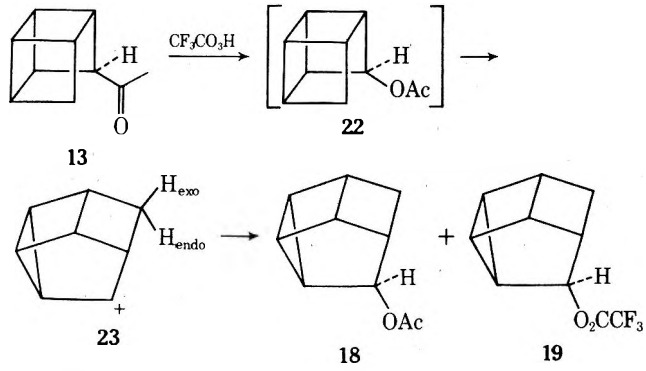
other cage and half-cage compounds, and this shift has been attributed to steric compression in the endo isomer.[15]

The synthetic route to *exo*-secocubane-3-mesylate (**17**) is illustrated in Scheme II. The acid mixture, **11** and **12**, was treated with oxalyl chloride, and the resultant crude acid chloride mixture was converted to a mixture of endo and exo methyl ketones **13** and **14** by treatment with lithium dimethylcuprate.[16] The mixture of methyl ketones was separated by silica gel chromatography, or alternatively, was quantitatively converted to exo isomer **14** by treatment with sodium methoxide in methanol. Baeyer–Villiger oxidation of **14** with trifluoroperacetic acid in buffered methylene chloride[17] gave exo acetate **15** in good yield. Lithium aluminum hydride reduction of **15** gave *exo*-secocuban-3-ol (**16**), which was converted to mesylate **17** in the usual manner.[18]

The NMR spectra of both alcohol **16** and mesylate **17** exhibited the characteristic doublet, J = 2 Hz, at δ 4.85 and 5.55 assigned to the protons α to the alcohol and mesylate group, respectively. In addition, both spectra had similar two-proton multiplets at δ 2.4 for the methylene protons and six-proton multiplets at δ 3.5 for the cage protons. The similarities between the spectra of **16** and **17** indicate that mesylate formation occurred without rearrangement of the cage skeleton.

Results

Baeyer–Villiger oxidation of endo ketone **13** with trifluoroperacetic acid in buffered methylene chloride proceeded at a much slower rate than **14**, presumably owing to steric hindrance in the endo isomer. The reaction gave a 90% yield of approximately equimolar amounts of an acetate **18** and a trifluoroacetate **19** with rearranged carbon skeletons. The acetate and trifluoroacetate had infrared carbonyl absorptions at 1730 and 1780 cm^{-1}, respectively, and both compounds had an ion corresponding to formula C_8H_9 for the parent carbon skeleton fragment in the mass spectrum, isomeric with the secocubyl cage system. The NMR spectra of **18** and **19** were very similar, with a signal for the α-oxy proton at δ 4.75 and 5.0, respectively. Both compounds exhibited broad, complex multiplets at δ 1.6–2.3 and 2.3–2.9, and the acetate had a three-proton singlet at δ 1.95 for the acetate methyl group.



The high-field multiplet at δ 1.6–2.3 is indicative of a fused cyclopropane ring in the rearranged carbon skeleton.[19] The absence of any NMR or infrared evidence for unsaturation suggests that the new structure is still a tetracyclic system. The production of both acetate and trifluoroacetate is consistent with ionization of the first-formed acetate, followed by carbonium ion rearrangement prior to collapse of the products. The equimolar ratio of acetate to trifluoroacetate, formed in spite of the overwhelming excess of trifluoroacetate ion in solution, is indicative of the much greater nucleophilicity of acetate anion and/or internal return of the acetate anion.

Lithium aluminum hydride reduction of the crude mixture of **18** and **19** gave a single alcohol **20**, which was oxi-

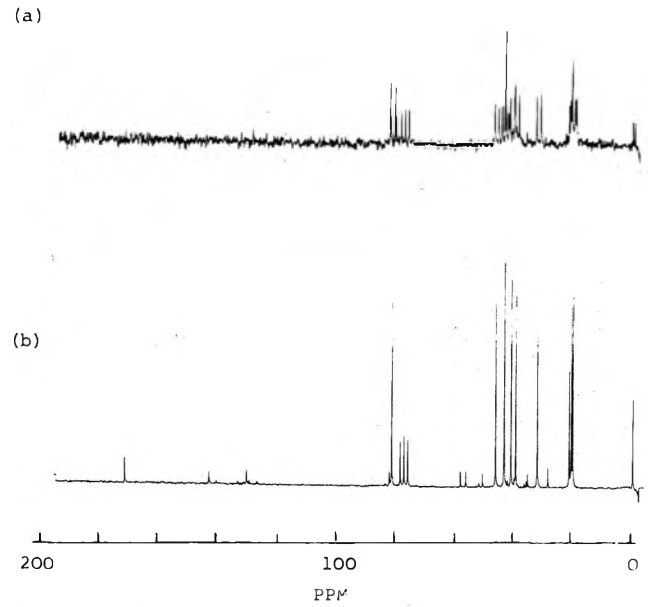
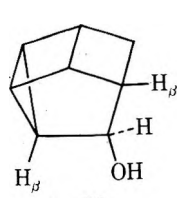


Figure 1. ^{13}C NMR spectrum of solvolysis acetate **18**: (a) off-resonance coupled; (b) wide-band coupled.

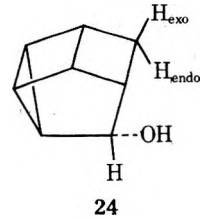
dized with chromium trioxide–pyridine to the corresponding ketone **21**. The ketone had the molecular formula C_8H_8O, determined by high-resolution mass spectroscopy, an infrared carbonyl absorption at 1750 cm^{-1}, and an ultraviolet λ_{max} at 202 nm (ϵ 2500), indicative of a cyclopropyl conjugated ketone.[20]

The above data are consistent with the proposal of a cyclobutyl–cyclopropylcarbinyl rearrangement of the first-formed *endo*-secocubyl acetate (**22**) to the tetracyclo[4.2.0.$0^{2,4}$.$0^{3,8}$]oct-5-yl ring system (**23**). A similar rearrangement of a strained cyclobutyl ketone, carvonecamphor, to a cyclopropylcarbinyl system under Baeyer–Villiger conditions has been reported by Buchi.[21] The formation of both acetate and trifluoroacetate products from rearrangement of **22** under Baeyer–Villiger conditions indicates that a solvated carbonium ion, free of acetate counterion, was formed. For steric reasons, it was expected that nucleophilic attack would give exo products **18** and **19**, due to the endo-methylene hydrogen (H_{endo}), which blocks approach from that side of the molecule.

The exo configuration of **18** and **19** was confirmed by addition of $Eu(fod)_3$ to a solution of alcohol **20** in carbon tetrachloride. The multiplet assigned tc the methylene protons of **20** at δ 1.90 moved downfield at a slower rate than the signals for the protons β to the hydroxyl group (H_β) when successive 1-mg portions of $Eu(fod)_3$ were added. Models indicate that the hydroxyl oxygen of endo alcohol **24** would be very close to H_{endo}, and the NMR resonance of



20

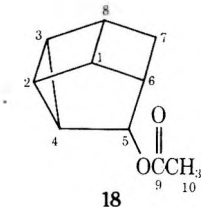


24

the methylene protons of **24** would be expected to separate as the H_{endo} signal was shifted downfield at a rapid rate.

Final proof of the structure of acetate **18** was obtained from its carbon-13 NMR spectrum. The off-resonance decoupled and wide-band decoupled ^{13}C NMR spectra of **18** are shown in Figure 1, and the chemical shifts and assignments of the various resonances are listed in Table I.

Table I
^{13}C NMR Assignments for Solvolysis Acetate 18

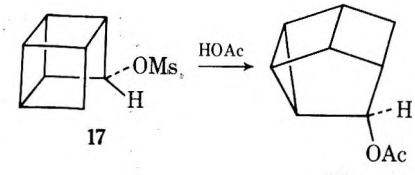


18

Carbon	δ, ppm	Splitting
1	41.0	Doublets
2,3	20.0,20.5	Doublets
4	21.2	Doublet
5	81.3	Doublet
6	46.2	Doublet
7	43.4	Triplet
8	39.4	Doublet
9	171.3	Singlet
10	32.0	Quartet

The presence of three cyclopropyl carbons at δ 20.0–21.2, one methylene carbon at δ 43.4, which appears as a triplet in the off-resonance spectrum (C-7), and the appropriate chemical shifts of the tertiary carbons in relationship to their surroundings confirm the structure of **18**.

When mesylate **17** was stirred for 22 hr in sodium acetate buffered acetic acid at 80°, a quantitative yield of a mixture of acetates was obtained. Analysis of the mixture by VPC showed 90% of one acetate, which proved to be identical with rearranged acetate **18** obtained from Baeyer–Villiger reaction of endo ketone **13**. In addition, trace amounts of several other products were obtained which were not investigated.

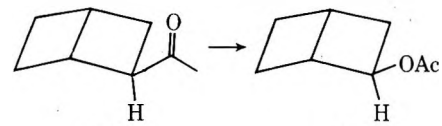


17 **18**

The acetolysis rate of **17** was determined at three temperatures by measuring the disappearance of the NMR signal for the proton α to the mesylate group vs. an internal standard (chloroform). Calculations based on these measurements give first-order rate constants of $k = 1.27 \times 10^{-4}$ sec^{-1} at 75.6°, $k = 2.61 \times 10^{-5}$ sec^{-1} at 60.0°, and $k = 2.95 \times 10^{-6}$ sec^{-1} at 44.7°. Extrapolation to 25° gives $k = 2.5 \times 10^{-7}$ sec^{-1}, $E_a = 30 \pm 3$ kcal/mol, and $\Delta H^{\ddagger} = 27 \pm 3$ kcal/mol.

Discussion

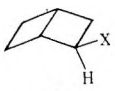
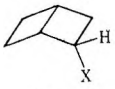
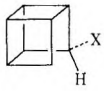
It is instructive to compare the reactivities of secocubyl derivatives with their corresponding bicyclo[2.2.0]hex-2-yl models. McDonald and Davis[22] found that *exo*- and *endo*-2-acetylbicyclo[2.2.0]hexanes (**25** and **26**) exhibited reactivity in the Baeyer–Villiger reaction similar to that of *exo*- and *endo*-secocubyl ketones **14** and **13**. Oxidation of exo ketone **25** gave the corresponding acetate **27**, but similar

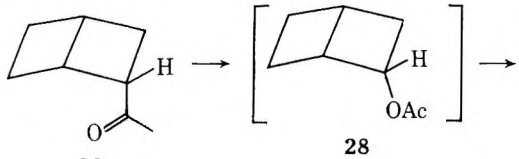


25 **27**

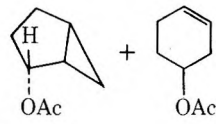
treatment of endo ketone **26** gave a mixture of the expected endo acetate **28**, rearranged acetate **29**, and a trace of **30**.

Table II

Compd	Relative solvolysis rate, X = OSO_2R	Ref
	1.0	23
	8×10^7	24
	9.0	25
	2.3	This study



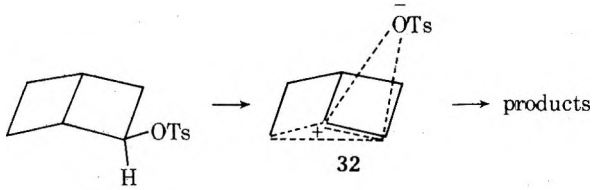
26 28



29 30

Endo acetate **28** underwent further rearrangement on standing at −26° in carbon tetrachloride solution, forming additional **29** and **30**.

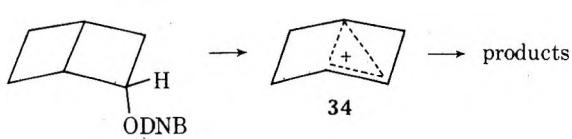
The relative solvolysis rates of the compounds relevant to this study are summarized in Table II. Acetolysis of bicyclo[2.2.0]hex-2-yl tosylate (**31**) proceeded with carbon–carbon bond migration to form ion pair **32**, which collapsed



31 32

to give rearranged tosylate and acetate products.[23] The cyclobutane rings of **31** are nearly planar. Hence, the formation of a stabilized bicyclobutonium ion, such as that generated from cyclobutyl tosylate, is prohibited. Since the solvolysis rate of cyclobutyl tosylate is faster than expected by bond-angle deformation considerations because of the formation of such a nonclassical ion, the fact that **31** solvolyzes only nine times slower than cyclobutyl tosylate is believed to indicate some anchimeric assistance to ionization due to β,γ-bond migration.

Solvolysis of *endo*-bicyclo[2.2.0]hex-2-yl 3,5-dinitrobenzoate (**33**) in aqueous acetone gave a mixture of rearranged

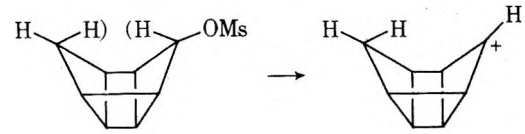


33 34

alcohols and internal returned dinitrobenzoates.[24] The greatly accelerated rate of **33** (Table II) was attributed to the formation of bicyclobutonium ion intermediate **34**.

The large endo/exo rate ratio for the bicyclo[2.2.0]hexyl system is in line with the observed rate ratios for the general series of bicyclo[*m*.2.0]alkyl derivatives.[26] The high solvolytic reactivity of the endo compounds is explained by a disrotatory opening of the central bond to maintain maximum overlap with the developing p orbital at the site of the leaving group. In this manner a bicyclobutonium ion similar to **34** can be formed. A similar mechanism in the exo compounds is prohibited owing to the steric interaction between the opposing bridgehead hydrogens.

In *exo*-secocubyl mesylate (**17**), the side cyclobutanes are puckered, and the leaving group is held in an axial configuration. Hence, **17** should solvolyze at a slow rate relative to cyclobutane.[27] Furthermore, a Wagner–Meerwein rearrangement in **17**, similar to that in **31**, is prohibited by steric and strain factors. Yet the relative solvolysis rate of **17** is the same order of magnitude as **31**; in fact, it is actually somewhat faster. The conformation of **17** prevents any anchimeric assistance to solvolysis, and hence it is unlikely that much, if any, rearrangement occurs during the rate-determining ionization. However, the unexpected rate acceleration can be explained by relief of steric compression of the endo-methylene hydrogens on ionization of **17** to a classical trigonal carbonium ion (**35**). The driving force attributed to such steric compression strain release does account for the observed solvolysis rate, and there is precedent for rate accelerations of solvolyses due to steric compression strain release.[28]



17 35

While rearrangement of **35** to carbonium ion **23** represents a calculated[1c] strain release of approximately 16 kcal, further rearrangements of the cyclopropylcarbinyl carbonium ion could release a great deal more strain energy. It is, therefore, somewhat surprising that the rearrangement sequence stops at **23**. An examination of molecular models indicates that **23** would be expected to be a stable cyclopropylcarbinyl carbonium ion owing to the rigid bisected geometry, and hence a significant barrier to further reaction would be anticipated. The formation of a cyclopropylcarbinyl rearrangement product is also consistent with the rearrangement of *endo*-2-acetylhicyclo[2.2.0]hexane (**26**), which gave mainly cyclopropylcarbinyl acetate product **29**.

The very reactive nature of the endo-secocubyl system is apparent from the results of the present study. Unfortunately, this extreme reactivity has thus far precluded the isolation of an endo-secocubyl derivative for solvolytic studies. However, based on the results of solvolysis studies on the bicyclo[2.2.0]hex-2-yl system, a minimum rate prediction for the endo-secocubyl system would be 10^8 relative to the exo system. Furthermore, the fact that the leaving group in an endo derivative would be equatorial relative to the puckered cyclobutane ring would be expected to enhance the endo/exo rate ratio to an even greater extent.

Experimental Section

Melting points were measured with a Büchi Schmelzpunktbestimmungsapparat, and are uncorrected. Infrared spectra were obtained with a Perkin-Elmer Model 137 spectrometer, and ultraviolet spectra were recorded with a Perkin-Elmer Model 202 spectrometer or a Beckman DK-2A spectrophotometer. Nuclear magnetic resonance spectra were obtained with Varian Model T-60 or HA-100 spectrometers.

Thin layer chromatography (TLC) was done on silica gel coated microscope slides. The plates were sprayed for analysis with a phosphomolybdic acid solution. Analytical vapor phase chromatography was carried out with a Hewlett-Packard Model 5750 research chromatograph and preparative vapor phase chromatography was done on a Wilkins Aerograph, Model A-90-P. Combustion analyses were performed by the Microanalytical Laboratory, and mass spectra were obtained from the Mass Spectroscopy Laboratory, College of Chemistry, University of California, Berkeley.

Technical grade ether distilled from potassium hydroxide and technical grade pentane distilled from phosphorus pentoxide were used for recrystallizations and chromatography. Dry ether was prepared by refluxing reagent grade ether with sodium and benzophenone. Dry tetrahydrofuran was refluxed with and distilled from lithium aluminum hydride. Irradiation grade acetone was refluxed with and distilled from potassium permanganate. All other solvents used were reagent grade unless otherwise specified.

***anti*-Dimethyl Tricyclo[4.2.2.0^{2,5}]deca-3,7,9-triene-7,8-dicarboxylate (6).** A solution of 5 g (0.048 mol) of cyclooctatetraene and 6.1 g (0.050 mol) of dimethyl acetylenedicarboxylate in 20 ml of *n*-octane (bp 125°) was refluxed for 6 days under nitrogen. The reaction was followed by the loss of cyclooctatetraene resonance in the NMR spectrum of the reaction mixture. When cyclooctatetraene was almost gone, the reaction was cooled and solvent and unreacted starting material were removed by distillation at aspirator pressure. The residue was distilled at diffusion pump pressure (20 μ) through a short-path distillation apparatus to give 8.7 g of a mixture of adduct **6** and dimethyl phthalate. Careful integration of the NMR spectrum of the mixture showed it to be about seven parts **6** to one part dimethyl phthalate, which indicated a 7.65-g (65%) yield of adduct **6**: bp 80–100° (20 μ) [lit.[11] bp 140–150° (2.0 mm)]; NMR (CCl_4) δ 2.7 (2 H, m, cyclobutene bridgehead), 3.7 (6 H, s, over 2 H, m, esters and bridgeheads), 6.0–6.2 (4 H, m, vinylic); ir (CCl_4) 1740, 1650, and 1600 cm^{-1}. No attempt to obtain the adduct in pure form, free from dimethyl phthalate, was made.

***anti-endo-anti*-Dimethyl 4,5,6,7-Tetrachloro-15,15-dimethoxypentacyclo[8.2.2.1^{4,7}.0^{2,9}.0^{7,8}]pentadeca-5,11,13-triene-11,12-dicarboxylate (7).** A solution of 170 g (0.75 mol) of **6** and 210 g (0.80 mol) of 1,2,3,4-tetrachloro-5,5-dimethoxycyclopentadiene[29] in 400 ml of chloroform was refluxed under nitrogen with constant stirring for 10 days. The solvent was removed by rotary evaporation and the crude solid residue was washed several times with 50% ether–pentane, collected by filtration, and dried under reduced pressure. The combined washings were concentrated and the residue was dissolved in chloroform and refluxed for another 7 days. The total yield of adduct **7** was 290 g (76%): mp 182.5–185.5° (lit.[10] mp 186°); NMR ($CDCl_3$) δ 2.1 (2 H, m), 2.4 (2 H, m), 3.6 and 3.8 (6 H, s, OCH_3), 4.1 (2 H, m), 6.6 (2 H, t, J = 4 Hz, vinylic); ir ($CHCl_3$) 1725, 1640, 1620, and 1200 cm^{-1}; mass spectrum *m/e* 473 (M − Cl).

Anal. Calcd for $C_{21}H_{20}O_6Cl_4$ (510.27): C, 49.40; H, 3.90; Cl, 27.80. Found: C, 49.34; H, 3.80; Cl, 27.92.

***endo*-1,6,7,8-Tetrachloro-9,9-dimethoxytricyclo[4.2.1.0^{2,5}]-nona-3,7-diene (8).** Adduct **7**, 237 g (0.465 mol), was pyrolyzed by heating at 200° for 15 min. The resultant oil was chromatographed on 1500 g of silica gel, and elution with 30% ether–pentane gave 145 g (100%) of crude **8**. The crude solid was dissolved in 95% ethanol, decolorized with Norit, and recrystallized to give pure **8**: mp 83.5–84.5° (lit.[10] mp 80–81°); NMR (CCl_4) δ 3.4 (2 H, s, bridgehead), 3.60 and 3.65 (3 H, s, OCH_3), 6.1 (2 H, s, vinylic); ir (CCl_4) 1625 and 1170 cm^{-1}; mass spectrum *m/e* 314, 316, 318.

Anal. Calcd for $C_{11}H_{10}O_2Cl_4$ (316.04): C, 41.75; H, 3.16; Cl, 44.90. Found: C, 41.58; H, 3.08; Cl, 44.74.

1,6,7,8-Tetrachloro-9,9-dimethoxypentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]nonane (9). A solution of 20 (64 mol) of diene **8** in 2 l. of irradiation grade acetone was deaerated with nitrogen and irradiated with a GE-AH6 high-pressure 1000-W mercury vapor lamp. The irradiation was followed by TLC (10% ether–pentane) and was ceased after 18 hr. The solvent was rotary evaporated and the residue was chromatographed on 1500 g of silica gel, eluting with 5% ether–pentane. The product was recrystallized from pentane to yield 15 g (75%) of **9**: mp 143–145° (lit.[10] mp 123°); NMR (CCl_4) δ 3.4–3.8 (6 H, s, on 4 H, m); ir (CCl_4) 3000 and 1200 cm^{-1}; mass spectrum *m/e* 314 (M^+), 279 (M − Cl).

Anal. Calcd for $C_{11}H_{10}O_2Cl_4$ (316.04): C, 41.75; H, 3.16; Cl, 44.90. Found: C, 41.89; H, 3.17; Cl, 44.68.

9,9-Dimethylpentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]nonane (10). A solution of 4.0 g (0.013 mol) of ketal **9** and 8.3 g (0.112 mol) of dry *tert*-butyl alcohol in 70 ml of dry tetrahydrofuran was stirred vigorously under anhydrous conditions and 1.6 g (0.224 mol) of finely cut lithium wire was added. The spontaneous exothermic reaction which ensued was moderated by ice-bath cooling to maintain a gentle reflux. When the reaction subsided the mixture was refluxed for an additional 3 hr and cooled. The mixture was strained (to remove excess lithium) into 500 ml of crushed ice. The aqueous solution was extracted with ether and the ether extracts were dried ($MgSO_4$), filtered, and rotary evaporated to yield 2.1 g (91%) of a colorless oil shown to be almost pure dechlorinated ketal **10** by VPC (SE-30 column, 130°). Short-path distillation gave pure ketal **10**: bp 67–75° (2.0 mm); NMR (CCl_4) δ 3.0–3.55 (8 H, m, cage protons), 3.15 (6 H, s, ketal protons); ir (CCl_4) 2940, 1450, 1100, and 1050 cm^{-1}; mass spectrum *m/e* 178 (M^+), 177 (M − H), 163 (M − CH_3), 147 (M − OCH_3).

Anal. Calcd for $C_{11}H_{14}O_2$ (178.20): C, 74.20; H, 7.87. Found: C, 74.43; H, 7.95.

Pentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]nonan-9-one (Homocubanone, 5). A suspension of 0.46 g (2.58 mmol) of ketal **10** in 25 ml of 5% aqueous sulfuric acid was stirred vigorously at room temperature for 9 hr. A white, crystalline solid gradually formed in the aqueous solution. The solid was extracted with ether, and the ether extracts were washed with 5% aqueous sodium bicarbonate solution until neutral and dried ($MgSO_4$). Solvent was removed by distillation through a short glass helix packed column to yield 0.3 g (88%) of crude homocubanone (**5**). An analytical sample of ketone was obtained by recrystallization from pentane: mp 66–68°; NMR (CCl_4) δ 3.0 (2 H, m, α protons), 3.5 (6 H, m, cage protons); ir (CCl_4) 1760 and 1716 cm^{-1}; mass spectrum *m/e* 132 (M^+).

Anal. Calcd for C_9H_8O (132.17): C, 81.80; H, 6.06. Found: C, 81.5; H, 5.9. There was difficulty with the analysis because of the compound's volatility and its tendency to hydrate readily.

***exo*- and *endo*-Tetracyclo[4.2.0.0^{2,5}.0^{4,7}]octane-3-carboxylic Acids (11 and 12).** A 300-ml, three-necked flask was fitted with a reflux condenser, a rubber septum inlet, and a nitrogen inlet, and was flushed with nitrogen. A slurry of 32.8 g (0.292 mol) of potassium *tert*-butoxide in 180 ml of dry tetrahydrofuran was introduced, and the flask was cooled in an ice bath. The slurry was stirred magnetically and 1.57 ml (0.087 mol) of water was slowly added via syringe. Homocubanone (3.5 g, 0.026 mol) was added at once, and the mixture was stirred at room temperature for 1 hr and heated at 50° for 6 hr. The mixture was cooled and poured into crushed ice, and the residual salts were washed out with water. The aqueous solution was washed with ether until the washings were colorless, and the aqueous layer was acidified with concentrated hydrochloric acid and extracted with ether. The combined extracts were dried ($MgSO_4$), filtered, rotary evaporated to yield 3.86 g (97%) of a yellow, waxy solid. Sublimation (80°, 0.2 mm) afforded 3.398 g (85% isolated yield) of a mixture of endo and exo acids **11** and **12** which were not separated: NMR ($CDCl_3$) δ 2.3 and 2.45 (2 H, 2 broad s in ratio of 9:1, methylene protons), 3.0–3.7 (7 H, m, cage protons and α-acid proton of endo isomer), 3.6 (1 H, s, α-acid proton of exo isomer); ir ($CHCl_3$) 3600–2500, 1695, and 1265 cm^{-1}; mass spectrum *m/e* 150 (M^+), 105 (M − CO_2H);

Anal. Calcd for $C_9H_{10}O_2$ (150.18): C, 72.00; H, 6.67. Found: C, 71.77; H, 6.69.

***exo*- and *endo*-3-Acetyltetracyclo[4.2.0.0^{2,5}.0^{4,7}]octane (13 and 14).** A 1.24-g (8.27 mmol) sample of a mixture of endo and exo acids **11** and **12** was dissolved in 50 ml of benzene and an excess (10 g) of oxalyl chloride was added. The mixture was stirred at room temperature for 1 hr and the solvent and excess oxalyl chloride were removed by rotary evaporation to yield a crude acid chloride mixture: ir (CCl_4) 1780 and 1720 cm^{-1}.

A solution of the acid chloride in dry ether was added via syringe to a solution of lithium dimethylcuprate (24.8 mmol) in 150 ml of ether at −78°.[16] The mixture was stirred at −78° for 20 min and hydrolyzed at that temperature with methanol. The mixture was warmed to room temperature and poured into water, and the solution was suction filtered through Celite. The organic layer was separated, the aqueous layer was extracted with ether, and the combined organic layers were washed with saturated salt solution and dried ($MgSO_4$). The solvent was removed by distillation through a glass helix column to yield 1.17 g (95%) of a yellow oil shown by VPC (SE-30 column, 130°) to be a mixture of endo and exo ketones **13** and **14**. The mixture was separated by chromatography on silica gel (10% ether–pentane) to give pure exo ketone **14** and endo ketone **13**. Analytical samples were obtained by preparative VPC (SF-96 column, 135°). Exo isomer **14**: mp 40–42°; NMR (CCl_4) δ 2.1 (3 H, s, methyl), 2.45 (2 H, broad s, methylene), 3.3 (6 H, broad s, cage), 3.65 (1 H, s, α-keto proton); ir (CCl_4) 2940 and 1700 cm^{-1}; mass spectrum *m/e* 148 (M^+), 147 (M − H), 133 (M − CH_3), 105 (M − $COCH_3$).

Anal. Calcd for $C_{10}H_{12}O$ (148.21): C, 81.04; H, 8.16. Found: C, 81.26; H, 8.27.

Endo isomer **13**: mp 35–36°; NMR (CCl_4) δ 2.1 (3 H, s, methyl group), 1.8–2.5 (2 H, m, methylene protons), 2.6–3.8 (7 H, m, cage protons and α-keto proton); ir (CCl_4) 2940 and 1750 cm^{-1}; mass spectrum *m/e* 148 (M^+), 147 (M − H), 133 (M − CH_3), 105 (M − $COCH_3$).

Anal. Calcd for $C_{10}H_{12}O$ (148.21): C, 81.04; H, 8.16. Found: C, 80.73; H, 8.22.

Isomerization of Methyl Ketones 13 and 14. A 2.32-g (0.016 mol) sample of endo ketone **13** was dissolved in 200 ml of anhydrous methanol and a trace of sodium methoxide was added. The mixture was stirred at room temperature under nitrogen for 5 days and poured into 10% aqueous hydrochloric acid, and the solution was extracted with ether. The combined extracts were washed with dilute sodium bicarbonate and dried ($MgSO_4$), and the solvent was removed by distillation to yield 2.19 g (94%) of exo ketone **14**, identical with an authentic sample, as the only product.

***exo*-Tetracyclo[4.2.0.0^{2,5}.0^{4,7}]octan-3-ol Acetate (15).** To a stirred suspension of 1.9 g (12.8 mmol) of exo ketone **14**, 24 g (167 mmol) of anhydrous disodium phosphate, and 140 ml of methylene chloride was added, dropwise, a methylene chloride solution of trifluorooperacetic acid [prepared from 12.6 ml (85.7 mmol) of trifluoroacetic anhydride]. The mixture was stirred for 1 hr at room temperature and filtered, and the inorganic salts were washed with additional methylene chloride. The combined organic phase was washed with 10% sodium carbonate solution and dried ($MgSO_4$), and the solvent was removed by distillation through a glass helix column to yield 2.036 g (97%) of acetate **15**. An analytical sample was obtained by preparative VPC (SF-96 column, 135°): NMR (CCl_4) δ 2.0 (3 H, s, methyl), 2.3–2.8 (2 H, m, methylene), 3.0–3.6 (6 H, m, cage), 5.5 (1 H, broad s, α-ester proton); ir (CCl_4) 2920, 1730, and 1235 cm^{-1}; mass spectrum *m/e* 164 (M^+), 121 (M − $COCH_3$), 105 (M − OAc).

Anal. Calcd for $C_{10}H_{12}O_2$ (164.21): C, 73.14; H, 7.37. Found: C, 72.90; H, 7.19.

***exo*-Tetracyclo[4.2.0.0^{2,5}.0^{4,7}]octan-3-ol (16).** Acetate **15**, 2.03 g (12.3 mmol), was reduced with a fivefold excess of lithium aluminum hydride at 0° in dry ether. The solution was hydrolyzed with aqueous ammonium chloride solution and extracted with ether, and the solvent was rotary evaporated to give 1.41 g (94%) of crystalline alcohol **16**. Recrystallization from ether–pentane gave a pure sample of **16**: mp 102–103°; NMR (CCl_4) δ 1.3 (1 H, broad s, hydroxyl proton), 2.0–2.4 (1, H, m, methylene proton), 2.4–2.7 (1 H, m, methylene proton), 2.9–3.7 (6 H, m, cage protons), 4.85 (1 H, d, *J* = 2 Hz, α-hydroxyl proton); ir (CCl_4) 3600–3100 and 2950 cm^{-1}; mass spectrum *m/e* 122 (M^+), 121 (M − H);

Anal. Calcd for $C_8H_{10}O$ (122.17): C, 78.65; H, 8.25. Found: C, 78.38; H, 8.12.

***exo*-Tetracyclo[4.2.0.0^{2,5}.0^{4,7}]octan-3-ol Mesylate (17).** A 300-ml, three-necked flask was fitted with a nitrogen inlet and an addition funnel, and was flamed out under nitrogen flush. A solution of 658 mg (5.4 mmol) of alcohol **16** and 688 mg (6.0 mmol) of methanesulfonyl chloride in 60 ml of benzene was added and the flask was placed in an ice bath. The solution was stirred magnetically and 800 mg (8.0 mmol) of triethylamine was added, dropwise, over a period of 2 min. The reaction mixture was removed from the ice bath and stirred at room temperature for 30 min. The mixture was filtered, the salts were washed with additional benzene, and the combined organic solution was rotary evaporated to yield a crude, colorless oil which solidified on standing. The crude residue was dissolved in pentane and concentrated to afford pure crystalline mesylate **17**: 1.04 g (96%); mp 83.5–85°; NMR (CCl_4) δ 2.3–2.8 (2 H, m, methylene), 2.9 (3 H, s, methyl), 3.2–3.9 (6 H, m, cage), 5.55 (1 H, d, *J* = 2 Hz, α-OMs proton); ir (CCl_4) 2930, 1455, 1210, and 1175 cm^{-1}; mass spectrum *m/e* 105 (M − OMs).

Anal. Calcd for $C_9H_{12}O_3S$ (200.26): C, 53.97; H, 6.04; S, 16.01. Found: C, 53.73; H, 5.96; S, 15.78.

***exo*-Tetracyclo[4.2.0.0^{2,4}.0^{3,8}]octan-5-acetate (18) and Trifluoroacetate (19) via Baeyer–Villiger Reaction of Endo Ketone 13.** Following the procedure described for the exo ketone **14**, 0.78 g (5.25 mmol) of ketone **13** was oxidized, and after stirring for 1 hr at room temperature, the mixture was refluxed for 5 hr. The solvent was removed by distillation through a glass helix column to yield 0.98 g of yellow oil. VPC (SE-30 column, 120°) examination of the product mixture showed two equal-intensity peaks accounting for about 90% of the material and several components present in small quantities. Preparative VPC (SF-96 column, 130°) of the two major components of the mixture afforded pure samples of acetate **18** and trifluoroacetate **19**. Acetate **18**: NMR (CCl_4) δ 1.5–2.2 (6 H, m, cyclopropyl and methylene), 1.95 (3 H, s, methyl), 2.3–2.9 (2 H, m, bridgehead), 4.75 (1 H, m, α-ester); ir (CCl_4) 3020, 2930, 1725, and 1240 cm^{-1}; mass spectrum *m/e* 164 (M^+), 121 (M − $COCH_3$), 105 (M − OAc);

Anal. Calcd for $C_{10}H_{12}O_2$ (164.21): C, 73.14; H, 7.37. Found: C, 73.00; H, 7.29.

Trifluoroacetate **19**: NMR (CCl_4) δ 1.6–2.4 (6 H, m, cyclopropyl and methylene), 2.4–2.9 (2 H, m, bridgehead), 5.0 (1 H, m, α-ester); ir (CCl_4) 3020, 2930, 1780, and 1155 cm^{-1}; mass spectrum *m/e* 218 (M^+), 105 (M − CO_2CF_3).

Reduction of the Rearranged Acetate 18–Trifluoroacetate 19 Product Mixture from Ketone 13. Formation of Rearranged Alcohol 20. A 1.1-g (ca. 5.8 mmol) portion of crude product mixture from the Baeyer–Villiger reaction on endo ketone **13** was reduced with excess lithium aluminum hydride at 0° in ether. The crude mixture was hydrolyzed with aqueous ammonium chloride and extracted with ether. Solvent was removed by distillation through a glass helix column to yield 0.50 g (70% from the ketone) of crude alcohol **20**. Recrystallization, sublimation, and column chromatography failed to produce pure **20**. However, a pure sample was obtained by preparative VPC (SF-96 column, 120°): NMR δ 1.45 (1 H, s, OH), 1.4–1.8 (4 H, m, cyclopropyl), 1.8–2.1 (2 H, m, methylene), 2.3 and 2.6 (1 H, m, bridgeheads), 3.95 (1 H, m, α-hydroxyl proton); ir (CCl_4) 3600–3100, 3020, 2930, and 1060 cm^{-1}; mass spectrum *m/e* 122 (M^+), 121 (M − H), 105 (M − OH).

Oxidation of Rearranged Alcohol 20. Formation of Ketone 21. A 100-ml, three-necked flask was flamed out under nitrogen flush and a solution of 1.58 g (20 mmol) of dry pyridine was added. The solution was stirred magnetically and 1.0 g (10 mmol) of chromium trioxide (dried over phosphorus pentoxide) was added. The mixture was stirred for 15 min to form the chromium trioxide–bispyridine complex and 200 mg (1.64 mmol) of crude alcohol **20** was added. The mixture was stirred at room temperature for 1 hr and filtered, and the residual tar was washed with several portions of ether. The combined filtrates were washed with 5% sodium hydroxide solution until the washings were colorless, 5% hydrochloric acid, saturated sodium bicarbonate, and saturated sodium chloride solutions. The organic phase was dried ($MGSO_4$), and the solvent was removed by distillation through a glass helix column to yield 110 mg (55%) of a colorless oil. VPC (SE-30 column, 100°) examination of the product mixture showed 90% of one component, ketone **21**, which was purified by preparative VPC (SF-96 column, 120°): nmr (CCl_4) δ 1.4–2.0 (3 H, m, cyclopropyl), 2.1–2.5 (3 H, m, methylene and α-keto), 2.85 (2 H, m, bridgehead); uv max (CH_3OH) 202 nm (ε 2500); ir (CCl_4) 3020, 2930, and 1750 cm^{-1}; high-resolution mass spectrum *m/e* 120.0577 (C_8H_8O), 91.0545 (C_7H_7).

Preparative Acetolysis of *exo*-Tetracyclo[4.2.0.0^{2,5}.-0^{4,7}]octan-3-ol Mesylate (17). Mesylate **17** (972 mg, 4.86 mmol) and 480 mg (5.86 mmol) of anhydrous sodium acetate were dissolved in 100 ml of dry acetic acid. The solution was stirred and heated to 80° for 22 hr, cooled, and poured into 500 ml of water. The solution was extracted with pentane twice and with ether once, and the combined extracts were washed with saturated sodium bicarbonate until the extract was neutral. The extract was dried ($MgSO_4$), and the solvent was removed by distillation through a glass helix column to yield 812 mg (100%) of a clear oil. This oil was examined by VPC (SE-30 column, 120°) and was found to consist of 90% acetate **18**, identical with an authentic sample.

Determination of the Acetolysis Rate of Mesylate 17. Approximately 0.5 ml of a solution of 69.3 mg (0.346 mmol) of mesylate **17** and 30 mg (0.364 mmol) of anhydrous sodium acetate in 2 ml of dry acetic acid was placed in an NMR sample tube. Two drops of chloroform was added and the tube was sealed under nitrogen atmosphere. The tube was placed in a constant-temperature bath at 75.6° and the solvolysis was followed by NMR by measuring the decrease of the α-mesylate proton signal at δ 5.55 against the internal standard chloroform signal, using repeated integration technique (error 5%). The rate calculated by computer using a least-squares analysis was 1.2×10^{-4} sec^{-1}.

Similar rate determinations were made at 60.0 and 44.7° and gave rates of 2.61×10^{-5} and 2.95×10^{-6} sec^{-1}, respectively. Good first-order plots were obtained in all three cases. These data give $E_a = 30 \pm 3$ kcal/mol and $\Delta H = 27 \pm 3$ kcal/mol.

Acknowledgment. This work was supported by the National Science Foundation (Grant No. GP-8700). L.N.R. expresses appreciation to the National Science Foundation for a predoctoral fellowship.

Registry No.—**5**, 15291-18-6; **6**, 25157-95-3; **7**, 54020-24-5; **8**, 20379-80-0; **9**, 20792-01-2; **10**, 53993-24-1; **11**, 53993-25-2; **12**, 54053-43-9; **13**, 53993-26-3; **14**, 54053-44-0; **15**, 53993-27-4; **16**, 53993-28-5; **17**, 53993-29-5; **18**, 53993-30-9; **19**, 53993-31-0; **20**, 53993-32-1; **21**, 53993-33-2; cyclooctatetraene, 629-20-9; dimethyl acetylenedicarboxylate, 762-42-5; 1,2,3,4-tetrachloro-5,5-dimethoxycyclopentadiene, 2207-27-4; oxalyl chloride, 79-37-8; trifluoroperacetic acid, 359-48-8; methanesulfonyl chloride, 124-63-0.

References and Notes

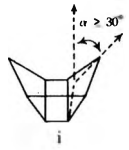
(1) For review articles in this field see (a) D. Seebach, *Angew. Chem., Int. Ed. Engl.*, **4**, 121 (1965); (b) L. N. Ferguson, *J. Chem. Educ.*, **46**, 404 (1969); (c) ibid., **47**, 46 (1970).

(2) (a) L. Cassar, P. E. Eaton, and J. Halpern, *J. Am. Chem. Soc.*, **92**, 3515 (1970); (b) W. G. Dauben and A. J. Kielbania, Jr., ibid., **93**, 7345 (1971).

(3) W. G. Dauben and D. L. Whalen, *J. Am. Chem. Soc.*, **93**, 7244 (1971).

(4) (a) P. v. R. Schleyer, J. J. Harper, G. C. Dunn, V. J. DiPasquo, and J. R. E. Hoover, *J. Am. Chem. Soc.*, **89**, 698 (1967); (b) J. C. Barborak and R. Pettit, *ibid.*, **89**, 3080 (1967).

(5) The pucker, α, in the secocubyl system is calculated from X-ray studies[6] on secocubyl derivatives to be greater than 30° (i).



i

(6) B. G. DeBoer and D. H. Templeton, personal communication.

(7) For an excellent review see W. L. Dilling, *Chem. Rev.*, **66**, 384 (1964).

(8) (a) W. G. Dauben and D. L. Whalen, *Tetrahedron Lett.*, 3743 (1966); (b) G. L. Dunn, V. J. DiPasquo, and J. R. E. Hoover, ibid., 3737 (1966); (c) R. L. Cargill and T. Y. King, ibid., 409 (1970).

(9) (a) C. G. Chin, H. Cuts, and S. Masamune, *Chem. Commun.*, 880 (1966); (b) W. G. Dauben, C. H. Schallhorn, and D. L. Whalen, *J. Am. Chem. Soc.*, **93**, 1446 (1971).

(10) C. M. Anderson, J. B. Bremner, I. W. McCoy, and R. N. Warrener, *Tetrahedron Lett.*, 1255 (1968).

(11) The established procedure for the preparation of **6** gave the reported yields of only 50%: (a) W. Reppe, O. Schlichting, K. Klager, and T. Toepel, *Justus Liebigs Ann. Chem.*, **560**, 1 (1948); (b) M. Avram, C. D. Nenitzescu, and E. Marica, *Chem. Ber.*, **90**, 1857 (1957); (c) E. E. Van Tamelen and B. C. T. Pappas, *J. Am. Chem. Soc.*, **93**, 6111 (1971). Recently an 82% yield preparation of **6** was reported.[12]

(12) A. G. Anderson, Jr., and D. R. Fagerburg, *Tetrahedron*, **29**, 2973 (1973).

(13) P. Bruck, D. Thompson, and S. Winstein, *Chem. Ind. (London)*, 405 (1960).

(14) P. G. Gassman, J. T. Lamb, and F. V. Zalar, *J. Am. Chem. Soc.*, **89**, 946 (1967).

(15) S. Winstein, P. Carter, F. A. L. Anet, and A. J. R. Bourn, *J. Am. Chem. Soc.*, **87**, 5247 (1965).

(16) G. H. Posner and C. E. Whitten, *Tetrahedron Lett.*, 4647 (1970).

(17) W. D. Emmons and G. B. Lucas, *J. Am. Chem. Soc.*, **77**, 2287 (1955).

(18) (a) J. F. King and T. Durst, *J. Am. Chem. Soc.*, **86**, 287 (1964); (b) W. E. Truce, R. W. Campbell, and J. R. Norell, ibid., **86**, 288 (1964).

(19) R. M. Coates and J. L. Kirkpatrick, *J. Am. Chem. Soc.*, **92**, 4883 (1970).

(20) W. G. Dauben and G. H. Berezin, *J. Am. Chem. Soc.*, **89**, 3449 (1967).

(21) G. Büchi and i. M. Goldman, *J. Am. Chem. Soc.*, **79**, 4741 (1957).

(22) R. N. McDonald and G. E. Davis, *J. Org. Chem.*, **34**, 1916 (1969).

(23) R. N. McDonald and C. E. Reineke, *J. Org. Chem.*, **32**, 1878 (1967).

(24) R. N. McDonald and G. E. Davis, *J. Am. Chem. Soc.*, **94**, 5078 (1972).

(25) H. C. Brown and G. Ham, *J. Am. Chem. Soc.*, **78**, 2735 (1956).

(26) K. B. Wiberg, B. A. Hess, Jr., and A. J. Ashe III in "Carbonium Ions", Vol. **3**, G. E. Olah and P. v. R. Schleyer, Ed., Interscience, New York, N.Y., 1968, Chapter 26.

(27) K. B. Wiberg, R. A. Fenoglio, V. Z. Williams, Jr., and R. W. Ubersax, *J. Am. Chem. Soc.*, **92**, 568 (1972).

(28) (a) P. D. Bartlett and M. Stiles, *J. Am. Chem. Soc.*, **77**, 2806 (1955); (b) P. D. Bartlett and T. T. Tidwell, ibid., **90**, 4421 (1968); (c) J. Slutsky, R. C. Bingham, P. v. R. Schleyer, W. C. Dickson, and H. C. Brown, ibid., **96**, 1969 (1974); (d) A. Streitwieser, "Solvolytic Displacement Reactions", McGraw-Hill, New York, N.Y., 1962, p 92.

(29) J. S. Newcomer and E. T. McBee, *J. Am. Chem. Soc.*, **71**, 946 (1949).

Rearrangements of 1,2,3,4-Tetrachloropentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]nonan-9-one[1]

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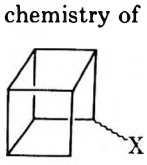
9,9-Dimethoxy-1,2,3,4-tetrachloropentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]nonane (**2**) was found to rearrange to cage-opened ketone **4** on treatment with concentrated sulfuric acid, but, with hydrogen bromide in acetic acid, ketal **2** was hydrolyzed to tetrachlorohomocubane (**3**). Treatment of **3** with aqueous base gave rise to the oxahomocubane acid **6**, while treatment with sodium hydroxide in benzene gave tetrachlorosecocubane acid (**8**). The conversion of **3** to **6** was shown to proceed through **8** via a sequence of intramolecular chlorine displacements by the isolation of intermediate lactone **10**. These results are discussed in relation to reactions of similar compounds which have been previously described in the literature.

As part of an investigation of the tetracyclo[4.2.0.0^{2,5}.0^{4,7}]octane (secocubane) ring system, various chlorinated cage compound intermediates have been studied in an attempt to devise an efficient synthetic route to secocuban-5-yl derivatives (**1**). The chemistry of polycyclic cage compounds is altered a great deal owing to the electron-withdrawing inductive effects and to the steric effects of multiple chlorine substitution,[3] and in the present study attention has been directed toward the role of these two effects upon the rearrangement pathways of the cage system.

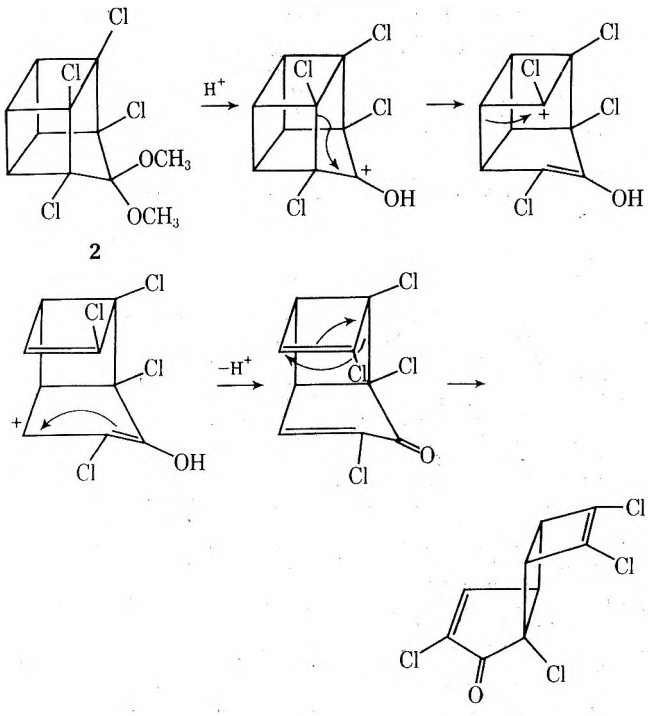


1

Tetrachlorohomocubanone ketal (**2**) was prepared in good yield by the method of Warrener and coworkers.[4] Attempts to hydrolyze ketal **2** with various concentrations of sulfuric acid (up to 75% acid at temperatures up to 80°) were unsuccessful, the ketal being recovered quantitatively. However, treatment of **2** with concentrated sulfuric acid at room temperature gave an unsaturated ketone **4**, which was isomeric with the expected cage ketone **3**, in 70% yield. The infrared absorption of the product at 1750, 1625, and 1590 cm^{-1} was compatible with an α-chloro conjugated carbonyl group and an additional chlorinated cyclobutene double bond.[5] The ultraviolet spectrum, λ_{max} 234 nm (ϵ 6700), also indicated a conjugated ketone. The NMR spectrum exhibited multiplets at δ 3.6 and 3.4 in a ratio of 2:1 in addition to a one-proton doublet at δ 7.7. Double irradiation of the signal at δ 3.6 caused the δ 7.7 doublet to collapse to a singlet.

The above data indicate cage-opening rearrangement of a hydrolysis intermediate with carbonium ion character at the carbonyl carbon to give the product, 3,4,6,8-tetrachlorotricyclo[4.3.0.0^{2,5}]nona-3,8-dien-7-one (**4**). One possible mechanism for the rearrangement to **4** is illustrated in Scheme I. The driving force behind the indicated 1,3-sigmatropic shift is not clear, but such a shift is necessary in

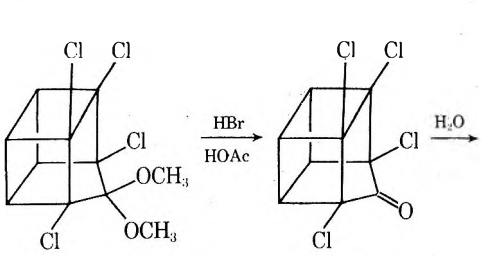
Scheme I

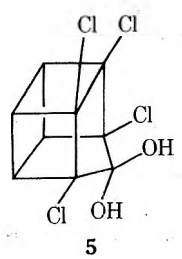


order to arrive at **4**, which has only one vinylic hydrogen. The exact nature of this rearrangement and the point at which the 1,3 shift occurs is an open point, and the sequence illustrated in Scheme I is purely arbitrary. In any event, generation of a very unstable carbonium ion at the carbonyl carbon and the great driving force due to strain release combine to bring about the observed rearrangement of **2** to **4**.

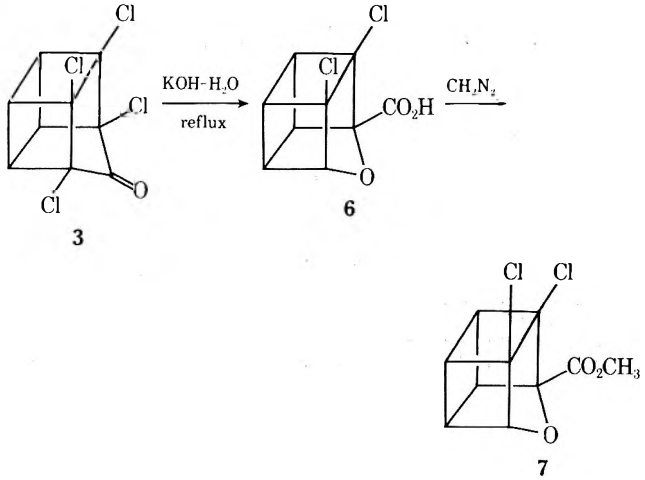
Acid-catalyzed hydrolysis of perchlorinated cage ketals generally requires quite vigorous conditions, usually concentrated or fuming sulfuric acid.[6] In such cases hydrolysis usually occurs without rearrangement and is due to the additional stability afforded to theex polycyclic systems by the presence of more than four chlorine substituents. Even though the perchlorinated cage ketals require more reactive conditions to initiate hydrolysis, they do not undergo the type of rearrangement pathway that is observed in the hydrolysis of **2**.

In an effort to hydrolyze ketal **2** without rearrangement, it was heated with 30% hydrogen bromide in acetic acid in a sealed tube. This procedure gave a quantitative yield of the desired ketone **3**, which hydrated rapidly to **5** on contact with the moisture in air. Pure **3** had a characteristic carbonyl absorption at 1800 cm^{-1}. This nucleophilic ketal cleavage reaction does not involve a carbonium ion intermediate and therefore rearrangement does not occur.[7]

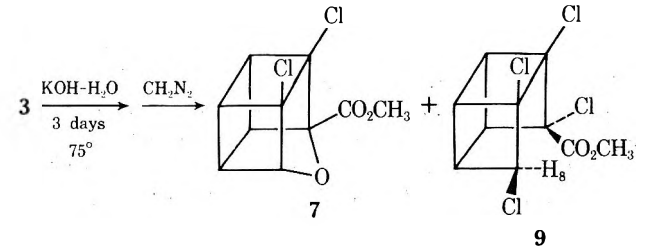




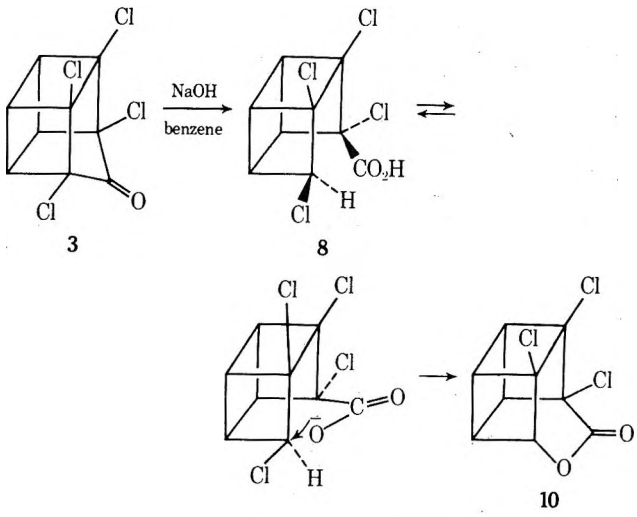
Treatment of ketone **3** or its hydrate **5** with an aqueous potassium hydroxide solution at reflux yielded oxahomocubanecarboxylic acid **6**, isolated as its methyl ester **7**. The structure of **7** was assigned on the basis of the following spectral evidence: NMR (CCl_4) δ 3.55 (m, 4 H), 3.9 (s, 3 H), 5.2 (m, 1 H); ir (CCl_4) 1760–1735 cm^{-1} (split carbonyl); mass spectrum *m/e* 231, 211. In addition, ester **7** gave correct elemental analysis for the molecular formula $C_{10}H_8O_3Cl_2$.



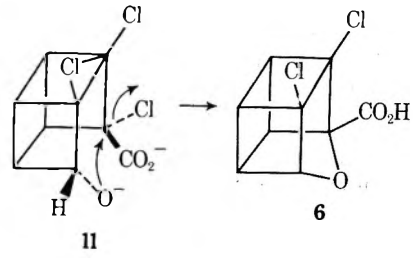
When **3** was treated with aqueous base at 75°, much longer reaction times were required for complete reaction. Esterification then gave an approximately equimolar mixture of **7** and the ester (**9**) of the desired cleavage product, tetrachlorosecocubanecarboxylic acid (**8**). Ester **9** had a single infrared carbonyl absorption at 1745 cm^{-1} and its NMR spectrum was similar to that of **7** with the exception of a sharp doublet (J = 2 Hz) at δ 4.5 for the endo α-chloro proton replacing the broad δ 5.2 multiplet for the exo α-oxy proton of **7**. The lack of complex splitting observed for the *endo*-secocubyl proton (H_8) of **9** is a rather general phenomenon which has been observed in other cage compounds.[8]



When ketone **3** was refluxed in benzene with solid, powdered sodium hydroxide, a quantitative yield of seco acid **8** was obtained. In an attempt to recrystallize **8**, the acid was dissolved in hot aqueous methanol; the solution upon concentration and cooling afforded a new compound, a crystalline solid which was not an acid. The new compound was assigned lactone structure **10** on the basis of its analysis for molecular formula $C_9H_5O_2Cl_3$, and the following spectral data: NMR ($CDCl_3$) δ 3.65 (m, 3 H), 4.1 (m, 1 H), 5.3 (doublet of doublets, J = 2 and 5 Hz, 1 H); ir ($CDCl_3$) 1780–1770 cm^{-1} (split carbonyl). Lactone **10** must be formed via intramolecular displacement of chlorine by carboxylate anion in the polar aqueous medium.

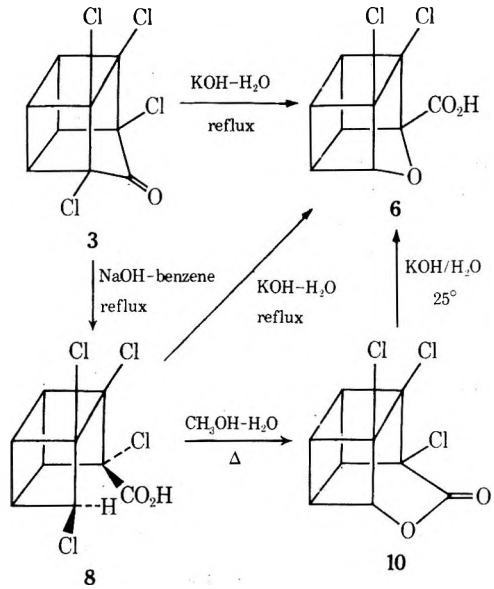


When lactone **10** was treated with aqueous potassium hydroxide at room temperature it was converted quantitatively to oxy acid **6**, indicating that the lactone is an intermediate in the conversion of ketone **3** to **6**. Thus, the saponification of the lactone must give ring-opened dianion **11**, which undergoes intramolecular chlorine displacement to yield the cyclic ether acid **6**.

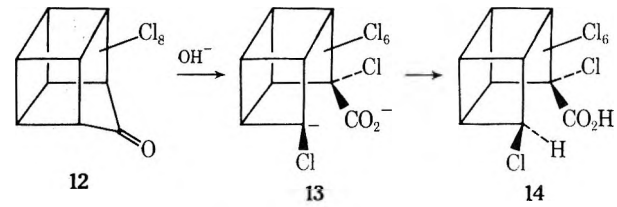


As a final proof that seco acid **8** is an intermediate in the conversion of **3** to **6**, it was also subjected to further treatment with aqueous potassium hydroxide solutions. At room temperature no reaction occurred, but at reflux **8** was rapidly and quantitatively converted to **6**. This result points out the necessity for a greater driving force and higher temperature in order to bring about the first intramolecular displacement to lactone **10**, and completes the cycle of intermediates capable of being converted into the end rearrangement product, oxy acid **6**. These results are summarized pn Scheme II.

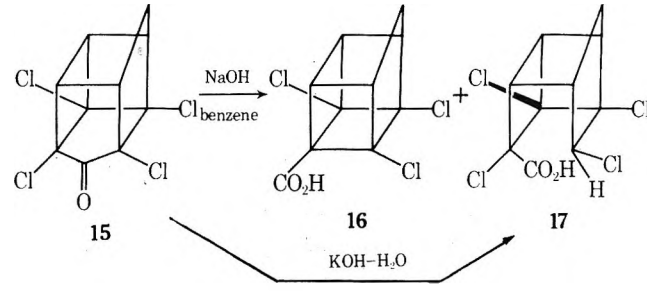
Scheme II



The reaction pathways for ketone **3** illustrated in Scheme II have been observed previously in related systems. Perchlorohomocubanone (**12**) was reported to give, stereospecifically, secocubane acid **14** in high yield when treated with either aqueous potassium hydroxide or sodium hydroxide in toluene.[9] Apparently the presence of four additional chlorine substituents stabilizes carbanion intermediate **13** sufficiently to prevent the further reactions observed in the tetrachloro compound.



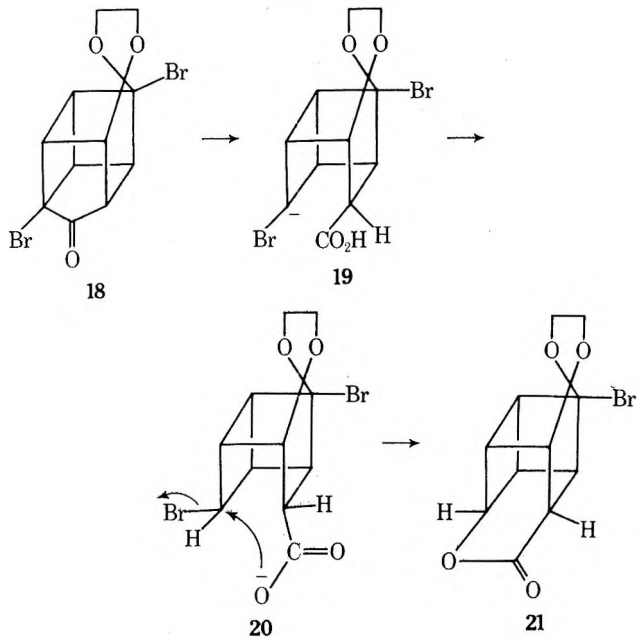
In a related study, tetrachloro ketone **15**, when heated with sodium hydroxide in benzene, was found to give a mixture of the ring-contracted product **16** and the ring-cleaved product **17** in a ratio of 3:2. However, on treatment with potassium hydroxide in either water or benzene, ketone **15** gave exclusively cleavage to **17** in near-quantitative yield.[10] While these results are less readily rationalized with the results of the present study, it is apparent that changes in steric and strain factors due to the extra one-carbon bridge in **15** must play a major role in determining what reaction pathways are open to the molecule.



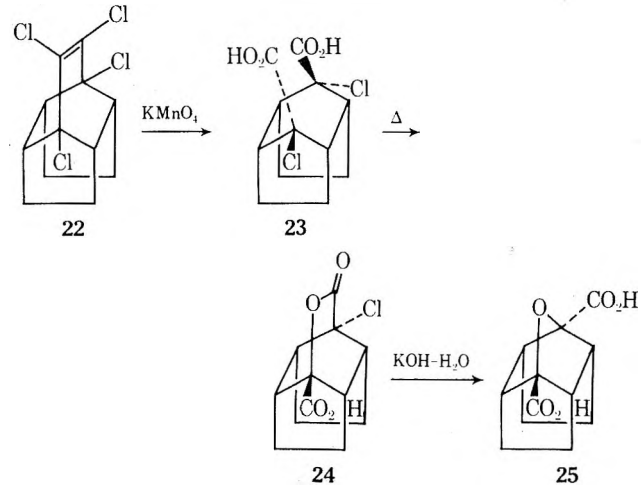
The formation of ring-cleaved products instead of the normal Favorskii-type contraction in these reactions can be attributed to a combination of factors due to ring strain and to the added stability of the chlorocarbanion intermediates. However, the less common intramolecular displacements occurring in the present study are most likely the result of severe steric interaction between the crowded endo substituents in the ring-opened intermediates. In both the formation of lactone **10** and its conversion to acid **6** the steric strain is relieved by closure of such an intermediate to the cyclic product.

The formation of lactone **10** is not without precedent; a similar intramolecular displacement to form lactone **20** has been observed in the attempted ring contraction of bromo ketone **18** in DMSO.[11] The absence of multiple halogen substituents to stabilize carbanion intermediate **19** inhibit the formation ringe cleavage products and permit the sequence of intramolecular proton transfer and subsequent bromine displacement to predominate (Scheme III). Also, the intramolecular displacement of halogen by alkoxide anion has been observed in the sequence outline in Scheme IV,[12] a result illustrating the generality of endo-endo-substituted cages undergoing intramolecular ring closure via chlorine displacement.

Scheme III



Scheme IV



Experimental Section

3,4,6,8-Tetrachlorotricyclo[4.3.0.0^{2,5}]nona-3,8-dien-7-one (4). A 125-mg (0.4 mmol) sample of ketal **2** was suspended in 5 ml of concentrated sulfuric acid and stirred at room temperature. The ketal gradually dissolved as the solution darkened in color. After 6 hr, the dark brown solution was poured into 60 ml of crushed ice and the precipitated yellow solid collected by filtration. The aqueous layer was extracted with ether and the combined ether layers were dried ($MgSO_4$). Rotary evaporation of the solvent afforded additional solid product. The combined crude product was chromatographed on 10 g of silica gel, eluted with 50% ether–pentane, and recrystallized from pentane to yield 70 mg (70%) of ketone **4**: mp 143–145°; NMR ($CDCl_3$) δ 3.4 (1 H, m) and 3.6 (2 H, m, bridgeheads), 7.7 (1 H, d, J = 3.5 Hz, vinylic) (irradiation of the δ 3.6 signal caused the vinylic signal at δ 7.7 to collapse to a singlet, and irradiation of the δ 7.7 signal greatly simplified the multiplet at δ 3.6); uv max (EtOH) 234 nm (ϵ 6700); ir ($CHCl_3$) 1750, 1625, and 1590 cm^{-1}; mass spectrum m/e 268 (M^+), 233 (M − Cl).

Anal. Calcd for $C_9H_4OCl_4$ (269.94): C, 40.04; H, 1.48; Cl, 52.60. Found: C, 40.13; H, 1.53; Cl, 52.38.

1,6,7,8-Tetrachloropentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]nonan-9-one (3). A 12.15-g (0.0385 mol) sample of ketal **2** was placed in a thick-walled Pyrex tube and 90 ml of 30% hydrogen bromide in acetic acid was added. The tube was sealed under nitrogen atmosphere and heated at 110° in a tube furnace for 10 days. The solvent was evaporated, carefully avoiding water, and the crude brown residue was chromatographed on 500 g of silica gel. Elution with 50% ether–pentane and recrystallization from hexane–methylene chloride yielded 10.0 g (96%) of **3** which hydrates readily on exposure to air: mp 175–178° (water loss at 100°); NMR (as hydrate **5**) ($CDCl_3$) δ 3.1 (2 H, broad, OH), 3.8 (4 H, s, cage protons); ir ($CHCl_3$) 1800 and 1150 cm^{-1} (after exposure to air a 360–3300-cm^{-1} absorption appears and the 1800-cm^{-1} peak is diminished); mass spectrum m/e 268 (M^+), 233 (M − Cl).

9-Oxa-2,3-dichloropentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]nonane-1-carboxylic Acid (6). Treatment of ketone **3** or its hydrate **5** with various concentrations of aqueous potassium hydroxide at reflux afforded acid **6**, while at lower temperatures mixtures of acids **8** and **6** were obtained. Longer reaction times were required when lower base concentrations were employed. The procedures in all cases were similar and are illustrated by the following example.

A mixture of 0.52 g (2.0 mmol) of ketone **2** in 50 ml of 30% aqueous potassium hydroxide was refluxed under nitrogen for 6 hr. The solution was allowed to cool, poured into crushed ice, and acidified with concentrated hydrochloric acid, and the resultant precipitate was extracted with ether. The combined ether layers were washed with saturated salt solution, dried ($MgSO_4$), and rotary evaporated to yield 0.42 g (92%) of crude acid **6**. A pure sample of acid 6 was obtained by recrystallization from ether–pentane: mp 201.5–202.5°; NMR (acetone-d_6) δ 3.6 (4 H, m, cage protons), 5.35 (1 H, m, α-ether); ir (KBr) 3400–2500 and 1710 cm^{-1}; mass spectrum m/e 232 (M^+), 234 (M + 2), 197 (M − Cl), 199 (M + 2 − Cl).

Anal. Calcd for $C_9H_6O_3Cl_2$ (233.06): C, 46.30; H, 2.57; Cl, 30.45. Found: C, 46.18; H, 2.56; Cl, 30.62.

A portion of the acid was esterified with ethereal diazomethane and the crude ester was recrystallized from pentane, giving an analytical sample of methyl ester **7**: mp 86–88°; NMR (CCl_4) δ 3.3–3.7 (4 Hm m, cage protons), 3.9 (3 H, s, ester), 5.1–5.3 (1 H, m, α-ether proton); ir (CCl_4) 1760–1735 cm^{-1} (split carbonyl); mass spectrum m/e 231 (M − CH_3), 211 (M − Cl).

Anal. Calcd for $C_9H_6O_2Cl_4$ (287.99): C, 37.55; H, 2.10; Cl, 49.20. Found: C, 37.74; H, 2.13; Cl, 48.98.

1,2,3-*exo*-8-Tetrachlorotetracyclo[4.2.0.0^{2,5}.0^{4,7}]octane-*endo*-3-carboxylic Acid (8). Powdered sodium hydroxide (5.0 g, 0.125 mol) was added to a solution of 5.2 g (0.02 mol) of ketone **2** in 600 ml of benzene. The suspension was stirred magnetically and heated to reflux under nitrogen. After 21 hr, the mixture was cooled and extracted with water. The aqueous solution was acidified with concentrated hydrochloric acid and extracted several times with ether. The combined ether layers were washed with saturated salt solution, dried ($MgSO_4$), and rotary evaporated to give 4.8 g (92%) of crude acid **8**. Pure acid 8 was obtained by recrystallization from pentane: mp 216–220°; NMR (DMSO-d_6) δ 3.4–4.1 (4 H, m, cage protons), 4.8 (1 H, d, J = 2 Hz, α-chloro); ir ($CHCl_3$) 3500–2500 and 1720 cm^{-1}; mass spectrum m/e 241 (M − CO_2H), 215 (M − Cl − CO_2H), 217 (M + 2 − Cl − CO_2H).

Anal. Calcd for C_9H infn$6O_2Cl_4$ (287.99): C, 37.55; H, 2.10; Cl, 49.20. Found: C, 37.74; H, 2.13; Cl, 48.98.

A portion of acid 8 was esterified with ethereal diazomethane to give ester **9**. The ester was purified by recrystallization from pentane: mp 127–128°; NMR (CCl_4) δ 3.3–4.0 (4 H, m, cage protons), 3.95 (3 H, s, ester), 4.5 (1 H, d, J = 2 Hz, α-chloro proton); ir (CCl_4) 1745 cm^{-1}; mass spectrum m/e 264 (M − Cl).

Anal. Calcd for $C_{10}H_8O_2Cl_4$ (302.02): C, 39.75; H, 2.65; Cl, 47.00. Found: C, 40.04; H, 2.75; Cl, 46.74.

9-Oxa-1,2,3-trichloropentacyclo[4.4.0.0^{2,5}.0^{3,8}.0^{4,7}]decan-10-one (10). A solution of 1.0 g (3.5 mmol) of acid **8** in 150 ml of 10% aqueous methanol was refluxed for 24 hr and cooled, and the white precipitate was collected. The mother liquor was concentrated and a second crop was collected to yield a total of 8.7 g (100%) of lactone **10**. The product was recrystallized from ether–pentane to afford an analytical sample: mp 168–171°; NMR ($CDCl_3$) δ 3.5–4.0 (3 H, m) and 4.0–4.3 (1 H, m, cage protons), 5.3 (1 H, doublet of doublets, J = 2 and 5 Hz, α-oxy proton); ir ($CHCl_3$) 1780 and 1770 cm^{-1} (split carbonyl); mass spectrum m/e 215 (M − Cl), 217 (M + 2 − Cl), 219 (M + 4 − Cl).

Anal. Calcd for $C_9H_5O_2Cl_3$ (251.56): C, 42.90; H, 1.99; Cl, 42.30. Found: C, 43.02; H, 2.13; Cl, 42.09.

Conversion of Lactone 10 to Acid 6. A. At Reflux. A mixture of 62 mg (2.46 mmol) of lactone **10** in 20 ml of 20% aqueous potassium hydroxide was refluxed for 5 hr. The mixture was cooled, poured into crushed ice, and acidified with concentrated hydrochloric acid. The precipitate was extracted into ether, and the ether solution was washed with saturated salt solution and dried ($MgSO_4$). The solution was rotary evaporated to give crude **6**, which on esterification with ethereal diazomethane yielded 58 mg (95%) of methyl ester 7 identical with an authentic sample.

B. At Room Temperature. Lactone **10** (97.5 mg, 3.88 mmol) was suspended in 40 ml of 20% aqueous potassium hydroxide and stirred. The solid gradually dissolved, and after 5 days the clear, colorless solution was acidified, worked up as in A, and esterified to yield 80 mg of methyl esters. VPC examination (XF-1150 column, 200°) showed ester **7** and an unidentified by-product in a ratio of 5:1.

Acid 6 from Acid 8. A 66-mg (2.29 mmol) sample of acid **8** was stirred in 25 ml of 20% aqueous potassium hydroxide under nitrogen for several days. An aliquot worked up as described below yielded only unreacted starting material. The mixture was then refluxed for 5 hr and allowed to cool. The solution was poured into crushed ice and acidified with concentrated hydrochloric acid, and the resulting precipitate was extracted with three portions of ether. The ether extracts were washed with saturated salt solution, dried ($MgSO_4$), and rotary evaporated to yield 50 mg (88%) of acid **6**. The formation of acid **6** was confirmed by esterification of the acid with ethereal diazomethane, which gave methyl ester **7** identical with an authentic sample.

Registry No.—**2**, 20792-01-2; **3**, 54119-85-6; **4**, 54119-86-7; **5**, 54119-87-8; **6**, 54119-88-9; **7**, 54119-89-0; **8**, 54119-90-3; **9**, 54119-91-4; **10**, 54119-92-5.

References and Notes

(1) This work was supported by National Science Foundation Grant GP-8700.
(2) National Science Foundation Predoctoral Fellow, 1970–1973.
(3) (a) E. T. McBee, C. W. Roberts, J. D. Idol, Jr., and R. H. Earle, Jr., *J. Am. Chem. Soc.*, **78**, 1511 (1956); (b) P. E. Eaton, E. Carlson, P. Lombardo, and P. E. Yates, *J. Org. Chem.*, **25**, 1225 (1960); (c) K. V. Scherer, Jr., G. A. Ungefug, and R. S. Lunt, *J. Am. Chem. Soc.*, **88**, 2859 (1966).
(4) (a) C. M. Anderson, J. B. Bremner, I. W. McCay, and R. N. Warrener, *Tetrahedron Lett.*, 1255 (1968); (b) W. G. Dauben and L. N. Reitman, *J. Org. Chem.*, **40**, 835 (1975).
(5) J. D. Park, J. R. Lacher, and J. R. Dick, *J. Org. Chem.*, **31**, 1116 (1966).
(6) (a) P. E. Hoch, *Joc. Org. Chem.*, **26**, 2066 (1961); (b) G. W. Griffin and A. K. Price, ibid., **29**, 3192 (1964); (c) R. J. Stedman, L. S. Miller, and J. R. E. Hoover, *Tetrahedron Lett.*, 2721 (1966); (d) R. J. Stedman and L. S. Miller, *J. Org. Chem.*, **32**, 35 (1967); (e) J. W. Wilt and E. Vasiliauskas, ibid., **37**, 1467 (1972).
(7) G. A. Ungefug, Ph.D. Thesis, University of California, Berkeley, 1968.
(8) F. A. L. Anet, A. J. R. Bourn, P. Carter, and S. Winstein, *J. Am. Chem. Soc.*, **87**, 5249 (1965).
(9) K. V. Scherer, Jr., R. S. Lunt, and G. A. Ungefug, *Tetrahedron Lett.*, 1199 (1965).
(10) G. L. Dunn, V. J. DiPasquo, and J. R. E. Hoover, *J. Org. Chem.*, **33**, 1454 (1968).
(11) N. B. Chapman, J. M. Key, and K. J. Toyne, *J. Org. Chem.*, **35**, 3860 (1970).
(12) I. A. Akhtar, G. I. Fray, and J. M. Yarrow, *J. Chem. Soc. C*, 812 (1968).

Synthesis of Some 4-Substituted Pentacyclo[4.3.0.0^{2,4}.0^{3,8}.0^{5,7}]nonane Derivatives and Their Reactions. Cyclopropane Ring Expansion and Cleavage

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The direct photolysis of 8-cyanodeltacyclene (**1**) gave 4-cyanopentacyclo[4.3.0.0^{2,4}.0^{3,8}.0^{5,7}]nonane (**2**) in a high yield. **2** was converted to the corresponding carboxylic acid **4**, carbinol **6**, and amine **10**. Buffered hydrolysis of **6** *p*-nitrobenzoate (**7**) and 3,5-dinitrobenzoate (**8**) afforded exclusively pentacyclo[5.3.0.0^{3,6}.0^{2,10}.0^{5,9}]decan-3-ol (**9**), a cyclopropylcarbinyl–cyclobutyl rearrangement product. Deamination of **10** in C_6H_6–AcOH gave unrearranged acetate **12** and rearranged acetate **13** in 7:13 ratio. Acid **4** was converted to isocyanate **18**, which gave the corresponding urea and urethane derivatives **19–22** on treatment with water, aniline, ethanol, and phenol, respectively. On refluxing with KOH in ethylene glycol, **19–22** afforded a ~1:9 mixture of *exo*-and *endo*-tetracyclo[4.3.0.0^{2,9}.0^{4,8}]nonan-3-ol (**23x** and **23e**) accompanied with a trace amount of ketone **24**. The formation of the alcohols was explained by base-catalyzed cyclopropylamine rearrangement, followed by the Meerwein–Ponndorf–Verley reduction.

The chemistry of small-ring compounds combined with cage structure has in recent years received a great deal of attention.[1] We were intrigued by the possibility of obtaining novel ring system by skeletal rearrangement of these systems. In this paper we wish to describe cyclopropylcarbinyl cation and cyclopropylamine anion rearrangements by using appropriately 4-substituted pentacyclo[4.3.0.0^{2,4}.0^{3,8}.0^{5,7}]nonane derivatives.

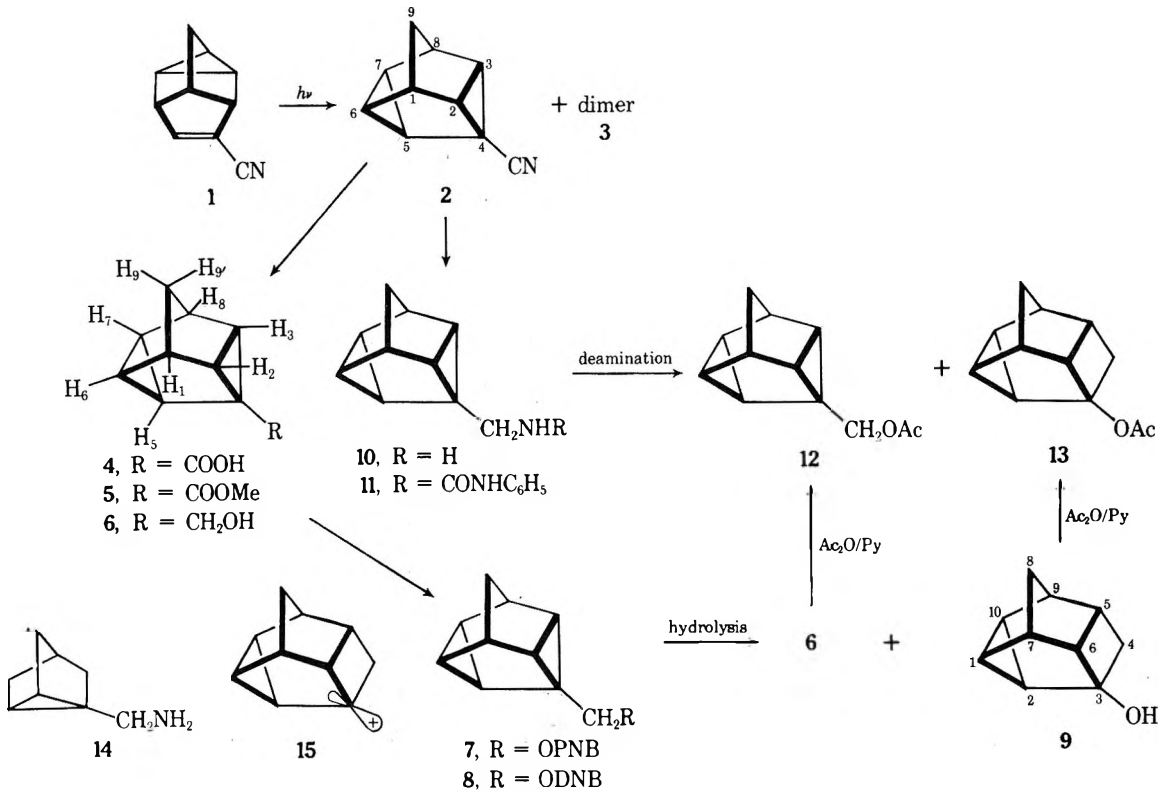
Results and Discussion

Photolysis of 8-cyanodeltacyclene (**1**)[2] in ether afforded a photoisomer **2** in 88% yield and a trace amount of dimer **3**[3] (Scheme I). **2** was identified as 4-cyanopentacyclo[4.3.0.0^{2,4}.0^{3,8}.0^{5,7}]nonane, an intramolecular $_{2\pi_s} + _{2\sigma_s}$ adduct, by spectral characteristics and the photochemical analogy.[4] Mass spectral molecular ion peak at *m/e* 143 and analysis indicated a formula $C_{10}H_9N$ for **2**. In the NMR ($CDCl_3$, 60 MHz) spectrum, **2** had characteristic signals as summarized in Table I. The lowest 4 H multiplet at δ 2.72 was assigned to H_1, H_8, H_2, and H_3 by comparison of the chemical shifts reported for 4,5-bismethoxycarbonyl[4a,d] and 4,5-dicarboxylic acid analogs[4a,b] as well as the parent pentacyclic compound.[4b] The broad triplet at δ 2.36 was assigned to H_5 because of its 1 H peak area and its signal pattern.[5] The complex multiplet at δ 2.17 and broad singlet at δ 1.88 were assigned to H_6 and H_7, and H_9 and $H_{9'}$, respectively. **3** had a molecular ion peak at *m/e* 286 ($C_{20}H_{18}N_2$) and ir (KBr) absorptions at 2250 (CN) and 814 and 790 cm^{-1} (nortricylene),[6] and hence **3** was characterized as an intermolecular $_{2\pi} + _{2\pi}$ photodimer.

On alkaline hydrolysis **2** afforded the corresponding carboxylic acid **4** in 90% yield. Esterification of **4** with diazomethane gave **5** quantitatively, which was reduced to carbinol **6** with lithium aluminum hydride (89%). The *p*-nitrobenzoate **7** and 3,5-dinitrobenzoate **8** were obtained in high yields by the usual method.[7] Lithium aluminum hydride reduction of **2** afforded the corresponding amine **10** (82%), which was characterized as its phenylurea derivative **11** (Scheme I). The structures of these derivatives were confirmed by the spectral and analytical data (Table I).[8]

On hydrolysis in 70% (v/v) aqueous dioxane in the presence of an excess amount of 2,6-lutidine at 170° for 24 hr, **7** afforded an alcoholic product **9** (40%, 77% based on **7** consumed), **6** (trace), and unreacted **7** (48%) after work-up on a

Scheme I



silica gel column. Similar hydrolysis of 8 at 140° for 40 hr gave 65% of **9** (83% based on 8 consumed), a trace amount of **6**, and 28% of unreacted 8. Compound **9**, mp 122–124°, had a formula $C_{10}H_{12}O$ on the basis of analysis and a mass spectral molecular ion peak at *m/e* 148. In the NMR spectrum, all protons appeared as a complex multiplet at δ 2.8–1.3, in which the signal at δ 2.30 (ca. 1 H) was assignable to OH by its disappearance on shaking with D_2O, and the absence of the signal due to $-CH_2O-$ suggested a ring-expanded structure for **9.** The spectrum was well dissolved on addition of a shift reagent, tris(dipivalomethanato)europium(III) [Eu(dpm)$_3$]. The shift gradient G[9] was calculated by the spectral change with various amounts of Eu(dpm)$_3$ and each signal was assigned with the aid of spin–spin decoupling experiments as shown in Figure 1. The two-proton multiplet at δ 8.82–8.2 was assigned to H_2 and H_6 because of their largest G values (17.3 and 15.0). The double doublet at δ 7.98 was assigned to H_{4x} because it had a large G value (15.7) and was decoupled to a doublet (J = 7.4 Hz), and to a doublet (J = 9.3 Hz) on irradiations of the doublet at δ 6.28 and of the signal at δ 3.6, respectively. On irradiation of the signal at δ 7.98, the doublet at δ 6.28 due to H_{4n} collapsed to a singlet, indicating that $J_{4n,4x}$ is 9.3 Hz.[10] The signal at δ 3.6 assigned to H_5 was overlapped on the AB quartet due to H_{8a} and H_{8s}, but the decoupling experiments indicated $J_{4x,5}$ to be 7.4 Hz. The dihedral angle for $H_{4n,5}$ on a Dreiding stereomodel is nearly 90°, which is in accord with $J_{4n,5}$ = 0 as observed. The other signals were also assigned as in Figure 1 by considering G values and signal pattern. Hence, **9** was identified as pentacyclo[5.3.0.0^{3,6}.0^{2,11}.0^{5,9}]decan-3-ol [or (trivial) 2,5,7,9-tetradehydroprotoadamantan-3-ol], a cyclopropylcarbinyl–cyclobutyl rearrangement product. The G values were correlated with the measured distance r between the oxygen and the hydrogen on a Dreiding stereomodel by the so-called $1/r^2$ method.[9,11] A good correlation was obtained as shown in Figure 2, supporting the above assignment.

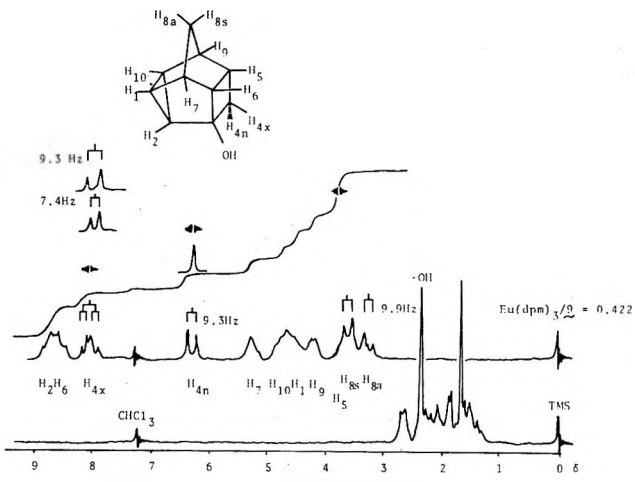


Figure 1. NMR spectra of **9** in $CDCl_3$ (60 MHz).

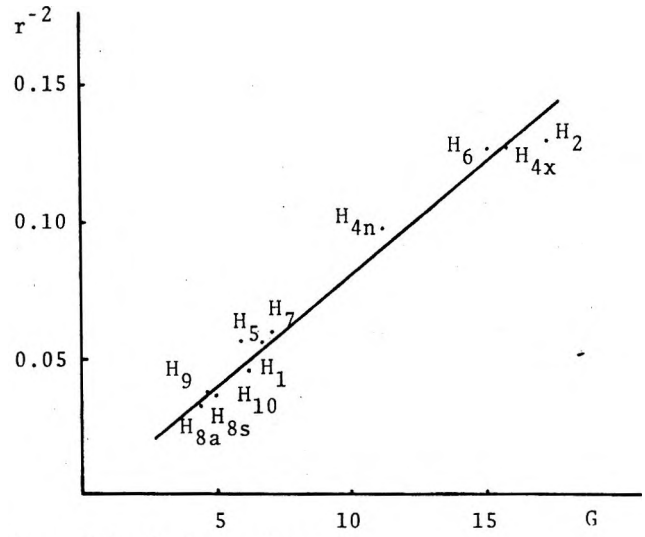


Figure 2. Graph of r^{-2} against G.

Table I
Spectral and Analytical Data of 4-Substituted Pentacyclo[4.3.0.0^{2,4}.0^{3,8}.0^{5,7}]nonane Derivatives

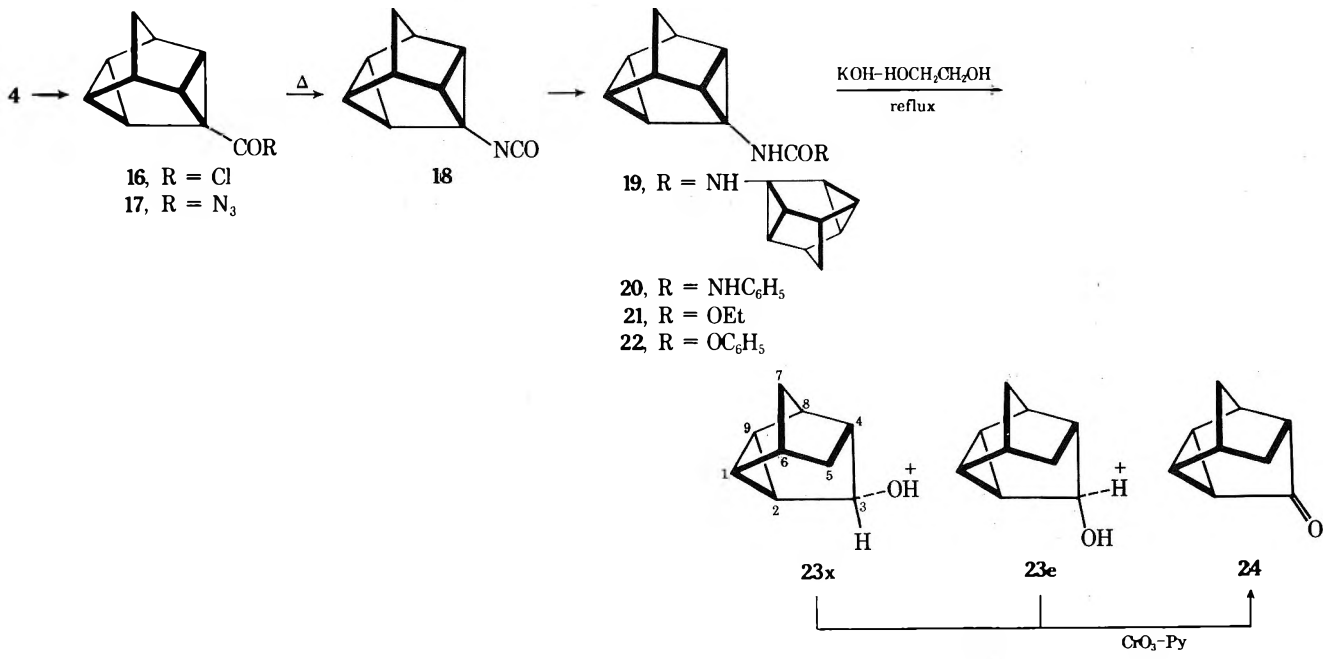
Compd[h]	Ir, cm^{-1} (KBr)	NMR chemical shift, δ (CDCl$_3$, 60 MHz)[b]	Formula[c]
2	2250, 1300, 775, 740[a]	2.72 (m, 4 H, $H_{1,8,2,3}$), 2.36 (bt, J = 6.0 Hz, 1 H, H_5), 2.17 (cm, 2 H, $H_{6,7}$), 1.88 (bs, 2 H, $H_{9,9'}$)	$C_{10}H_9N$
4	2660–2400, 1670, 1300, 790, 770, 755	10.48 (s, 1 H, COOH),[d] 2.75 (m, 4 H, $H_{1,8,2,3}$), 2.50 (bt, J = 6.0 Hz, 1 H, H_5), 2.10 (cm, 2 H, $H_{6,7}$), 1.86 (bs, 2 H, $H_{9,9'}$)	$C_{10}H_{10}O_2$
5	1720, 1300, 1275, 1210, 786, 760	3.58 (s, 3 H, OMe), 2.53 (m, 4 H, $H_{1,8,2,3}$), 2.50 (bt, J = 6.0 Hz, 1 H, H_5), 2.08 (cm, 2 H, $H_{6,7}$), 1.86 (bs, 2 H, $H_{9,9'}$)	$C_{11}H_{12}O_2$
6	3360, 1300, 765, 745[a]	3.58 (d, J = 3.6 Hz, 2 H, CH_2O),[f] 3.12 (t, J = 3.6 Hz, 1 H, OH),[d] 2.55 (bs, 2 H, $H_{1,8}$), 2.25–1.60 (cm, 5 H, $H_{2,3,5,6,7}$), 1.82 (m, ~2 H, $H_{9,9'}$)[e]	$C_{10}H_{12}O$
7	1705, 1520, 1345, 1300, 1275, 1103, 780, 755	8.25 (s, 4 H, C_6H_4), 4.50 (s, 2 H, CH_2O), 2.65 (bs, 2 H, $H_{1,8}$), 2.11 (cm, 5 H, $H_{2,3,5,6,7}$), 1.86 (bs, 2 H, $H_{9,9'}$)	$C_{17}H_{15}NO_4$
8	1715, 1615, 1530, 1340, 1279, 1158, 717	8.87 (s, 3 H, C_6H_3), 4.45 (s, 2 H, CH_2O), 2.57 (bs, 2 H, $H_{1,8}$), 2.3–1.45 (cm, 7 H, $H_{2,3,5,6,7,9,9'}$)	$C_{17}H_{14}N_2O_6$
10	3360, 3280, 1620, 1300, 765, 745	2.85 (s, 2 H, CH_2N), 2.60 (bs, 2 H, $H_{1,8}$), 2.02 (bs, 2 H, $H_{2,3}$), 1.90 (cm, 5 H, $H_{5,6,7,9,9'}$), 1.84 (2, 2 H, NH_2)[d]	$C_{10}H_{13}N$
11	3360, 3280, 1640, 1600, 1300, 765	7.28 (m, 5 H, C_6H_5), 7.03 (t, J = 4.5 Hz, 1 H, CH_2NHCO),[d] 5.32 (bs, 1 H, $CONHC_6H_5$),[d] 3.45 (d, J = 4.5 Hz, 2 H, CH_2NH),[f] 2.59 (m, 2 H, $H_{1,8}$), 1.99 (cm, 5 H, $H_{2,3,5,6,7}$), 1.82 (bs, 2 H, $H_{9,9'}$)	$C_{17}H_{18}N_2O$
12	1735, 1372, 1300, 1240, 1025, 770[a]	4.13 (s, 2 H, CH_2O), 2.58 (bs, 2 H, $H_{1,8}$), 2.05 (bs, 8 H, O=CMe, $H_{2,3,5,6,7}$), 1.82 (bs, 2 H, $H_{9,9'}$)	$C_{12}H_{14}O_2$
17	2140, 1690, 1370, 1248, 1190, 734[a]	2.75 (bs, 4 H, $H_{1,8,2,3}$), 2.50 (m, 1 H, H_5), 2.13 (cm, 2 H, $H_{6,7}$), 1.87 (bs, 2 H, $H_{9,9'}$)	$C_{10}H_9N_3O$
18	2250, 1342, 1290, 759[a]	2.67 (bs, 2 H, $H_{1,8}$), 2.25 (m, 2 H, $H_{2,3}$), 2.06 (cm, 3 H, $H_{5,6,7}$), 1.71 (bs, 2 H, $H_{9,9'}$)	$C_{10}H_9NO$
19	3320, 3038, 1635, 1562, 1295, 1260, 759, 704	5.37 (bs, 2 H, 2 NH),[d] 2.68 (bs, 4 H, 2 $H_{1,8}$), 2.23 (bs, 4 H, 2 $H_{2,3}$), 2.10 (m, 6 H, 2 $H_{5,6,7}$), 1.75 (s, 4 H, 2 $H_{9,9'}$)	$C_{19}H_{20}N_2O$
20	3310, 1646, 1593, 1550, 760, 690	7.34 (m, 5 H, C_6H_5), 5.80 (m, 2 H, 2 NH),[d] 2.60 (bs, 2 H, $H_{1,8}$), 2.23 (m, 2 H, $H_{2,3}$), 2.05 (cm, 3 H, $H_{5,6,7}$), 1.70 (bs, 2 H, $H_{9,9'}$)[g]	$C_{16}H_{16}N_2O$
21	3390, 1690, 1520, 1264, 1258, 1072, 784, 772	5.21 (bs, 1 H, NH),[d] 4.41 (q, J = 7.5 Hz, 2 H, OCH_2), 2.65 (bs, 2 H, $H_{1,8}$), 2.21 (m, 2 H, $H_{2,3}$), 2.05 (m, 3 H, $H_{5,6,7}$), 1.71 (s, 2 H, $H_{9,9'}$), 1.25 (t, J = 7.5 Hz, 3 H, Me)	$C_{12}H_{15}NO_2$
22	3340, 3050, 1705, 1590, 1293, 1243, 764, 682	7.20 (bs, 5 H, C_6H_5), 5.55 (bs, 1 H, NH),[d] 2.66 (bs, 2 H, $H_{1,8}$), 2.30 (m, 2 H, $H_{2,3}$), 2.07 (m, 3 H, $H_{5,6,7}$), 1.71 (bs, 2 H, $H_{9,9'}$)	$C_{16}H_{15}NO_2$

[a] As neat film. [b] For hydrogen numbering, see Scheme I; bs = broad s, bt = broad t, cm = complex m. [c] Satisfactory analytical data for C, H, N (±0.3%) were provided for these compounds. Ed. [d] Disappeared on shaking with D_2O. [e] In CCl_4. [f] The signal became a singlet on shaking with D_2O. [g] In 30% (v/v) pyridine-$CDCl_3$. [h] Registry no. are, respectively, 53940-92-4, 42132-22-9, 42132-21-8, 53940-93-5, 53940-94-6, 53940-95-7, 53940-96-8, 53940-97-9, 53940-98-0, 53940-99-1, 53941-00-7, 53941-05-2, 53941-01-8, 53941-02-9, 53957-19-0.

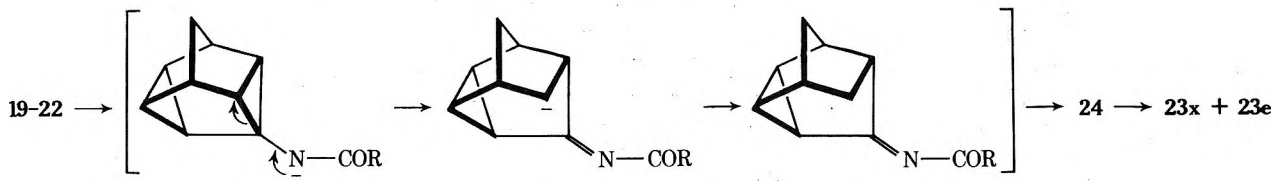
On deamination with isoamyl nitrite in acetic acid–benzene **10** afforded acetates **12** and **13** in 7:13 ratio (58% yield). The structures of **12** and **13** were determined as the acetates of **6** and **9** respectively, on the basis of analysis, spectral data, and the same GLC retention times with samples prepared by acetylation of **6** and **9** (Scheme I).

In the above solvolysis and deamination of **7**, **8**, and **10**, the formation of the ring-expansion product in higher ratio but no formation of cyclopropylcarbinyl-homoallylic rearrangement products or of secondary rearrangement products might be useful for synthesis of such strained cyclobutane derivatives combined with cage structure. However,

Scheme II



Scheme III



2-nortricyclylcarbinylamine (14) as one of some related systems is known to afford only unrearranged acetate as the major product on deamination.[12] For the present system the prohibition of further rearrangement of an intermediate cation 15 could be rationalized in terms of a nonbisected geometry of the cyclopropylcarbinyl cation moiety.[13,14]

Primary cyclopropylamine has recently been shown to rearrange with base, similar to the well-known cyclopropanol rearrangement.[15] For example, 1-methyl-2,2-diphenylcyclopropylamine gives 4,4-diphenyl-2-butanone on treatment with aqueous sodium bicarbonate at room temperature.[15] The present pentacyclic system was converted to appropriate cyclopropylamine derivatives **19–22** and their base-catalyzed rearrangement was examined (Scheme II).

Carboxylic acid 4 was converted to the corresponding carbonyl azide **17** via acid chloride **16,** which on heating in refluxing benzene afforded isocyanate **18** as an oil in 89% overall yield from **4. 18** gave the corresponding urea and urethane derivatives **19–22** on treatment with water, aniline, ethanol, and phenol, respectively. The structures of these derivatives were confirmed by analytical and spectral data (Table I). In the nmr spectra, **19–22** revealed characteristic signals due to the pentacyclo[4.3.0.$0^{2,4}$.$0^{3,8}$.$0^{5,7}$]nonane moiety in 2:2:3:2 ratio at δ 2.68–1.70.

Treatment of bisurea **19** with sodium bicarbonate in 20% aqueous ethanol at 80° for 3 days resulted only in recovery of **19.** However, on refluxing with potassium hydroxide in ethylene glycol **19** afforded crystalline products in 73% yield, which on GLC analysis revealed three peaks (**23x, 23e,** and **24**) in 10:89:1 ratio. The major product **23e** was isolated after repeated sublimations, mp 141–143°, and had a formula $C_9H_{12}O$ on the basis of analysis and mass spectral molecular ion peak at *m/e* 136. Ir (KBr) absorption at 3400 cm^{-1} indicated **23e** to be an alcohol, and the NMR ($CDCl_3$, 100 MHz) spectrum after addition of Eu(dpm)$_3$ [Eu(dpm)$_3$/**23e** = 0.12] had signals at δ 12.9 (broad s, 1 H, OH), 7.60 (d, J = 6.0 Hz, 1 H, H_3), 4.05 (d, J = 12.0 Hz, 1 H, H_5), 3.44 (m, 1 H, H_4), 3.05 (m, 3 H, H_2, H_6, H_8), and 2.25–1.70 (m, 5 H, other protons). From these spectral data **23e** was characterized as *endo*-tetracyclo[4.3.0.$0^{2,9}$.$0^{4,8}$]-nonan-3-ol. Conclusive evidence for the structure assigned was obtained by oxidation (Sarett) of **23e** to the known tetracyclo[4.3.0.$0^{2,9}$.$0^{4,8}$]nonan-3-one (**24**), mp 89.5–9.5° (lit.[16] mp 90.5–92°), which was identified with an authentic sample by ir and NMR spectal comparison.[17] The minor product **24** in the above base-catalyzed reaction was identified as this ketone also by the same GLC retention times. The second major product **23x,** was identified as an exo isomer of **23e** because comparison of the NMR spectrum of the mixture with that of **23e** indicated that **23x** had a characteristic H_3 signal at δ 4.15 as unsymmetrical triplet ($J \simeq$ 1.5 Hz),[17,18] and oxidation (Sarett) gave the ketone **24** on GLC analysis. Under the same conditions **20–22** afforded also **23x** and **23e** in ~1:9 ratio accompanied with a trace amount of **24** (Scheme III).

The formation of **23x** and **23e** can be rationalized by considering an initial cyclopropylamine rearrangement to give **24,** followed by its Meerwein–Ponndorf–Verley reduction.[19]

These results are of interest in view of the applicability of base-catalyzed cyclopropylamine rearrangement to urea and urethane derivatives also.

Experimental Section[20]

Photolysis of 8-Cyanodeltacyclene (1). A solution of **1**[2] (4.0 g, 28 mmol) in ether (1.0 l.) was irradiated through a quartz jacket with a 300-W high-pressure mercury lamp under nitrogen at ~5° for 49 hr. After removal of the solvent, an oily residue (4.8 g) was

purified on a silic gel column eluting with *n*-hexane–CH_2Cl_2 to afford **4-cyanopentacyclo[4.3.0.0^{2,4}.0^{3,8}0^{5,7}]nonane (2)** as the first fraction (3.53 g, 88%), mp 48–49°.

The second fraction gave **3** (20 mg, 1%): mp 187–190°; NMR ($CDCl_3$, 60 MHz) δ 2.50 (m, 4 H), 2.12 (m, 4 H), 1.72 (broad s, 4 H), 1.35 (m, 4 H), and 1.05 (m, 2 H).

Anal. Calcd for $C_{20}H_{18}N_2$: C, 83.88; H, 6.34; N, 9.78. Found: C, 83.82; H, 6.43; N, 9.76.

Similar irradiation of **1** in *n*-hexane gave **2** and **3** in yields of 13 and 35%, respectively. Irradiation of **1** in acetone gave **2** (39%) and an acetone adduct as an oil (20%), n^{19}D 1.5296.

Anal. Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.45; H, 7.57; N, 7.26.

Pentacyclo[4.3.0.0^{2,4}.0^{3,8}.0^{5,7}]nonane-4-carboxylic Acid (4). A mixture of **2** (3.31 g, 23.2 mmol), potassium hydroxide (25.5 g), water (85 ml), and ethanol (7 ml) was refluxed under nitrogen for 18 hr. Neutralization of the cooled mixture with 10% hydrochloric acid afforded **4** as colorless crystals (3.39 g, 90%): mp 169–170°; mass spectrum *m/e* 162 (M^+) and 117 ($M - CO_2H$).

Methyl Ester 5 from 4. Treatment of **4** with a ca. threefold excess amount of diazomethane in ether gave the corresponding methyl ester **5** quantitatively after removal of the solvent and excess diazomethane as an oil which on standing crystallized, mp 55–56°.

Pentacyclo[4.3.0.0^{2,4}.0^{3,8}.0^{5,7}]nonane-4-methyl Alcohol (6). A mixture of **5** (360 mg, 2.04 mmol) and lithium aluminum hydride (400 mg, 10.5 mmol) in dry ether (30 ml) was stirred for 15 hr. After decomposition of the excess reagent by addition of water, the mixture was extracted with ether (5 × 30 ml) and dried (Na_2SO_4). Removal of the solvent gave carbinol **6** as an oil (270 mg, 89%), n^{22}D 1.5223.

***p*-Nitrobenzoate (7) of 6.** To an ice-cooled and stirred mixture of *p*-nitrobenzoyl chloride (560 mg, 3.26 mmol) in pyridine (3.5 ml) was added a solution of **6** (400 mg, 2.70 mmol) in pyridine (3.5 ml). After stirring was continued for 2 hr at room temperature, the mixture was poured onto ice–water (50 ml) to afford faintly yellowish crystals which were filtered and recrystallized from aqueous ethanol to give analytically pure **7** (565 mg, 70%), mp 69–70°.

3,5-Dinitrobenzoate (8) of 6. To an ice-cooled and stirred mixture of 3,5-dinitrobenzoyl chloride (1.169 g, 5.07 mmol) in pyridine (5 ml) was added a solution of **6** (0.750 g, 5.07 mmol) in pyridine (3 ml). After stirring was continued for 3 hr at room temperature, the mixture was poured onto ice–water (50 ml). Resulting precipitates were collected and recrystallized from ethanol to give **8** as needles (1.38 g, 79%), mp 97–98°.

Hydrolysis of 7 and 8. A mixture of **7** (250 mg, 0.875 mmol) and 2,6-lutidine (360 mg, 3.36 mmol) in 70% dioxane–water (v/v) (20 ml) was heated in a sealed tube under nitrogen for 24 hr at 170°. The cooled mixture was diluted with water (50 ml) and extracted with ether (4 × 50 ml). The combined extracts were washed with 10% hydrochloric acid (3 × 50 ml), saturated aqueous sodium bicarbonate (3 × 50 ml), and water (50 ml) successively and dried (Na_2SO_4). After removal of the solvent, the residue was purified on a silica gel column eluting with chloroform. The first fraction gave unreacted **7** (120 mg, 48% recovery) and the second fraction afforded **pentacyclo[5.3.0.0^{3,6}.0^{2,10}.0^{5,9}]decan-3-ol (9)** as crystals which were sublimed to afford an analytical sample (52 mg, 40%), mp 122–124°.

GLC analysis of the crude product indicated that a trace amount of unrearranged alcohol **6** was also produced.

A similar hydrolysis of **8** at 140° for 40 hr and work-up as above afforded **9** (65%), **6** (trace), and unreacted **8** (28%).

Lithium Aluminum Hydride Reduction of 2. A mixture of **2** (0.80 g, 5.6 mmol) and lithium aluminum hydride (0.42 g, 11 mmol) in dry ether (30 ml) was stirred at room temperature for 1 day. After decomposition of the excess reagent by addition of water, the mixture was extracted with ether (6 × 30 ml). The combined extracts were dried (Na_2SO_4) and the solvent was removed to give crude product which was purified by sublimation (100°, 23 mm) to afford **pentacyclo[4.3.0.0^{2,4}.0^{3,8}.0^{5,7}]nonane-4-methylamine (10)** as colorless crystals (0.67 g, 82%), mp 86–88°.

Stirring of a mixture of **10** (40 mg, 0.27 mmol) and phenyl isocyanate (40 mg, 0.33 mmol) in benzene (5 ml) for 0.5 hr at room temperature afforded colorless precipitates which were collected and recrystallized from ethanol to give phenylurea derivative **11** (60 mg, 67%), mp 181–183°.

Acetylation of 6. A mixture of **6** (50 mg, 0.34 mmol) and acetic anhydride (48 mg, 0.47 mmol) in dry pyridine (0.25 ml) was stirred at room temperature for 15 hr. After addition of water (10 ml) the mixture was extracted with chloroform (2 × 10 ml) and the combined extracts were washed with water (5 ml) and dried (Na_2SO_4). Removal of the solvent gave an oily residue which was purified on a silica gel column ($CHCl_3$) to give **4-pentacyclo[4.3.0.0^{2,4}.0^{3,8}.0^{5,7}]nonylcarbinyl acetate (12)** as a viscous oil (50 mg, 78%), n^{20}D 1.5022.

Deamination of 10. A mixture of **10** (1.0 g, 6.8 mmol), acetic acid (0.40 g, mmol), and isoamyl nitrite (0.81 g, 6.1 mmol) in benzene (13 ml) was refluxed for 4 hr. After removal of the solvent the residue was chromatographed on a silica gel column eluting with benzene to give an acetate mixture (0.73 g, 58%) which on GLC analysis revealed two peaks in 13:7 ratio. The mixture was purified by preparative GLC (30% silicone SE-30 on 45/60 mesh Chromosorb W at 165°). The minor product, however, decomposed under the GLC conditions employed but it was characterized as the unrearranged acetate **12** based upon the same retention times as an authentic sample. The major product was isolated as a viscous oil which was identified as the rearranged acetate **13**: ir (neat) 1735, 1250, and 1016 cm^{-1}; nmr ($CDCl_3$, 60 MHz) δ 2.93 (m, 1 H), 2.67 (m, 1 H), 2.38 (m, 1 H), 2.24 (m, 1 H), 2.01 (s, 3 H), 2.13–1.9 (m, 5 H), 1.75 (d, J = 9.0 Hz, 1 H), and 1.59 (d, J = 9.0 Hz, 1 H).

Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.92; H, 7.26.

Acetylation of 9. A mixture of **9** (11.0 mg, 0.0743 mmol) and acetic anhydride (20.4 mg, 0.200 mmol) in pyridine (0.3 ml) was heated at 75° for 5 hr. The cooled mixture was diluted with chloroform (10 ml), washed with water (2 × 10 ml), and dried (Na_2SO_4). Removal of the solvent gave crude acetate, which was purified on a silica gel column ($CHCl_3$) to give acetate **13** as a viscous oil (13.0 mg, 93%), n^{20}D 1.5028, which was identical with the sample from deamination by ir and GLC comparisons.

Pentacyclo[4.3.0.0^{2,4}.0^{3,8}.0^{5,7}]nonane-4-carbonyl Azide (17). A mixture of **4** (973 mg, 6.00 mmol) and thionyl chloride (5.0 ml, 8.35 g, 70.0 mmol) in *n*-pentane (50 ml) was stirred for 87 hr at room temperature. Removal of the solvent and excess reagent under reduced pressure gave crude acid chloride, to which dry benzene (5 ml) was added and the solvent was removed under reduced pressure repeatedly to give acid chloride **16** as an oil (1.08 g, 100%), ir (neat) 1770 cm^{-1}.

To an ice-cooled and stirred solution of **16** (0.54 g, 3.0 mmol) in dry acetone (10 ml) was added sodium azide (0.60 g, 9.2 mmol) in water (3 ml) and the mixture was stirred for 4 hr at room temperature. Diluted mixture with water (80 ml) was extracted with ether (3 × 50 ml). The combined extracts were washed with saturated sodium bicarbonate solution (3 × 30 ml) and dried (Na_2SO_4), and removal of the solvent under reduced pressure afforded **17** as an oil (0.50 g, 89%).

Pentacyclo[4.3.0.0^{2,4}.0^{3,8}.0^{5,7}]nonan-4-isocyanate (18). A solution of **17** (1.00 g, 5.35 mmol) in dry benzene (25 ml) was added dropwise to refluxing dry benzene (65 ml) in 40 min and the refluxing was continued for 3 hr. The solvent was removed under reduced pressure (25 mm) to afford **18** as an oil (0.850 g, 100%) which was practically pure. An analytical sample was obtained after dry distillation (80°, 0.2 mm), n^{19}D 1.5240.

***N,N'*-Bis-4-pentacyclo[4.3.0.0^{2,4}.0^{3,8}.0^{5,7}]nonylurea (19).** A mixture of **18** (971 mg, 6.10 mmol) in 50% aqueous tetrahydrofuran (35 ml) was stirred for 1 day at room temperature. Concentration of the mixture to ~20 ml afforded colorless precipitates (645 mg) which were collected and recrystallized from methylene chloride to give **19** (530 mg, 59%), mp 259–260° dec.

***N*-Phenyl-*N'*-4-pentacyclo[4.3.0.0^{2,4}0^{3,8}.0^{5,7}]nonylurea (20).** A mixture of **18** (40 mg, 0.25 mmol) and aniline (24 mg, 0.26 mmol) in dry benzene (3 ml) was stirred for 0.5 hr at room temperature. The resulting precipitates were filtered and washed with benzene to give **20** as colorless crystals which were analytically pure (60 mg, 95%), mp 261–262°.

Ethyl *N*-4-Pentacyclo[4.3.0.0^{2,4}.0^{3,8}.0^{5,7}]nonylcarbamate (21). A mixture of **18** (330 mg, 2.08 mmol) and pyridine (0.1 ml) in ethanol (10 ml) was refluxed for 17 hr. Concentration of the mixture gave crude product which was recrystallized from ethanol to give **21** as colorless crystals (285 mg, 67%), mp 79–81°.

Phenyl *N*-4-Pentacyclo[4.3.0.0^{2,4}.0^{3,8}.0^{5,7}]nonylcarbamate (22). A mixture of **18** (460 mg, 2.89 mmol), phenol (315 mg, 3.35 mmol), and potassium hydroxide (10 mg) in benzene (9 ml) was stirred for 15 hr at room temperature. Removal of the solvent gave crude product which was recrystallized from *n*-hexane to give **22** as colorless crystals (270 mg, 37%), mp 132–134°.

Base-Catalyzed Rearrangement of 19. A mixture of **19** (274 mg, 0.971 mmol) and potassium hydroxide (21 g) in ethylene glycol (50 ml) was refluxed for 15 hr under nitrogen. A colorless solid was sublimed at the refluxing condenser, which was taken up in ether.

The reaction mixture was diluted with ice–water (200 ml) and extracted with ether (5 × 50 ml). The combined extracts and sublimed portion were washed with water (30 ml) and dried (Na_2SO_4). Removal of the solvent afforded a colorless solid (185 mg, 73%) of a 10:89:1 mixture of **23x**, **23e**, and **24** (GLC analysis). Three sublimations of the mixture (100°, 25 mm) gave pure *endo*-**tetracyclo[4.3.0.0^{2,9}.0^{4,8}]nonan-3-ol (23e)** as a colorless solid (79 mg, 30%): mp 141–143° (lit.[21] mp 143.5–145.5°); mass spectrum *m/e* 136 (M^+); NMR ($CDCl_3$, 100 MHz) δ 4.55 (d, J = 6.0 Hz, 1 H, H_3), 1.95 (s, ~1 H, OH, disappeared on shaking with D_2O), and 2.7–0.8 (m, 10 H, other protons).

Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.27; H, 8.98.

In the nmr spectrum of the mixture, an unsymmetrical triplet signal was observed at δ 4.15 (H_3 of **23x**) in addition to others overlapped with the signals due to **23e**. The integral ratio of the signals at δ 4.55 (H_3 of **23e**) and 4.15 (H_3 of **23x**) was 9:1.

Oxidation of 23e to Tetracyclo[4.3.0.0^{2,9}.0^{4,8}]nonan-3-one (24). To an ice-cooled and stirred mixture of chromic anhydride (200 mg, 2.00 mmol) in pyridine (4 ml) was added **23e** (136 mg, 1.00 mmol) and the mixture was stirred for 2 days at room temperature. The diluted mixture with water (60 ml) was extracted with ether (3 × 20 ml) and the combined extracts were washed with water (10 ml) and dried (Na_2SO_4). Removal of the solvent gave crude product (80 mg) which was purified by preparative TLC (silica gel, $CHCl_3$) to afford **24** as colorless crystals (45 mg, 34%), mp 89.5–90.5° (lit.[16] mp 90.5–92°). **24** gave a 2,4-dinitrophenylhydrazone, mp 196–198° (lit.[16] mp 210–211°).

Oxidation of the mixture of **23x** and **23e** gave also **24** (GLC analysis).

Base-Catalyzed Rearrangement of 20–22. A mixture of **20** (or **21**, or **22**) (5 mg) and potassium hydroxide (0.5 g) in ethylene glycol (3 ml) was refluxed for 15 hr under nitrogen. The mixture was diluted with water (10 ml) and extracted with ether (3 × 10 ml). The combined extracts were dried (Na_2SO_4), concentrated to ~2 ml, and analyzed on GLC.

Acknowledgment. We are grateful to Professor A. Nickon for sending us copies of a number of spectra of **23x**, **23e**, and **24**.

Registry No.—**1**, 34627-34-4; **3**, 53941-06-3; **9**, 53941-03-0; **13**, 53973-54-9; **16**, 53941-04-1; **23e**, 53941-07-4.

References and Notes

(1) For some examples related to adamantane and noradamantane, see (a) A. C. Udding, J. Strating, and H. Wynberg, *Tetrahedron Lett.*, 1345 (1968); (b) H. W. Geluk and T. J. De Boer, *Tetrahedron*, **28**, 3351 (1972); (c) J. E. Baldwin and W. D. Foglesong, *J. Am. Chem. Soc.*, **90**, 4303 (1968); (d) R. M. Coates and J. L. Kirpatrick, ibid., **92**, 4883 (1970); P. v. R. Schleyer and R. E. Leone, ibid., **90**, 4164 (1968); (e) B. R. Ree and J. C. Martin, ibid., **92**, 1660 (1970); V. Buss, R. Gleiter, and P. v. R. Schleyer, ibid., **93**, 3927 (1971); (f) K. J. Shea and P. S. Skell, ibid., **95**, 6728 (1973); (g) J. E. Baldwin and M. W. Grayston, ibid., **96**, 1629 (1974).

(2) T. Sasaki, S. Eguchi, M. Sugimoto, and F. Hibi, *J. Org. Chem.*, **37**, 2317 (1972). The yield of **1** in the homo-Diels–Alder reaction of norbornadiene with cyanoacetylene was improved up to 52% from 31% by using a catalytic amount of polymerization inhibitor such as hydroquinone.

(3) Photolysis of **1** in *n*-hexane afforded **2** and **3** in yields of 13 and 35%, while photolysis in acetone gave **2** and an acetone adduct in yields of 39 and 20%, respectively.

(4) (a) C. F. Huebner, E. Donoghue, L. Dorfman, E. Wenkert, W. E. Streth, and S. W. Donely, *Chem. Commun.*, 419 (1966); (b) P. K. Freeman and D. M. Balls, *J. Org. Chem.*, **32**, 2354 (1967); (c) E. Wiskot and P. v. R. Schleyer, *Angew. Chem., Int. Ed. Engl.*, **6**, 694 (1967); (d) H. Prinzbach and D. Hunkier, ibid., **6**, 247 (1967); see also ref 1d.

(5) For the characteristic long-range coupling between H_5 and $H_{9'}$, see ref 1d.

(6) P. K. Freeman, D. M. Balls, and J. N. Blazevich, *J. Am. Chem. Soc.*, **92**, 2051 (1970).

(7) For example, cf. R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds", 5th ed, Wiley, New York, N.Y., 1965; see also ref 1c.

(8) Compounds **5**, **6**, and **12** have been synthesized recently by heavy metal ion (e.g., Ag^+) catalyzed rearrangement of 4-substituted homocubane derivatives but detailed characterization seems not to be reported: L. A. Paquette and J. S. Ward, *Tetrahedron Lett.*, 4909 (1972); L. A. Paquette, *Acc. Chem. Res.*, **4**, 280 (1971).

(9) For a recent review on the lanthanide shift reagent, see A. F. Cockerill, G. L. O. Davies, R. C. Harden, and D. M. Rackham, *Chem. Rev.*, **73**, 553 (1973).

(10) For geminal coupling constants of methylene group in cyclobutane derivatives, see R. Cahill, R. C. Cookson, and T. A. Crabb, *Tetrahedron*, **25**, 4724 (1969).

(11) This is an approximate method but many successful applications have been reported, especially for rigid system such as adamantanol; A. F. Cockerill and D. M. RacKham, *Tetrahedron Lett.*, 5153 (1970).

(12) H. Hart and R. A. Martin, *J. Am. Chem. Soc.*, **82**, 6362 (1960).

(13) For recent extensive reviews on cyclopropylcarbinyl cation, see (a) H. G. Richey, Jr., in "Carbonium Ions", Vol. III, G. A. Olah and P. v. R. Schleyer, Ed., Interscience, New York, N.Y., 1972, pp 1201–1294; (b) K. B. Wiberg, B. A. Hess, Jr., and A. J. Ashe, III, in ref 13a, pp 1295–1345.

(14) For a cyclopropylcarbinyl cation system having an unfavorable perpendicular conformation, see ref 13b, pp 1300–1305, and ref 1e.

(15) H. M. Walborsky and P. E. Ronman, *J. Org. Chem.*, **38**, 4213 (1973), and references cited therein.

(16) A. Nickon, H. Kwasnick, T. Swartz, R. O. Williams, and J. B. DiGiorgio, *J. Am. Chem. Soc.*, **87**, 1615 (1965).

(17) Professor A. Nickon has kindly sent us the spectral data of **24** as well as the epimeric alcohols **23x** and **23e**.

(18) The dihedral angles between H_3 and H_4, and H_3 and H_2 were ca. 80 and 70°, respectively, on a Dreiding stereomodel, suggesting that the coupling constants between these protons are very small.

(19) Cf. H. O. House, "Modern Synthetic Reactions", 2nd ed, W. A. Benjamin, Menlo Park, Calif., 1972, p 154.

(20) Microanalyses were performed with a Perkin-Elmer 240 elemental analyzer. Melting points were determined with a Yanagimoto micromelting point apparatus (hot-stage type) and are uncorrected. Ir spectra were obtained with a Jasco IRA-1 spectrophotometer. Nmr spectra were taken with a Jeol-C-60HL or a Jeol-JNM-MH-100 spectrometer using Me_4Si as internal standard, and mass spectra with a Jeol-O1SG spectrometers at 75 eV. Glc analyses were performed with a Neva gas chromatograph, Model 1400, and preparative glc with a Varian Aerograph Model 700 (silicone SE-30 column).

(21) Private communication from Professor A. Nickon; see ref 17.

Cyclization during the Dehydrohalogenation of Perfluoroalkyl-Substituted Iodoalkylmalonates. Thermal Rearrangement of the Derived 2-(Perfluoroalkyl)methylcyclopropane-1,1-dicarboxylates

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3-Perfluoroalkyl-2-iodopropylmalonic esters (**1a–e**) cyclized during reaction with bases in aqueous and nonaqueous systems to give 2-(perfluoroalkyl)methylcyclopropane-1,1-dicarboxylic acids (**6a–e**) and diesters (**5a–e**) in excellent yield. The higher homolog 4-perfluoroalkyl-3-iodobutylmalonate cyclized only in part, but was also dehydrohalogenated to $R_FCH{=}CHCH_2CH_2CH(COOR)_2$, R = Et, H. The cyclopropane diesters **5b** and **5c** rearranged thermally at 225–240° by a sigmatropic, 1,5-hydrogen shift to $R_FCH{=}CHCH_2CH(COOEt)_2$ (**3b, 3c**). The cyclopropanedicarboxylic acids **6b** and **6c** decarboxylated and rearranged at 175–200° to a mixture of $R_FCH{=}CHCH_2CH_2COOH$ (**13**) and *cis*- and *trans*-2-(perfluoroalkyl)methylcyclopropanecarboxylic acids (**15**). At reduced CO_2 pressure rearrangement was almost completely suppressed in favor of decarboxylation to **15**. *cis*-**15**, but not *trans*-**15**, slowly isomerized at a higher temperature to **13**. No reaction occurred under conditions which gave **13** from **6**. A concerted rearrangement and decarboxylation of **6** is probable, facilitated by both opening of the strained ring and release of CO_2.

The purpose of this research was to explore the behavior of perfluoroalkyl-substituted iodoalkylmalonic acids and esters, readily obtained by free-radical addition of iodoperfluoroalkanes (R_FI) to alkenylmalonic acids and esters.[1] These addition reactions were efficiently catalyzed by 2,2′-azobis-2-(methylpropionitrile) (ABN) initiator at 70°.

$$R_FI + CH_2{=}CH(CH_2)_mCH(COOEt)_2 \xrightarrow{ABN} R_FCH_2CHI(CH_2)_mCH(COOEt)_2$$

	R_F	m	convn	yield
1a	$(CF_3)_2CF$	1	87%	88%
1b–e	$CF_3(CF_2)_n$ n = 1–7	1	85	95
1f	$CF_3(CF_2)_3$	2	85	95
1g	$CF_3(CF_2)_5$	2	89	95

Certain perfluoroalkyl-substituted iodoalkenylmalonic esters were also prepared by addition of R_FI to 2-propynylmalonic ester. This was an inefficient reaction, however,

$$R_FI + HC{\equiv}CCH_2CH(COOEt)_2 \xrightarrow{ABN} R_FCH{=}CICH_2CH(COOEt)_2 \xrightarrow{Zn/H^+} R_FCH{=}CHCH_2CH(COOEt)_2 \xrightarrow{OH^-} R_FCH{=}CHCH_2CH(COOH)_2$$

	R_F	convn	yield
2b	$CF_3CF_2CF_2$	39%	85%
2c	$CF_3(CF_2)_3$	23	95

	R_F	yield
3b	$CF_3CF_2CF_2$	86%
3c	$CF_3(CF_2)_3$	86

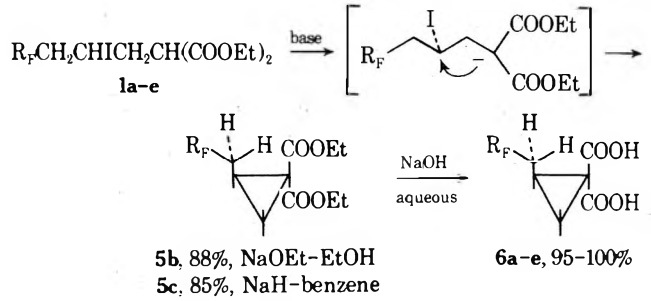
	R_F	yield
4b	$CF_3CF_2CF_2$	95%
4c	$CF_3(CF_2)_3$	96

and suffered from wastage of the initiator by the acetylenic ester. Reduction of adducts **2b** and **2c** by zinc and acid in anhydrous ethanol, followed by hydrolysis,[2] gave a group of related unsaturated esters (**3b, 3c**) and acids (**4b, 4c**) which were useful in comparing structures and properties. These syntheses were similar to those previously reported.[3,4] Reactions of diethyl perfluoroalkyl-2- or -3-iodoalkylmalonates **1a–g** were found to give unexpected and varied results. Additionally, thermal behavior of the novel cyclic products proved to be of unusual interest.

Results

Dehydrohalogenation of 3-perfluoroalkyl-2-iodopropylmalonic esters **1a–e** gave entirely cyclization to 2-(perfluoroalkyl)methylcyclopropanedicarboxylic acids and esters, as reported in a preliminary fashion.[5] Reaction of **1a–e** with ethoxide ion in anhydrous ethanol or by sodium hydride in benzene suspension took place via the carbanion (Chart I), and internal displacement of iodide ion gave cyclization to the cyclopropane-1,1-dicarboxylates **5a–e**. No olefinic product was formed by E2 elimination, as was shown by comparison with authentic compounds **3b** and **3c**.

Chart I
Cyclization of
Diethyl 3-Perfluoroalkyl-2-iodopropylmalonates



5b, 88%, NaOEt-EtOH
5c, 85%, NaH-benzene

6a–e, 95–100%

Subsequent hydrolysis of **5b** in aqueous ethanol using sodium hydroxide as base gave crystalline 2-(perfluoropropyl)methylcyclopropane-1,1-dicarboxylic acid (**6b**) in 89% yield. In aqueous ethanol at 40–80° cyclization of iodopropyl esters **1a–e** (all R_F groups) with excess hydroxide went rapidly and exothermically; hydrolysis of the ester groups occurred inter alia and a quantitative yield of the corresponding R_F-substituted cyclopropane-1,1-dicarboxylic acids **6a–e** was obtained in each case. Reaction conditions and some physical constants of the acids are briefly recorded in Table I.

Reaction undoubtedly occurred by the sequence shown in Chart I, since reaction of the iodopropyl ester **1c** with a deficiency of base in aqueous ethanol gave some diethyl 2-(perfluorobutyl)methylcyclopropane-1,1-dicarboxylate

Table I
Preparation of 2-(Perfluoroalkyl)methylcyclopropane-1,1-dicarboxylic Acids (6a–e)

Iodopropyl ester							
	R_F	mol	NaOH, mol	Time, hr	Temp, °C	Acid	Mp, °C
1a	$(CF_3)_2CF$	0.030	0.12	5	80	6a	128–129
1b	$CF_3(CF_2)_2$	0.030	0.15	7	80	6b	81–82[a]
1c	$CF_3(CF_2)_3$	0.0183	0.0652	5	40	6c	95
1d	$CF_3(CF_2)_5$	0.0200	0.0700	5	50	6d	127[b]
1e	$CF_3(CF_2)_7$	0.0100	0.0400	4	50	6e	132[b]

[a] Monohydrate, mp 94–95°, from benzene solution. [b] Monohydrate.

Table II
NMR Spectral Data for Isomeric 2-(Perfluoropropyl)methylcyclopropane-1,1-dicarboxylic Acids (6a and 6b)

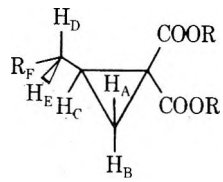
Proton	δ	Multiplicity	J, Hz (±0.2 Hz)
H_A	1.8	Doublet of doublets	$J_{AB} = 3.5^{a,b}$
H_B	2.02	Doublet of doublets	$J_{BC} = 9.0^{a}, 8.7^{b}$
H_C	2.49	Multiplet[c]	$J_{AC} = 7.5^{a,b}$
H_D, H_E[a]	2.75[a]	Multiplet of doublet[a]	$J_{DC} = J_{EC} = 7.7^{a}, 7.5^{b,d}$
H_D, H_E[b]	2.9[b]	Multiplet of doublet[b]	$J_{HF} = 21.5^{a}, 19.5^{b,d}$

[a] NMR spectrum of **6a**. [b] NMR spectrum of **6b**. [c] Actually a quintet owing to essentially equal values of coupling constants. [d] J_{DE} could not be determined owing to similar chemical shifts for H_D and H_E.

(**5c**), albeit in reduced yield. In subsequent studies it is hoped to determine whether it is possible to trap the carbanion in anhydrous systems before cyclization occurs, by reaction with another alkyl halide, for example.

Spectral Data. The R_F-substituted cyclopropane-1,1-dicarboxylic acids and esters were characterized by ir and nmr spectra. The dicarboxylic acids **6a–e** showed a carbonyl stretching band at 1735 cm^{-1} and a very strong band at 1640 cm^{-1}, not affected by method of analysis. This was unusual, as other 1,1-dicarboxylic acids such as **4b** or $R_F(CH_2)_3CH(COOH)_2$ had a single stretching band at 1705 cm^{-1}.[3] The diesters **5a–e** had a carbonyl band at 1735 cm^{-1} and CH bands at 1400 and 1325 cm^{-1} (cyclopropyl ring).[6] A band at 1350 cm^{-1} appeared in both **1b** and **5b** and is probably associated with R_FCH_2 deformation. It appears that bands at 1410, 1070, 990, and 940 cm^{-1} are characteristic of these substituted cyclopropanes and are absent in the straight-chain compounds.

NMR spectra of **6a–e** (acetone-d_6) at 60 HMz gave a cluster of lines for cyclopropyl ring protons (H_A, H_B, H_C) at δ 1.5–2.5, R_FCH_2 protons (H_D, H_E) at δ 2.9, and carboxyl group protons as a single line at δ 10.75, having correct areas for each type of proton. NMR spectra of isomeric 2-(perfluoropropyl)methylcyclopropane-1,1-dicarboxylic acids **6a** and **6b** were also run at 100.1 MHz in pyridine solution, as these structures afforded an opportunity to observe the effect of two closely related R_F groups in a well-defined structure (Table II).[7]



5a–e, R = Et
6a–e, R = H

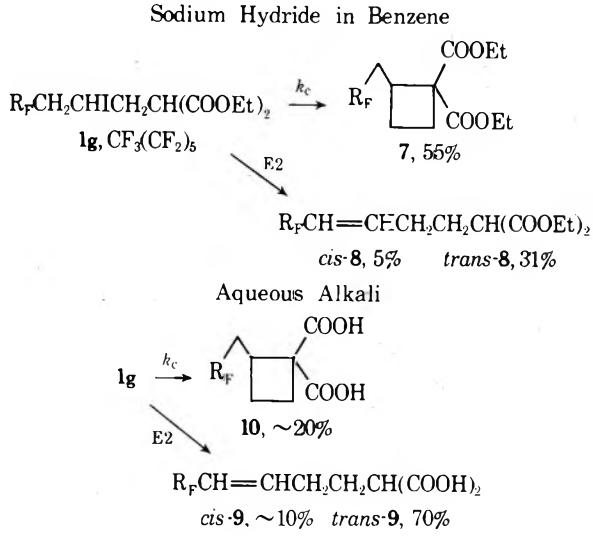
The R_FCH_2 protons (H_D, H_E) of **6a** appeared as a multiplet of a doublet, owing to coupling of the single F with adjacent nonequivalent CH_2 protons (J_{HF} = 21.5 Hz, J_{DE} = J_{EC} = 7.7 Hz). Further analysis, using ^{19}F resonance and decoupling showed the CF_3 groups to be nonequivalent and coupled to each other and to the CF group. Each CF_3 resonance appeared as five lines, having $J_{CF_3CFCF_3} = 8 \pm 0.3$ and $J_{CF_3CF} = 6.5 \pm 0.3$ Hz. The CF resonance consisted of a multiplet of at least 16 lines, which were reduced to an approximate triplet having J_{HF} = 21.5 Hz by double ^{19}F resonance. The triplet nature of the CF resonance was only evident after decoupling from the CF_3 signals. The R_FCH_2 protons of **6b** gave a multiplet of a triplet as expected for two adjacent F atoms (J_{HF} = 19.5 Hz). The proton resonance for H_C turned out to be a quintet from nearly equal coupling constants of four adjacent hydrogens.

Diesters **5b** and **5c** gave two overlapping quartets at δ 4.18 for two methylenes of the ethyl ester groups, as the two CH_2 proton sets were evidently nonequivalent. By contrast, the unsaturated isomers **3a** and **3c** gave a single quartet at δ 4.2; they also showed typical olefinic proton resonances at δ 5.2–6.8 (very useful later for identification) and a multiplet near δ 3.0 for the methine proton.

Cyclization of Higher Homologs. Dehydrohalogenation of $R_FCH_2CHICH_2CH_2CH(COOEt)_2$ (**1g**) by sodium hydride at 60–70° gave 96% of an ester mixture (Chart II). Gas chromatography (GLC) of a sample removed before distillation showed 54.7% of cyclobutyl ester **7**, 5.0% of cis ester, and 31.4% of trans ester **8**. Pure **7** had no olefinic resonance in its pmr spectrum; cyclobutyl protons were seen at δ 1.8–2.7 and two quartets of the nonequivalent methylenes of the ester groups at δ 4.2 and 4.25. The cis and trans olefinic ester **8** showed the methine proton at δ 3.2 as a triplet (J = 6 Hz). Reaction of **1g** with sodium hydroxide in aqueous ethanol at 50° gave solid acid mixture **9–10** in quantitative yield. Recrystallization afforded pure *trans* **9** in a recovery of 70%, and a residue of *cis*- and *trans* **9** with **10**. Quantitative estimation was difficult because of the thermally sensitive nature of the malonic acid **9**. Similarly, reaction of **1f** gave the isomeric unsaturated malonic acid (*cis*- and *trans* **11**) as the chief product with a little of the cyclobutyl compound **12**, as shown by comparison of NMR spectra.

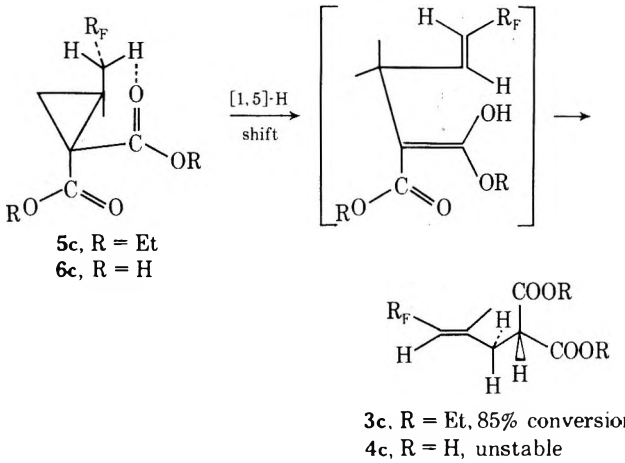
1,5-Hydrogen Shift Rearrangement of 2-(Perfluoroalkyl) Methylcyclopropanedicarboxylates. Isomerization of **5c** to diethyl 3-perfluorobutyl-2-propenylmalon-

Chart II
Cyclization vs. Elimination in Dehydrohalogenation of 4-Perfluoroalkyl-3-iodobutylmalonic Ester



ate (**3c**) occurred very slowly at 200° but more rapidly at 225–242° (Chart III). Reaction was followed by GLC, using as standard reference compound the diester **3c** previously prepared (see introduction). The course of isomerization is summarized in Table III, and was accompanied by the formation of two side products in small yield.

Chart III
Rearrangement of Perfluoroalkyl Methylcyclopropanedicarboxylates



5c, R = Et
6c, R = H

3c, R = Et, 85% conversion
4c, R = H, unstable

The unsaturated dicarboxylic acid **4c**, obtained by the 1,5-hydrogen shift pathway (or synthesized by an independent route), was unstable and immediately decarboxylated. The malonic acid **4c** thus could not be isolated from this reaction. The conditions were too severe. The product actually isolated was $R_FCH{=}CHCH_2CH_2COOH$ (**13**), which does not cyclize to a cyclopropane derivative. Experimental evidence was obtained as follows. The malonic acids **4b** and **4c** were prepared via addition of perfluoroalkyl iodides to an alkynylmalonate and subsequent steps, as previously shown. The crystalline malonic acid **4b** or **4c**, with the double bond adjacent to the R_F group, when heated to just over 125° decarboxylated, giving the perfluoroalkyl-4-pentenoic acid **13**. This is the same acid as found in the thermal rearrangement of **6b** or **6c**. **13b** had been previously prepared by dehydrohalogenation as indicated, and its structure determined.[4]

Table III
Isomerization of Diethyl 2-(Perfluorobutyl)-methylcyclopropane-1,1-dicarboxylate (5c) to Diethyl 3-Perfluorobutyl-2-propenylmalonate (3c)

Time, hr	Total, hr	Temp, °C	5c, %	3c, %	Others, %
3	3	200	90.3	2.8	1.5, 3.5
5	8	225	75.4	20.4	1.3, 2.5
4	12	242	57.7	42.4	4.6, 2.5
12	24	242	14.0	85.2	6.0

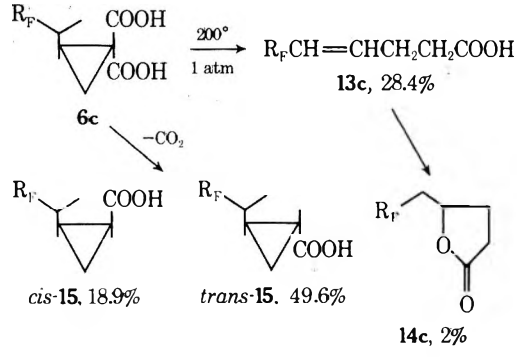
$R_FCH{=}CHCH_2CH(COOH)_2 \xrightarrow{\text{heat}}$
4b, 4c

$R_FCH{=}CHCH_2CH_2COOH$
13b, $R_F = CF_3CF_2CF_2$
c, $R_F = CF_3CF_2CF_2CF_2$

$R_FCH_2CHICH_2CH_2COOH + OH^- \longrightarrow$ 13b
$CF_3CF_2CF_2$

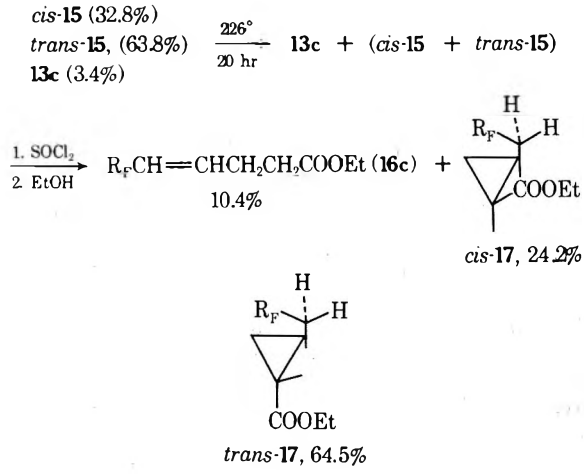
Thermal behavior of the cyclopropanedicarboxylic acids **6b** and **6c** was actually much more complex than that of the corresponding diesters **5b** and **5c**. It was found that two simultaneous reactions occurred when the diacids were heated and their relative rates depended on reaction conditions. Also the diacids were very much more labile than the diesters. At 200° in 1 hr *in an open flask* decomposition of **6c** was complete and the evolution of CO_2 (quantitative) had ceased. Subsequent analysis of the product mixture revealed that both 1,5-hydrogen shift and simple decarboxylation to *cis*- and *trans*-2-(perfluoroalkyl)methylcyclopropanecarboxylic acid (**15**) had occurred (Chart IV). The ratio of **13c** to **15** was 3:7. When **6c** was heated *in a sealed tube* at 196° for 3 hr the relative amounts of **13c** and *cis*- and *trans*-**15** was 3:2. If CO_2 was continuously swept out *under reduced pressure in a distilling apparatus*, thermal rearrangement was almost completely suppressed. At 165–173° and 15–25 mm pressure the ratio of **13c** to **15** was 3:97. Distillation afforded 3.4% of **13c**, 63.8% of *trans*-**15**, and 32.8% of *cis*-**15** in 95% yield. Even at 202° (65 mm) the product comprised nearly pure *cis*- and *trans*-**15**. *trans*-**15** crystallized from the mixture and was characterized by spectral and other means.

Chart IV
Rearrangement and Decarboxylation of 2-(Perfluoroalkyl)methylcyclopropane-1,1-dicarboxylic Acids



The small amount of lactone **14** formed under certain conditions was indicated by a strong band at 1780 cm^{-1} in ir spectra, and a separate peak in GLC analysis. Lactonization had previously been observed in reactions of related substances.[3]

At a considerably higher temperature the *cis*-2-(perfluoroalkyl)methylcyclopropanecarboxylic acid (*cis*-**15**) slowly isomerized to **13**. A mixture of cis and trans or pure trans isomer of **15** was unchanged by heating at 196° for 3 hr or longer, but at 226° *cis*-**15** gave 7% of **13c** in 20 hr, while the amount of *trans*-**15** present remained unchanged. In order to quantify these reactions the acid mixtures (**13c**, *cis*- and *trans*-**15**) were converted to ethyl esters (**16c** and *cis*- and *trans*-**17**) by way of the acid chlorides. Conversions were quantitative and GLC analysis correlated well with area ratios of olefinic protons for **13c**:**15** or **16c**:**17**. Nearly pure *trans*-**17** was isolated by fractional distillation and served to identify GLC peaks.



Discussion

Dehydrohalogenation of perfluoroalkyl-2- or -3-iodoalkylmalonic esters (**1a–g**, Charts I and II) may be contrasted with analogous reactions of ω-halogenoalkymalonic esters [$X(CH_2)_nCH(COOEt)_2$, X = Cl or Br, n = 2, 3, 4, or 5] which gave as sole product the cycloalkane-1,1-dicarboxylic ester. Intramolecular nucleophilic substitution of the intermediate carbanion in the rate-determining step was demonstrated.[8–10] Formation of three-membered rings was very much faster than that of four-, five-, or six-membered rings. When X = Br relative rates were 3:5:4:6 ring = 80,000:800:2.5:1.[8] For the perfluoroalkyl-substituted esters the acidifying effect of an R_F group should increase the rate of base attack on the R_FCH_2 protons of **1a–g** at the expense of internal displacement (k_c) by the carbanion of the CHI group.[11,12] Steric hindrance for the approach of the carbanion to a secondary CHI would be greater than to a terminal CH_2I. These considerations help to explain the lack of specificity for base attack on the R_F-substituted iodobutylmalonates, **1f** and **1g**. For the 3-perfluoroalkyl-2-iodopropylmalonates **1a–e**, the unfavorable enthalpy of activation for three-membered ring formation may be partly offset by a higher entropy term, since closing the ring becomes more difficult as the ends become farther separated.[13,14]

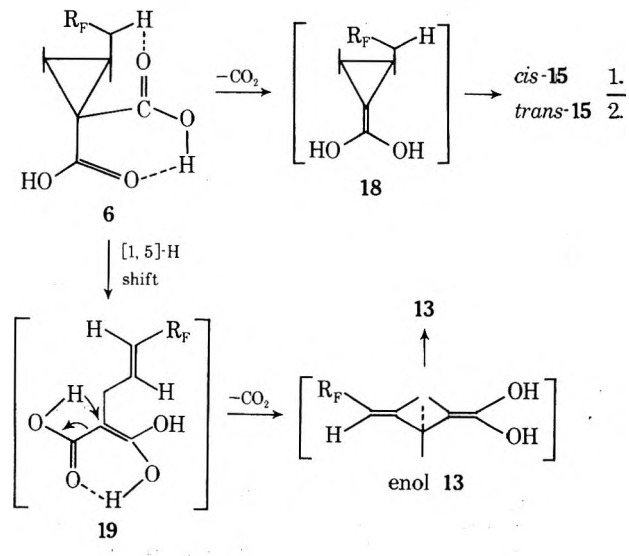
Knipe and Stirling further suggested that resonance interaction of the cyclopropane ring (as a conjugated unsaturated system) and a substituent serves to lower the enthalpy of activation.[8] There is good evidence for stabilization by cyclopropane, but not for higher homologs.[10] Thermal isomerization of R_FCH_2-cyclopropane-1,1-dicarboxylates belongs to the class of Cope rearrangements.[15] A six-membered transition state, drawn in the form of a chair (Chart III), is postulated. This type of reaction has been called an "enolene rearrangement" since the intermediate possesses an enol form, and the process generates an alkene.[16] It has formal similarity to other suprafacial sigmatropic 1,5-hydrogen shift processes.[17] Previous studies employing ethyl *cis*- and *trans*-1-methyl-2-methylcyclopropanecarboxylate[18] and *cis*- and *trans*-1-acetyl-2-methylcyclopropane[16] have shown that hydrogen transfers from the same side but not from the opposite side of the ring.[19] Conversion of *cis*-**15** to **13c** is another example and failure of *trans*-**15** to rearrange fits into this picture nicely.

Thermal rearrangement of diesters **5a–e** constitutes a potentially useful synthesis of R_F-substituted malonic esters **3** or the acids **4**, as free-radical addition of perfluoroalkyl iodides to the alkynylmalonates was an inefficient process.

The most surprising results of this study were (a) the remarkable dependence of thermal rearrangement–simple decarboxylation of diacids **6** on the conditions of reaction; and (b) the facility with which decomposition of the diacids **6** occurred compared with the diesters **5**. Decarboxylation of **6c** to *cis*- and *trans*-**15** was favored over Cope rearrangement to **13c** by reduced CO_2 pressure. This appears to involve an intermediate **18** leading to the final product **15**, and a competitive pathway leading to another intermediate **19** and final products, CO_2 and **13** (Chart V).[20]

Decarboxylation is known to proceed by means of a cyclic intermediate which achieves the highly strained structure **18** at the expense of release of energy in CO_2 formation.[21,22] The 2:1 preference for *trans*-**15** over *cis*-**15** (Chart IV) is then explained by proton transfer back to the ring in such a way as to minimize steric repulsion between the bulky and electronegative R_FCH_2 and COOH groups.

Chart V
Cope Rearrangement vs. Decarboxylation of 2-(Perfluoroalkyl)methylcyclopropane-1,1-dicarboxylic Acids



The intermediate form **19** depicted in Chart V should be compared with the Cope intermediate shown in Chart III. It can be seen that simultaneously with enolene formation, transfer of a proton of the second carboxyl group to an ene carbon of **19** will permit the departure of the CO_2 molecule and generate directly the enol form of **13**. In this way the [1,5]-hydrogen shift and decarboxylation to **13** may become concerted. Indeed, relief of ring strain in opening the cyclopropane would assist the decarboxylation step as well.[21] These suggestions appear to offer a consistent explanation for the unusual results of this study. Further work will be necessary to determine thermodynamic values, rate factors, and the influence of structural variations on the course of this rearrangement.

Table IV
Preparation of Diethyl 3-Perfluoroalkyl-2-iodoalkylmalonates (1a-g)[a]

			Alkenyl malonate			Iodoalkyl ester					
R_F	R_FI, mol	ABN, mol × 10^{-3}	Compd	Mol	Reaction time, hr	Compd	Convn, %	Yield, %	Bp, C	(mm)	$n^{25}D$
$(CF_3)_2CF$	0.100	1.00	20	0.075	20	1a	87	88	97	(0.30)	1.4200
$CF_3(CF_2)_2$	0.100	1.00	20	0.075	19	1b	81	94	104	(0.30)	1.4210
$CF_3(CF_2)_3$	0.179	3.00	20	0.150	17	1c	85	96	100	(0.10)	1.4122
$CF_3(CF_2)_3$	0.0413	0.610	21	0.0325	17	1f	85	93	111	(0.20)	1.4168
$CF_3(CF_2)_5$	0.0500	1.00	20	0.050	20	1d	89	95	124	(0.50)	1.3994
$CF_3(CF_2)_5$	0.0500	1.00	21	0.050	20	1g	89	95	137	(0.60)	1.4040
$CF_3(CF_2)_7$	0.0250	0.500	20	0.0250	18	1e	87	94	142	(0.60)	1.3905

[a] Satisfactory analytical data (±0.4% for C, H, F, or I) were reported for all new compounds listed in the table.

Experimental Section

Source of Materials and Physical Measurements. Diethyl 2-propenylmalonate (**20**), bp 115° (19 mm), $n^{25}D$ 1.4307 [lit.[23] bp 116–124° (20 mm)], diethyl 3-butenylmalonate (**21**), 36% yield from 4-chloro-1-butene or 59% yield from 4-bromo-1-butene, bp 132° (23 mm), $n^{25}D$ 1.4315 [lit.[24] bp 116–121° (12 mm)], and diethyl 2-propynylmalonate (**22**), bp 117° (9 mm), $n^{25}D$ 1.4356 [lit.[25] bp 109.5° (13 mm), $n^{20}D$ 1.4384], were prepared by the literature method.[26] 2-Iodoperfluoropropane was a gift from E. I. du Pont de Nemours and Co. The perfluoroalkyl iodides, $CF_3(CF_2)_nI$ (n = 3, 5, 7), were a gift from Ciba-Geigy Corp., through the courtesy of Dr. E. K. Kleiner. The physical constants were those previously given.[2] 2,2′-Azobis-2-(methylpropionitrile) (ABN) was obtained from Eastman Kodak Co.

Melting points were observed using a Thomas-Hoover Unimelt apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 337 spectrophotometer. NMR spectra were observed using a Varian T-60 spectrophotometer and as indicated, at 100.1 MHz.[7] Gas chromatographic analyses were done using a Sargent-Welch thermal conductivity instrument and under conditions which are listed where appropriate.

Preparation of Diethyl 3-Perfluoroalkyl-2-iodopropylmalonates and Diethyl 4-Perfluoroalkyl-3-iodobutylmalonates. Table IV summarizes the free-radical addition of perfluoroalkyl iodides to **20** and **21**. Analytical data for all new compounds are presented in Table V.[27] NMR and ir spectral data were consistent in each case. A typical procedure follows Table IV.

Diethyl 3-Perfluorooctyl-2-iodopropylmalonate (1e). A heavy-wall glass tube was charged with 1-iodoperfluorooctane (13.65 g, 0.0250 mol), **20** (5.00 g, 0.0250 mol), and ABN (0.0821 g, 5.00 mmol), cooled to −78°, evacuated and filled three times with nitrogen, and sealed. The tube was immersed in an oil bath at 70° for 18 hr, opened, and rinsed out with pentane through a sintered glass filter. The clear, colorless liquid was distilled in a short-path still without a column, heating with an oil bath up to 170°: **1e**, bp 142° (0.65 mm), $n^{25}D$ 1.3900, 16.3 g (87%); ir $\nu_{C=O}$ 1735 cm^{-1}; NMR δ 3.75 (t, J = 6 Hz, $CH_2CH(COOEt)_2$), 4.18 (m, overlapped peaks of CHI and $COOCH_2CH_3$). Residual oil (0.60 g), trap liquid (0.47 g), and a few drops of forerun were also obtained. Analyses are in Table V.

Preparation of Diethyl 3-Perfluoroalkyl-2-iodo-2-propynylmalonates. A. 2b from 1-Iodoperfluoropropane and Diethyl 2-Propynylmalonate (22). **22** (15.85 g, 0.0800 mol), 1-iodoperfluoropropane (29.6 g, 0.100 mol), and ABN (0.164 g, 1.00 mmol) under identical conditions with those given above gave recovered R_FI (19.4 g, 65%), **22** (9.0 g, 57%), and diethyl 2-iodo-4,4,5,5,6,6,6-heptafluoro-2-hexenylmalonate (**2b**), bp 122° (2.4 mm), $n^{25}D$ 1.4282, 12.7 g, and residual oil, 1.0 g. Redistillation of combined cuts in a 2-ft platinum spinning band column afforded pure **2b**, 14.4 g (39.2% conversion, 85% yield): ir ν_{OH} 3080 (w), $\nu_{C=O}$ 1750, $\nu_{C=C}$ 1640, bands at 1040, 975, 960, 940, 920, 860, 750, and 540 cm^{-1} (these results indicated that both cis and trans isomers were present);[4] NMR δ 3.30 (2 protons, d, J = 7 Hz, CH_2CH), 3.80 (1 proton, t, J = 7 Hz, CH_2CH), 6.60 (1 proton, t, J_{HF} = 14 Hz, $CF_2CH{=}CI$).

B. From 1-Iodoperfluorobutane and 22. **22** (19.8 g, 0.100 mol), 1-iodoperfluorobutane (27.6 g, 0.0800 mol), and ABN (0.164 g, 1.00 mmol) gave diethyl 2-iodo-4,4,5,5,6,6,7,7,7-nonafluoro-2-heptenylmalonate (**2c**), bp 98° (0.32 mm), $n^{24}D$ 1.4210, 10.3 g, 23% conversion and 95% yield based on recovered starting materials.

Zinc Reduction of Diethyl 2-Iodo-4,4,5,5,6,6,6-heptafluoro-2-hexenylmalonate (2b) to Diethyl 4,4,5,5,6,6,6-Heptafluoro-2-hexenylmalonate (3b). **2b** (10.0 g, 0.0202 mol), ethanol (50 ml), and zinc (6.5 g, 0.10 g-atom, 30 mesh) was stirred while anhydrous hydrogen chloride was passed in at 75° until hydrogen gas evolution began. After 0.5 and 4 hr reaction times, zinc (6.5 g) was added. HCl gas was fed in momentarily as needed, to maintain gas evolution during the reaction. After 6.5 hr the liquid was poured into 100 ml of water and extracted three times with 20 ml of CCl_4. The organic layer was rinsed with water, dried over $MgSO_4$, and distilled in a 24-in. platinum spinning band column. Diethyl 4,4,5,5,6,6,6-heptafluoro-2-hexenylmalonate (**3b**) had bp 120° (8.0 mm); $n^{25}D$ 1.3805; 6.4 g (86%); ir (neat, KBr) $\nu_{C=O}$ 1750, $\nu_{C=C}$ 1675, δ_{CH} 1470, 1450, 1375, 1350; and bands at 970, 940 (w), 860, and 750 cm^{-1}; NMR δ 1.25 (6 protons, t, J = 7 Hz, OCH_2CH_3), 2.85 (2 protons, m, CH_2CH), 3.3–3.9 (1 proton, m, $CH(COOC_2H_5)_2$), 4.2 (4 protons, q, J = 7 Hz, OCH_2CH_3), 5.0–6.8 (2 protons, m, cis and trans CH=CH.

Diethyl 4,4,5,5,6,6,7,7,7-Nonafluoro-2-heptenylmalonate (3c). In similar fashion diethyl 2-iodo-4,4,5,5,6,6,7,7,7-nonafluoro-2-heptenylmalonate (**2c**, 7.3 g, 0.013 mol) gave *cis*- and *trans*-**3c**, bp 116° (3.0 mm), $n^{25}D$ 1.3747, 4.4 g (70%).

Hydrolysis of 3b to $CF_3CF_2CF_2CH{=}CHCH_2CH(COOH)_2$ (4b) and Decarboxylation of 4b to $CF_3CF_2CF_2CH{=}CHCH_2CH_2COOH$ (13b). **3b** (4.6 g, 0.0125 mol) was added to a solution of NaOH (1.1 g, 0.050 mol) in water (2.5 ml) and ethanol (23 ml), kept at 70° for 5 hr, diluted to 100 ml with water, and acidified with 6*N* HCl (20 ml). 4b was extracted into dichloromethane (three times, 15 ml), dried over $MgSO_4$, and evaporated (2.7 g, 95%) to partly crystalline *cis*- and *trans*-**4b**: ir $\nu_{C=O}$ 1725, $\nu_{C=C}$ 1675 (w), δ_{CH} 1410, 1350, $\gamma_{C=C}$ 970 (s) and 940–930 cm^{-1}. The mixture when recrystallized from CCl_4 and then $HCCl_3$ gave pure *trans*-**4b**, mp (sinter 75°) 79–80°, evolved CO_2 at 122–130°. The residual oil was heated to ca. 150° for 10 hr and **13b** distilled, bp 68° (0.25 mm), $n^{25}D$ 1.3630, 1.4 g, identical with the sample previously prepared.[4]

2-(Perfluoroalkyl)methylcyclopropane-1,1-dicarboxylic Acids (6a–e). Typical Procedure. NaOH (6.0 g, 0.15 mol) in water (7 ml) and ethanol (63 ml) was added while stirring to **1b** (14.8 g, 0.0299 mol) in ethanol (60 ml) and kept at 60–80° for 7 hr, diluted to 200 ml with water, and acidified with hydrochloric acid. Solid acid **6b**, dried at ambient temperature, was obtained as the monohydrate (9.4 g, 96% of theory), mp (sinter 89°) 91–92°, recrystallized from benzene, mp 94–95°. **6b** monohydrate lost water of hydration when stored over P_2O_5 for several weeks, or dried in a vacuum oven at 60° overnight; the melting point dropped to 81–82°. Samples of **6b** monohydrate and of **6b** were titrated in 50% aqueous ethanol with 0.02514 *N* sodium hydroxide solution, using a pH meter. A pH–volume plot for **6b** monohydrate gave midpoints of breaks in the curve at pH 5.6 and 10.6, with equivalent weights of 343 and 164. Anhydrous **6b** gave midpoints at pH 5.3 and 10.1, with equivalent weights of 318 and 155. Ir (KBr disk) ν_{COOH} 3560, $\nu_{C=O}$ 1730, 1640, δ_{CH} 1410, 1360, ν_{CF} 1290, 1270, 1225; bands at 1170, 1165, 1125, 1105, 1070, 1060, 995, 945, 805, 780, 775, 695, and 530 cm^{-1}. For NMR spectral data see Table II. Preparations of related compounds are listed in Table I.

Sodium Ethoxide Induced Cyclization. Diethyl 2-(2,2,3,3,4,4,4-Heptafluorobutyl)-1,1-cyclopropanedicarboxylate (5b). **1b** (10.0 g, 0.0200 mol) was added dropwise to a solution of sodium (0.4702 g, 0.0204 mol) in anhydrous ethanol [distilled from $Mg(OCH_3)_2$] at 56–62° during 20 min, with stirring by a magnet bar. The clear yellow solution was kept at 62° for 16 hr, 55 ml of 6.0 *N* HCl and 50 ml of water were added, and the orange oil

Table VI
Fractionation of 7, 8 Mixture

Fraction	Bp, °C (mm)	Wt, g	Ketention time, min[a] 6.5	8.2	9.2	15.2	20.8	23.0
I	95(0.30)	0.79	5.0%	3.1%		89.1%	0.60%	1.2%
II	93–97 (0.25)	1.93	4.3	5.8		68.5		
III	97(0.20)	0.74	2.4	1.4	4.5	16.4	72.3	3.0
IV	82(0.15)	1.04	1.1	0.63	0.94	4.26	78.2	14.9
Original sample		6.4				54.7	31.4	4.95
Identity of substance								*cis*-8 7 *trans*-8

[a] GLC analysis using a 6-ft SE-30 silicone oil column at 160°.

was extracted with ether (3 × 15 ml) and benzene (15 ml), using salt to aid in separating layers. The organic extract was rinsed with dilute sodium sulfite solution and dried over $MgSO_4$. Distillation without a column gave **5b**, bp 79° (0.75 mm), $n^{25}D$ 1.3840, 6.5 g (88%), and an oil residue (0.2 g). Redistillation in a 2-ft platinum spinning band column gave **5b**, 99% pure by GLC analysis (SE-30 silicone oil column, up to 150°), bp 113° (8.0 mm), $n^{25}D$ 1.3802, having unchanged ir spectrum. **5b** reacted slowly with bromine in carbon tetrachloride solution or with dilute aqueous $KMnO_4$ solution in acetone. Ir ν_{CH} 2995, 2950, 2920, 2880, $\nu_{C=O}$ 1730, δ_{CH} 1470, 1445, 1400, 1370, 1350, ν_{CF} 1300–1200; bands at 1140, 1120, 1100, 1070, 1060, 1028, 995, 965, 940, 860, 830, 755, 735, 710, 640, and 530 cm^{-1}. Bands at 995, 965, 940, and 755 cm^{-1} were common to both **5b** and **6b**. NMR (50% in CCl_4) δ 1.33 [6 protons, t, J = 7 Hz, $(OCH_2CH_3)_2$], 1.49–2.18, [5 protons, m, CH_2CH (ring) and CF_2CH_2], 4.18 [4 protons, q, J = 7 Hz, $(OCH_2CH_3)_2$]. Hydrolysis of 2.00 g (5.40 mmol) of **5b** in 6.0 ml of 80% ethanol containing 0.65 g (0.016 mol) of sodium hydroxide at 80° for 7.5 hr gave **6b** as the monohydrate, 1.50 g (89%), mp (sinter 90°) 91–93°.

Sodium Hydride Induced Cyclization of 1c to Diethyl 2-(2,2,3,3,4,4,5,5,5-Nonafluoropentyl)-1,1-cyclopropanedicarboxylate (5c). 1c (5.00 g, 9.16 mmol) in dry benzene (10 ml) under nitrogen atmosphere was added during 10 min to sodium hydride (0.40 g, 9.46 mmol, 57% dispersion in mineral oil) in benzene (10 ml) stirred by a magnet bar at 24°. The evolution of hydrogen was followed by displacing water from a vertical tube. At 62° reaction began and evolution of gas continued at 79–81° for 3 hr until quantitative. The tan slurry was kept at 26° for 18 hr and filtered through a fritted disk. Sodium iodide (1.34 g, 94%) was collected. Distillation through a 10-cm packed column was attended by much foaming at first. **5c** distilled without a column, bp 133° (17 mm), $n^{25}D$ 1.3762, 3.3 g (85%), leaving 1.0 g of hold-up and residue. GLC analysis gave 98.35% area under one peak, and the ir was identical with that of **5c**.

Sodium Hydroxide Induced Cyclization of 1c to 5c. 1c (10.0 g, 0.0183 mol) was added to a solution of NaOH (0.732 g, 0.0183 mol) in water (75 ml), stirred and heated at 70° for 3 hr, without evident reaction. Ethanol (25 ml) was added and after 20 min the solution was neutral to litmus. Neutral product (**5c**) was extracted into benzene leaving **6c** (as salt) in the aqueous layer. **5c**, bp 103° (4.0 mm), $n^{25}D$ 1.3766, 4.40 g (58%), was recovered by distillation. GLC analysis gave 99% area at 7.4 min, using a 6-ft SE-30 silicone oil column, temperature programmed from 135 to 200° at 15°/min.

Sodium Hydride Induced Dehydrohalogenation of Diethyl 3-Iodo-4-(perfluorohexyl)butylmalonate (1g). Ester **1g** (8.316 g, 0.0126 mol), sodium hydride (0.5326 g, 57% in mineral oil, 0.0126 mol), and benzene (20 ml) were stirred by a magnet bar under nitrogen atmosphere. Gas evolution at 60–70° was followed by displacing water from a flask; when heated to reflux for 8 hr the slurry became noticeably tan in color. Ethanol (9 ml) gave a clear alkaline solution. Water (50 ml) and 6 N HCl (10 ml) were added, and the solution was extracted three times with benzene (10 ml) and with ether and dried over magnesium sulfate. Glpc analysis showed that olefinic and cyclobutyl compounds were present (Table VI). Product mixture was first distilled, bp 110–113° (0.50 mm), 6.4 g, $n^{25}D$ 1.3750 (96%), and then fractionated in a spinning band column (Table VI). Spectral data for **7**: ir $\nu_{C=O}$ 1730, a band at 1042 but not at 970 cm^{-1}; NMR δ 1.3 (6 protons, t, J = 7 Hz), 1.8–2.7 (broad multiplet, 6 protons), 3.4 (1 proton, m), 4.2 and 4.25 (4 protons, overlapping q, J = 7 Hz, nonequivalent ester groups); ir for *cis*- and *trans*-**8** $\nu_{RfCH=CH}$ 1670 and a band at 970 cm^{-1}; NMR δ 1.3 (6 protons, t, J = 7 Hz), 2.2 (4 protons, broad multiplet, CH_2CH_2CH), 3.2 (1 proton, t, J = 6 Hz), 4.1 (4 protons, q, J = 7 Hz, ethyl ester), 5.0–6.8 (2 protons, broad multiplet of olefinic protons).

Dehydrohalogenation of Diethyl 3-Iodo-4-(perfluorobutyl)butylmalonate (1f) by Sodium Hydroxide in 90% Ethanol. Ester **1f** (5.6 g, 0.010 mol) and a solution of sodium hydroxide (2.0 g, 0.050 mol) in 25 ml of 90% aqueous ethanol was stirred at 65–72° for 7 hr, 15 ml of 6 N HCl and 50 ml of water were added, and the solution was extracted with ether (three times, 25 ml) and benzene (25 ml). The organic layer was rinsed with bisulfite solution, dried over magnesium sulfate, and evaporated to an oil, 3.3 g, 88% yield; ir and NMR indicated a mixture of olefinic and cyclobutylcarboxylic acids. Recrystallization twice from dichloromethane (50 ml) afforded pure *trans*-**11**: 1.30 g, mp 82–83° (gas evolution at 126°); ir (KBr disk) ν_{COOH} 3300–2800, $\nu_{C=O}$ 1710, $\nu_{C=C}$ 1670, δ_{CH} 1460, 1420, 1360, 1300; ν_{CF} 1250–1200, 1170, 1130; bands at 1072, 1008, 970, 920, 880, 812, 775, 740, 700, and 675 cm^{-1}; NMR (acetone-d_6) δ 2.4 (4 protons, CH_2CH_2CH), 3.44 (1 proton, t, J = 7 Hz, $CH_2CH(COOH)_2$), 5.90 (1 proton, m, ca. 4 lines, J = 14 Hz, $CF_2CH{=}CH$), 6.55 (1 proton, complex multiplet, $CF_2CH{=}CHCH_2$), 11.0 [2 protons, s, $(COOH)_2$]. The large coupling constant for olefinic protons is consistent with a trans configuration for this substance.

Dehydrohalogenation of 1g by Sodium Hydroxide in 90% Ethanol Solution. Similar treatment of **1g** (6.60 g, 0.0100 mol) gave 5.00 g (100%) of **9, 10** acid mixture, mp 60–75°. NMR and ir spectra showed that olefinic and cyclobutyl compounds were present in proportion of **9:10** = 0.80, from integrated areas of nmr spectra. A 1.00 g sample recrystallized from CCl_4 (20 ml) gave *trans*-**9**, 0.631 g, mp 81.5–87°, a second crop, mp 71–72°, 0.0488 g, and an oil residue, 0.167 g. An NMR spectrum of *trans*-**9** was identical with that of *trans*-**11**.

Decarboxylation and Rearrangement of 2-(Perfluoroalkyl)methylcyclopropane-1,1-dicarboxylic Acids. A. *cis*- and *trans*-2-Perfluorobutyl)methylcyclopropanecarboxylic Acid (15c). **6c** (10.00 g, 0.02761 mol, mp 95–96°) was stirred by a magnet bar and heated in a 25-ml round-bottom flask, immersed in an oil bath at 169–176°; under reduced pressure CO_2 was evolved and *cis*- and *trans*-**15c** distilled, bp 122–111° (24–15 mm), 7.48 g, during 1 hr. Crystalline solid residue (1.13 g) remained (93% total recovery). Ir of both materials was identical and showed $\nu_{C=O}$ 1700, δ_{CH} 1470, 1440, 1350,; bands at 1130, 1075, 1050, 1025, 1000–995, 965–955, 915, 885, 840, 770, 740, 710, 690, 670, 550, and 530 cm^{-1}. Bands at 1075, 1030, 950, 770, 710, and 675 cm^{-1} were not present in **6c**, and a strong band at 1640 cm^{-1} in **6c** was also absent. Bands at 1675 and 975 cm^{-1} in **13c** were absent. [However, conversion of the product to ethyl esters showed that *cis*-**17c** (32.78%), *trans*-**17c** (63.83%), and **16c** (3.39%) (average of four analyses) were present.] Pure *trans*-**15c** was obtained from CCl_4 solution, mp 69–71°. Similarly, **6c** (7.00 g, 0.0220 mol) when heated at 202° under reduced pressure evolved CO_2 and gave *cis*- and *trans*-**15c**, bp 166° (65 mm), 6.02 g, as a crystalline solid (**13c** absent by ir and NMR analysis).

B. At Atmospheric Pressure. **6c** (6.00 g, 0.0165 mol) in the same flask connected to a gas bubbler system was heated to 188° (194° bath temperature) without evolution of CO_2; at 198° (202° bath) gas was evolved during 1 hr and stopped. The solid which remained (5.29 g) contained no **6c**, but *cis*-and *trans*-**15c** (about 70–80%) and **13c** (about 20–30%) were present, according to NMR area ratios and ir spectra. The product mixture (4.768 g) was con-

verted to ethyl esters (5.24 g) and analyzed by GLC before and after distillation; *cis*-**15c** (20.96%), *trans*-**15c** (50.6%), and **13c** (28.43%) were present.

C. In Closed Vessel. 6c (0.3076 g, 0.849 mmol) was heated at 196° for 3 hr in a tightly capped "Reactivial" and the products were analyzed by NMR and ir; none of **6c** remained but a mixture of approximately 60% of **13c**, 40% of *cis*- and *trans*-15c, and a small amount of **14c** (band at 1780 cm^{-1}) was present.

D. Decarboxylation of 6b to *cis*- and *trans*-2-(Perfluoropropyl)methylcyclopropanecarboxylic Acid (15b) and 5-Perfluoropropyl-4-pentenoic Acid (13b). 6b (5.00 g, 0.0152 mol, mp 91–92°, monohydrate) was heated at 152° for 2 hr in a 10-ml flask, fitted with a bubbler tube, without apparent reaction or change in ir spectrum of the melt. At 200° evolution of CO_2 occurred during 1 hr. Distillation gave *cis*- and *trans*-**15b, 13b,** and **14b,** bp 124° (21 mm), 2.8 g, and a residue (0.70 g). The distillate was neutralized with 15.0 ml of 5% sodium bicarbonate solution and extracted with dichloromethane; evaporation gave 0.6 g of γ-lactone (**14b,** ir band at 1780 cm^{-1}). The aqueous layer was acidified with 6 *N* HCl and an oil separated (1.8 g); ir and NMR showed it to consist of **13b** (about 60%) and *cis*- and *trans*-**15b (about 40%).**

E. NMR Spectra of *cis*- and *trans*-15c. The spectrum resembled that of **6c** in the region of δ 0.8–3.0, but the COOH proton was at δ 11.22, with the area of one proton. The ir spectrum gave $\nu_{C=O}$ 1700 cm^{-1} (only) and had bands at 1135, 1050, 965, 890, and 710 cm^{-1} not in **6b.**

Thermal Rearrangement of *cis*-2-(Perfluorobutyl)methylcyclopropanecarboxylic Acid (*cis*-15c) to 5-Perfluorobutyl-4-pentenoic Acid (13c). A mixture (1.9683 g, 0.1867 mmol) containing relative amounts of *cis*-**15c,** *trans*-**15c,** and **13c** of 33.78:63.83:3.39 (by GLC analysis of ethyl esters) was placed in a heavy-walled glass tube, evacuated and filled three times with nitrogen at −78°, and sealed. After heating in a stirred oil bath at 226° for 4 hr, a sample showed no change in NMR spectrum; after 14 hr about 12% of **13c** was present from integrated area of olefinic protons, and after 21 hr the area was unchanged. The remaining material (1.10 g) was converted to ethyl esters and analyzed by GLC (FFAP column, 105°) which showed relative amounts of *cis*-**15c,** *trans*-**15c,** and **13c** of 20.39:69.93:9.55 (average of four analyses). Analysis on another column (QF-1 silicone oil) with temperature programming to 180° showed about 1–2% of higher boiling substances also. There appeared to be a 12% decrease in *cis*-**15c** and an increase of about 6% in *trans*-**15c** and **13c.** An attempt to analyze the mixture of the three acids by means of the trimethylsilyl derivatives gave volatile product which could be separated into only two well-resolved peaks on four different columns.

B. Nonisomerization of *cis*- and *trans*-15c at 198°. A mixture of *cis*- and *trans*-**15c** (2.50 g, 0.786 mmol) in a small reactor under positive nitrogen pressure was heated by an oil bath at 198°, removing samples for NMR and ir analysis after 5, 8.5, and 21 hr reaction times. There was no detectable change in the spectra of the samples.

Preparation of Ethyl *cis*- and *trans*-2-(Perfluorobutyl)-methylcyclopropanecarboxylates (17c) and Ethyl 5-Perfluorobutyl-4-pentenoate (16c). A mixture containing *cis*-**15c,** *trans*-**15c,** and **13c** formed by heating **6c** at 200° and atmospheric pressure (4.768 g, 0.01499 mol) and thionyl chloride (5 ml) was heated at 60–80° for 1 hr in a flask connected to a trap; gas evolution ceased and the mixture was evacuated at the water pump to 20 mm. The mixture of acid chlorides showed ir bands for COCl at 1785 and for $R_FCH{=}CH$ at 1670 cm^{-1}. Ethanol (5.0 ml) was added and the mixture was heated for 2 hr at 60–80° and then allowed to distil up to 105° pot temperature. The residual oil [5.24 g (100%), ir weak band for lactone at 1790 and a strong band for ester at 1730 cm^{-1}] was fractionated in a 16-in. spinning band column. The three fractions were analyzed by GLC on an 8-ft FFAP column at 105° and on a 6-ft QF-1 silicone oil column, temperature programmed from 135 to 180° after 5 min. Fraction I, bp 79° (9 mm), 1.34 g (39.21% *cis*-**17c,** 29.47% *trans*-**17c** and 31.32% **16c**) gave the correct elemental analysis and its ir and NMR spectra were recorded. Fraction II, bp 79° (9 mm), 62° (2.0 mm), 1.30 g, also contained these three substances, but fraction III, bp 66° (0.35–0.12 mm), 0.53 g, contained 80% of *cis*- and *trans*-**17c** and **16c,** and also 20% of four higher boiling substances, which were also present in the hold-up and residue. The original undistilled mixture contained 19.1% of *cis*-**17c,** 48.6% of *trans*-**17c,** 24.4% of **16c,** and 1.5, 2.2, and 2.7% of three higher boiling substances. One of these was probably the lactone **14c** but the small quantity precluded firm identification.

Another mixture containing *cis*- and *trans*-**15c** and a little of **13c,** obtained by heating **6c** under reduced pressure at 176° (2.00 g, 0.629 mmol), was similarly converted to ethyl esters (2.04 g, 95%). No lactone was detected in the product (ir) and distillation in a microstill gave *cis*- and *trans*-**17c,** bp 82° (13 mm), $n^{25}D$ 1.3582, 1.64 g. GLC analysis (FFAP column, 105°) of the mixture before and after distillation was identical (±0.5%) and showed *cis*-**17c,** 32.78%, *trans*-**17c,** 63.83%, and **16c,** 3.39% (average of four). The sample gave the correct elemental analysis.

Thermal Rearrangement of Diethyl 2-(2,2,3,3,4,4,4-Heptafluorobutyl)cyclopropane-1,1-dicarboxylate (5b) to $CF_3(CF_2)_3CH{=}CHCH_2CH(COOEt)_2$ (3c). 5b (2.09 g, 0.00500 mol) was placed in a heavy-wall glass tube, cooled to 0°, evacuated and filled with nitrogen three times, and sealed. After periods of time indicated in Table III, the tube was opened and a sample removed for GLC analysis on two different columns, using a known mixture of **5b** and **3c** for comparison. A 6-ft SE-30 silicone oil column, 10% on Chromosorb W at 150°, and a 6-ft QF-1 silicone oil column, 10% on Chromosorb W at 150°, were used. The NMR and ir spectra also showed that the substances listed were formed.

Registry No.—**1a,** 54019-87-3; **1b,** 2094-35-1; **1c,** 54019-88-4; **1d,** 54019-89-5; **1e,** 54019-90-8; **1f,** 54019-91-9; **1g,** 54019-92-0; *cis*-**2b,** 54062-06-5; *trans*-**2b,** 54019-93-1; **2c,** 54019-94-2; *cis*-**3b,** 54019-95-3; *trans*-**3b,** 54019-96-4; *cis*-**3c,** 54019-97-5; *trans*-**3c,** 54019-98-6; *cis*-**4b,** 54019-99-7; *trans*-**4b,** 54020-00-7; **4c,** 54020-01-8; **5b,** 27311-61-1; **5c,** 54020-02-9; **6a,** 54020-03-0; **6b,** 27311-60-0; **6c,** 54020-04-1; **6d,** 54020-05-2; **6e,** 54020-06-3; **7,** 54020-07-4; *cis*-**8,** 54020-10-9; *trans*-**8,** 54020-11-0; *cis*-**9,** 54020-12-1; *trans*-**9,** 54020-13-2; *trans*-**11,** 54020-09-6; **13b,** 54020-14-3; **13c,** 54020-15-4; **14b,** 54020-16-5; **14c,** 54020-17-6; *cis*-**15b,** 54020-18-7; *trans*-**15b,** 54020-19-8; *cis*-**15c,** 54020-20-1; *trans*-**15c,** 54020-21-2; **16c,** 54020-08-5; *cis*-**17c,** 54020-22-3; *trans*-**17c,** 54020-23-4; **20,** 2049-80-1; **21,** 31696-00-1; **22,** 17920-23-9; 1-iodoperfluoropropane, 754-34-7; 1-iodoperfluorobutane, 423-39-2; 1-iodoperfluorohexane, 355-43-1; 1-iodoperfluorooctane, 507-63-1; 2-iodoperfluoropropane, 677-69-0.

Supplementary Material Available. Table V and infrared and NMR spectra of the substances **1d, 3c, 4c, 5c, 6b, 6c, 7, 14c,** and **15c** will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washigton, D.C. 20036. Remit check or money order for $4.50 for photocopy or $2.50 for microfiche, referring to code number JOC-75-851.

References and Notes

(1) N. O. Brace, U.S. Patent 3,145,222 to E. I. du Pont de Nemours and Co., Aug. 18, 1964.
(2) N. O. Brace, *J. Org. Chem.*, **27,** 4491 (1962).
(3) N. O. Brace, *J. Org. Chem.*, **36,** 1904 (1971).
(4) N. O. Brace, *J. Org. Chem.*, **32,** 430 (1967).
(5) N. O. Brace, *Tetrahedron Lett.*, **No. 20,** 1697 (1970).
(6) Compare with cyclopropanes in H. A. Syzmanski, "Interpeted Infrared Spectra", Vol. 1, Plenum Press, New York, N.Y., 1964, p 143.
(7) I am indebted to Dr. Robert Grulich of Ciba-Geigy Corp., Ardsley, N.Y., for assistance in obtaining these spectra.
(8) A. C. Knipe and C. J. M. Stirling, *J. Chem. Soc. B,* 808 (1967); 67 (1968).
(9) C. J. M. Stirling, *J. Chem. Educ.*, **50,** 844 (1973).
(10) See appropriate data and leading references in ref 8.
(11) S. Andreades, *J. Am. Chem. Soc.*, **86,** 2003 (1964). (12) K. J. Klabunde and D. J. Burton, *J. Am. Chem. Soc.*, **94,** 820 (1972).
(13) E. L. Eliel, "Stereochemistry of Carbon Compounds", McGraw-Hill, New York, N.Y., 1962, p 198.
(14) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis", Interscience, New York, N.Y., 1965, p 190.
(15) J. March, "Advanced Organic Chemistry: Reactions, Mechanisms and Structure", McGraw-Hill, New York, N.Y., 1968, p 834.
(16) R. M. Roberts, R. G. Landolt, R. N. Greene, and E. W. Heyer, *J. Am. Chem. Soc.*, **89,** 1404 (1967).
(17) C. H. DePuy and O. L. Chapman, "Molecular Reactions and Photochemistry", Prentice-Hall, Englewood Cliffs, N.J., 1972, p 100.
(18) D. E. McGreer, N. W. K. Chiu, and R. S. McDaniel, *Proc. Chem. Soc.*, 415 (1964).
(19) P. H. Mazzocchi and J. J. Tamburin, *J. Org. Chem.*, **38,** 2221 (1973).

(20) I am indebted to a reviewer for pointing out that decarboxylation of **6** should give predominantly *trans*-**15** and that Cope rearrangement would not proceed from *trans*-**15** to **13**, but through a ring-opening reaction prior to decarboxylation. These predictions were amply demonstrated by experiment.
(21) J. B. Hendrickson, D. J. Cram, and G. S. Hammond, "Organic Chemistry", 3rd ed, McGraw-Hill, New York, N.Y., 1970, p 535.
(22) H. Henecka, Houben-Weyl, "Methoden der Organischen Chemie", Band VIII, Sauerstoff Verbindungen III, Georg Thieme Verlag, Stuttgart, 1952, p 490.
(23) R. P. Linstead and H. N. Rydon, *J. Chem. Soc.*, 580 (1933).
(24) R. P. Linstead and H. N. Rydon, *J. Chem. Soc.*, 1995 (1934).
(25) G. Eglinton and M. C. Whiting, *J. Chem. Soc.*, 3052 (1953).
(26) "Organic Syntheses", Collect. Vol. I, Wiley, New York, N.Y., 1946, p 250.
(27) See paragraph at end of paper regarding supplementary material.

Thermal Rearrangement of Trimethylsilyl Enol Ethers of Cyclopropyl Methyl Ketones. A Cyclopentanone Annelation Procedure[1]

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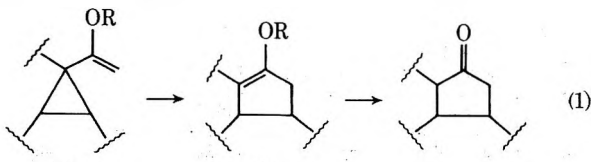
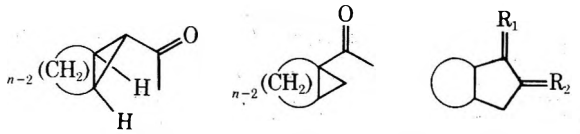
Pyrolysis of the conjugated enol trimethylsilyl ethers derived from methyl cyclopropyl ketone and methyl bicyclo[*n*.1.0]alkan-1-yl ketones (*n* = 3, 4, 5) at 450° yielded, after acidic hydrolysis of the resulting cyclopentene enol silanes, cyclopentanone (73%), bicyclo[3.3.0]octan-2-one (21%), bicyclo[4.3.0]nonan-7-one (99%), and bicyclo[5.3.0]decan-8-one (85%). Rearrangement of the enol silyl ether of methyl *exo*-bicyclo[4.1.0]heptan-7-yl ketone furnished a 1:2 mixture of *cis*- and *trans*-bicyclo[4.3.0]nonan-8-one (52%) and the γ,δ-unsaturated ketone, 2-cyclohexenylacetone (28%). The major products obtained from the enol silyl derivatives of methyl *exo*-bicyclo[3.1.0]hexan-6-yl and methyl *exo*-bicyclo[5.1.0]octan-8-yl ketones were the corresponding γ,δ-unsaturated ketones. This enol silane vinylcyclopropane–cyclopentene rearrangment pathway results in the regioselective annelation of a cyclopentanone ring onto an α,β-unsaturated ketone or an olefin. This overall process furnishes 1-hydroindanone and 1-hydroazulenone in good yields.

The occurrence of five-membered rings in an increasing number of natural products of biological importance has stimulated the development of a variety of new cyclopentane ring synthesis methods. These recent approaches include intramolecular ring closure of acyclic precursors,[2] formal [3 + 2][3] and [4 + 1][4] cycloaddition reactions, and ring contraction[5] and expansion[6] of cyclic substrates. In considering the various general routes to cyclopentanoid ring construction, it appeared to us that the well-established thermal vinylcyclopropane–cyclopentene rearrangement[7] could serve as the basis of a five-membered ring synthesis method in which the newly constructed ring contained a masked ketone functionality. In a general sense, rearrangement of conjugated cyclopropyl enol ethers of part structure **1** would yield cyclopentene enol derivatives **2**. Unmasking of the latent ketone functionality by acidic hydrolysis would then complete the sequence to give the cyclopentanone ring skeleton (eq 1). In particular, thermal



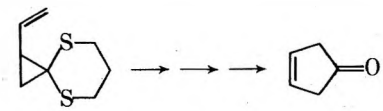
(1)

1 **2**

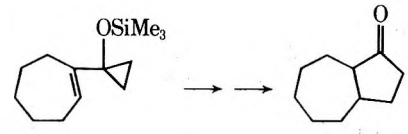


3a, *n* = 5 **4a**, *n* = 5 **5**, $R_1 = H_2$; $R_2 = O$
b, *n* = 6 **b**, *n* = 6 **6**, $R_1 = O$; $R_2 = H_2$
c, *n* = 7 **c**, *n* = 7

rearrangement of the enol derivatives derived from cyclopropyl methyl ketones **3** and **4** would furnish cyclopentanone **5** and **6** regioselectively. Since the cyclopropyl ketone substrates are readily prepared from olefin or α,β-unsaturated ketone precursors, the overall transformation constitutes a net cycloaddition of a one- or a three-carbon atom unit to an existing skeleton to give an annelated cyclopentanone. We have undertaken an examination of the thermal behavior of a series of cyclopropyl enol trimethylsilyl ethers (**1**, R = $SiMe_3$) and the results of this study are detailed below. During the course of our investigation two cyclopentanone ring synthesis methods based on the thermal vinylcyclopropane–cyclopentene rearrangement (eq 2[4a] and 3[6]) were reported.



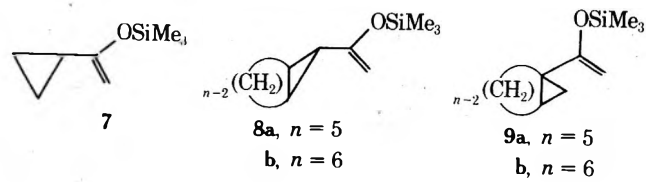
(2)



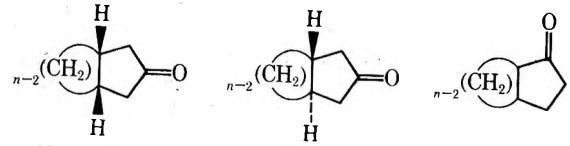
(3)

Results

The specific vinylcyclopropane substrates examined in this study, the parent trimethylsilyl enol ether **7**, and the two bicyclo[*n*.1.0]alkane series **8** and **9**, were prepared from the corresponding cyclopropyl methyl ketones under equil-



7 **8a**, *n* = 5 **9a**, *n* = 5
b, *n* = 6 **b**, *n* = 6
c, *n* = 7 **c**, *n* = 7



10a, *n* = 5 **11a**, *n* = 5 **12a**, *n* = 5
b, *n* = 6 **b**, *n* = 6 **b**, *n* = 6
c, *n* = 7 **c**, *n* = 7 **c**, *n* = 7

Table I
Thermal Rearrangement of Cyclopropyl Trimethylsilyl Enol Ethers[a]

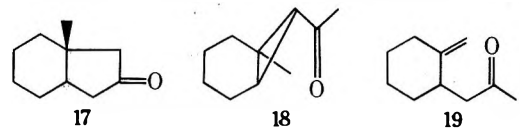
Substrate	Products (% yield)[b]
7	Cyclopentanone (73)
8a	**10a** (8), **11a** (3), **13a** (71)[c]
8b	**10b** (17), **11b** (35), **13b** (28)
8c	**10c** + **11c** (5),[d] **13c** (80)
14	**16a** (64), **15a** + **16b** (7),[d] **15b** (7)
9a	**12a** (21)[e]
9b	**12b** (99)
9c	**12c** (85)

[a] See text for reaction conditions. [b] Yields determined by VPC using an internal standard and corrected for recovered starting material. [c] An unidentified product (ca. 10%) was also formed. [d] Both isomers present but not separated cleanly. [e] Extensive decomposition was observed.

ibrating conditions (Me_3SiCl, Et_3N, DMF)[8] or, more conveniently, by kinetic enolate generation (lithium diisopropylamide, THF) followed by quenching with trimethylsilyl chloride.[8] Both methods results in regioselective formation[9] of the conjugated vinylcyclopropane enol silanes **7**, **8**, and **9**. The exo ketones **3** were prepared from the appropriate cycloalkene by the following sequence: copper sulfate catalyzed addition of ethyl diazoacetate, hydrolysis and separation of the exo carboxylic acid by crystallization, and then treatment with methyllithium.[10] The bridgehead substituted ketones **4** were obtained by dimethyloxosulfonium methylide addition to the corresponding α,β-unsaturated ketones.[11] Attempted thermal rearrangement of enol silane **7** by passing a pentane solution through a conditioned[6] hot tube packed with glass helices at ca. 520° gave, after hydrolysis, substantial amounts of recovered cyclopropyl methyl ketone as well as the desired rearrangement product, cyclopentanone. Satisfactory conversion to products was obtained, however, when the vinylcylopropyl enol silanes (**7**, **8**, and **9**) were heated in base-washed, sealed ampoules for 0.5–3 hr at 360–450°. The crude rearrangement products were quenched with methanolic hydrochloric acid and the resulting ketones were identified by comparison of VPC retention times with those of authentic samples. Material balances of ca. 80–95% were obtained when the rearrangements were done in benzene solution containing some triethylamine; pyrolysis of neat samples gave similar product distribution with ca. 50% recovery of material. Table I summarizes the ketone products obtained in these rearrangements.

As shown in Table I, one methylvinylcyclopropyl enol silane **14** was examined. Ether **14** was prepared from the corresponding cyclopropyl ethyl ketone by kinetic enolate quenching (vide supra) to give a nonseparable mixture (67:33) of geometric isomers. Unambiguous structure assignment to the major and minor components was not possible owing to the similar chemical shifts for the vinyl hydrogen of each isomer.[8] The data presented in Table I correspond to ca. 30% conversion of **14** into rearrangement products, although essentially the same product composition was obtained for 50% conversion. Authentic samples of the four possible products, hexahydroindan-2-ones **15** and **16**, were prepared from the cis and trans ketones **10b** and **11b**. Kinetic alkylation of the cis ketone **10b** by sequential treatment with lithium diisopropylamide and then methyl iodide furnished a single monomethyl product in 80% yield. This material was assigned structure **15a** on the basis of alkylation from the less hindered, convex face of **10b**. Epimerization of **15a** with methanolic sodium methoxide gave an equilibrium mixture in which **15a** was the major product (ratio **15a**:**15b** = 4.4:1). The analogous kinetic alkylation of the trans isomer **11b** also gave a single monomethyl derivative in 70% yield. Tentative structure assignment of this kinetic product as **16b** was based on a consideration of the stereoelectronic requirements for alkylation. In order to maintain maximum orbital overlap during bond formation, alkylation will occur from the quasi-axial direction (β face of **11b**) to yield the less stable isomer **16b**.[12] Confirmation of this assignment was obtained by base-catalyzed epimerization of the kinetic product **16b** to yield the more stable epimer **16a** (ratio **16a**:**16b** = 11:1). Appropriate control experiments showed that the epimers of ketones **15** and **16** did *not* equilibrate under the methanolic hydrochloric acid conditions used to hydrolyze the cyclopentene enol ether products.

An attempt to prepare the 8-methylhexahydroindanone **17** by this general sequence was thwarted at an early stage in that attempted distillation of ketone **18** resulted in formation of the exocyclic methylene derivative **19**. Formation

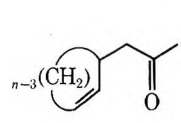


17 **18** **19**

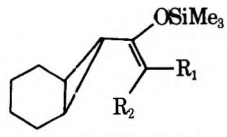
of **19** from **18** is readily explained by a thermal homo[1,5]hydrogen shift involving the cisoid carbonyl and methyl groups (an enolene rearrangement[13]).

Discussion

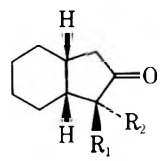
Examination of the data in Table I indicates that the formation of cyclopentanone products via the scheme outlined in eq 1 depends critically on the structure of the starting vinylcyclopropyl enol silane, **8** and **9**. Rearrangement of the angular-substituted enol derivatives **9b** and **9c** proceeds in good yield to give 1-hydroindanone (**12b**) and 1-hydroazulenone (**12c**). In contrast, the exo enol silane derivatives **8** yield two distinct types of products, the expected 3,4-disubstituted cyclopentanones **5** and monocyclic, γ,δ-unsaturated ketones **13**. The formation of unsaturated ketones **13** is readily rationalized by postulating an initial isomerization[14] of the exo starting material **8** into the endo isomer **20**, followed by a facile homo[1,5]hydrogen shift[13] to



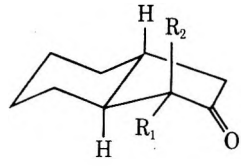
13a, $n = 5$
b, $n = 6$
c, $n = 7$



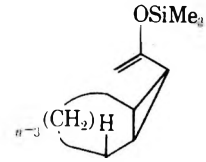
14a, R_1 = Me; R_2 = H
b, R_1 = H; R_2 = Me



15a, R_1 = Me; R_2 = H
b, R_1 = H; R_2 = Me



16a, R_1 = Me; R_2 = H
b, R_1 = H; R_2 = Me



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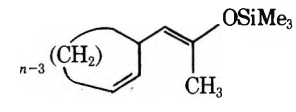
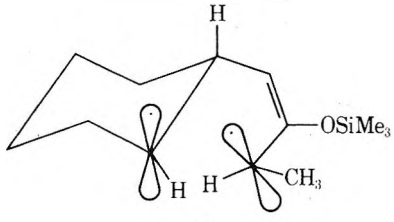


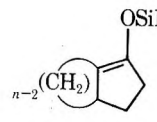
21

give ketone **13** after hydrolysis of the intermediate enol silane **21**. The major products observed from both the bicyclo[3.3.0]octan-3-one precursor **8a** and the hydroazulenone precursor **8c**, ketones **13a** and **13c**, respectively, result from this competing thermal process. In the case of the six-membered ring substrate **8b**, the major products were the annulated hydroindanones **10b** and **11b** together with a smaller amount of **13b**. In the bridgehead-substituted series **9** the analogous exo-endo isomerization would result in the highly strained trans-fused bicyclo[*n*.1.0]skeleton. Accordingly the vinylcyclopropane–cyclopentene rearrangement is the only thermal process observed in this series.

It is interesting to note that both the cis and trans hydroindanones **10b** and **11b** are formed in appreciable yield from **8b** and that the cis:trans ratio (~1:2) remains constant over the range of low to high conversion of starting material to products. Mechanistically the formation of **10b** and **11b** is consistent with either a diradical process[15] or a concerted pathway[16] ($_{\pi}2_a$, $_{\sigma}2_s \rightarrow$ **10**; $_{\pi}2_s$, $_{\sigma}2_a \rightarrow$ **11**). A potential way to distinguish between these possibilities would be to examine the rearrangement of the unhindered, maximally labeled[16] trans vinylcyclopropyl enol silane **14a**. At least three distinct pathways need to be considered for the rearrangement of **14a**: the orbital symmetry allowed process which would yield the cis ketone **15a** ($_{\pi}2_a$, $_{\sigma}2_s$) and the trans ketone **16a** ($_{\pi}2_s$, $_{\sigma}2_a$); a completely random stepwise (diradical) process which would give a mixture of the four possible hexahydroindanones **15** and **16**; and a diradical process involving an intermediate analogous to **22** in which



22



23, $n = 5, 6,$ or 7

the conformationally restricted[17] allyl radical adopts an equatorial position on the cyclohexane ring. If closure of **22** to a five-membered ring occurs before geometric isomerization of the allylic radical, a consideration of molecular models suggests that the preferred modes of closure of **22** would lead stereoselectively to ketones **15a** and **16a**, i.e., the products expected for the concerted reaction. Experimentally the rearrangement was carried out on the cis–trans mixture **14**. Since the rearrangement of the trans isomer of a cis–trans mixture is known to occur with greater facility,[18] the product distribution shown in Table I corresponds to ca. 30% conversion of starting material to products and should reflect the thermal behavior of the trans isomer **14a**. In practice, the major product observed in the rearrangement of **14**, trans ketone **16a**, supports either the first or third mechanistic possibility. These data, however, do not provide a basis for making an unambiguous distinction between these two pathways for the rearrangement of unhindered transoid vinylcyclopropanes.[19] It should be noted that preferential ring closure of diradical **22** to give the trans-fused product **16a** might be expected based on analogy to cationic olefin ring closures.[20]

The reaction conditions necessary to rearrange the oxygen-substituted vinylcyclopropanes **1** to **2** are comparable to those for simple vinylcyclopropane substrates and considerably more severe than the conditions necessary to rearrange the heteroatom-substituted derivatives shown in eq 2[4a] and 3.[6] In both of the latter cases the heteroatom is located on a carbon atom directly involved in the bond-making, bond-breaking process, and it may provide assistance in the rearrangement. For substrates of structure **1**, the oxygen atom is located at an sp^2-hybridized carbon atom in both the reactant and the product and it will have only a minimal effect on the net transformation.

In summary, the cyclopentanone annelation sequence shown in eq 1 provides a reasonable synthetic route to 2,3-disubstituted cyclopentanones such as **12b** and **12c**. Furthermore, the initial rearrangement products derived from enol silanes of general structure **9**, the cyclopentene enol derivatives **23**, can serve as regioselective precursors[21] to the *more* substituted enolate anion of ketones **12**.

Experimental Section

General. Melting points were determined on a Mel-Temp apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer Model 237B grating infrared spectrometer in carbon tetrachloride solution unless otherwise stated. NMR spectra were measured on a Varian Associates A-60 or a Perkin-Elmer R-12 spectrometer in carbon tetrachloride solution and chemical shifts are reported in parts per million downfield (δ) from internal Me_4Si. Gas chromatography analyses were performed on a Varian Aerograph 1200 using a 3% SE-30 on Varaport 30 column (10 ft × 1/16 in.). Combustion analyses were done by Chemalytics, Inc., Tempe, Ariz.

Cyclopropyl Ketones. Cyclopropyl methyl ketone[22] and 1-acetylbicyclo[4.1.0]heptane (**4b**)[11] were obtained as indicated.

6-Acetylbicyclo[3.1.0]hexane (3a). Using the general procedure of Jorgenson,[10] bicyclo[3.1.0]hexane-6-carboxylic acid[23] furnished a 92% yield of **3a**: bp 66–68° (7 mm) [lit.[24] bp 60–63° (10 mm)]; ir (CCl_4) 1700 cm^{-1} (C=O); NMR (CCl_4) δ 2.10 (s, 3, CH_3C=O) and 0.9–2.0 ppm (m, 9).

7-Acetylbicyclo[4.1.0]heptane (3b). Using the general procedure of Jorgenson,[10] bicyclo[4.1.0]heptane-7-carboxylic acid[25] furnished a 98% yield of **3b**: bp 39–40° (0.25 mm) [lit.[24] bp 83–86° (10 mm)]; ir (CCl_4) 1695 cm^{-1} (C=O); NMR (CCl_4) δ 2.10 (s, 3, CH_3C=O), and 1.0–2.0 ppm (m, 11).

8-Acetylbicyclo[5.1.0]octane (3c). Using the general procedure of Jorgenson,[10] bicyclo[5.1.0]octane-8-carboxylic acid[26] furnished a 90% yield of **3c**: bp 80–83° (2 mm); ir (CCl_4) 1695 cm^{-1} (C=O); NMR (CCl_4) δ 2.10 (s, 3, CH_3C=O), and 0.8–2.3 ppm (m, 13).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.93; H, 10.56.

Ethyl Bicyclo[4.1.0]heptan-7-yl Ketone. Using the general procedure of Jorgenson,[10] bicyclo[4.1.0]heptane-7-carboxylic acid[25] was treated with ethyllithium to furnish a 60% yield of product: bp 121–123° (29 mm); ir (CCl_4) 1670 cm^{-1} (C=O); NMR (CCl_4) δ 0.98 (t, 3, CH_3), 1.0–2.2 (m, 11) and 2.48 ppm (q, 2).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 79.23; H, 10.35.

1-Methyl-7-acetylbicyclo[4.1.0]heptane (18). Using the general procedure of Jorgenson,[10] 1-methylbicyclo[4.1.0]heptane-7-carboxylic acid[27] furnished a 100% yield of **18**: bp 50–54° (0.07 mm); ir (CCl_4) 1690 cm^{-1} (C=O); NMR (CCl_4) δ 2.14 (s, 3, CH_3C=O), 1.1–2.1 (m, 9), and 1.10 ppm (s, 3, CH_3).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 79.12; H, 10.61.

Distillation of **18** at 1.3 mm, bp 90–95°, yielded two new products that showed carbonyl absorptions at 1715 cm^{-1}. The NMR spectrum of this mixture indicated the presence of both two vinyl hydrogens (δ 4.44 and 4.60 ppm) and a singlet vinyl methyl group (δ 1.43). Redistillation, bp 58–60° (2.0 mm), gave a single substance tentatively assigned as 1-(1-methylcyclohexen-2-yl)propan-2-one on the basis of spectral data: ir (CCl_4) 1715 cm^{-1}; NMR (CCl_4) δ 1.0–2.3 (m, 10), 1.43 (s, 3), and 2.08 (s, 3). The initial rearrangement product is assigned structure **19** on the basis of the vinyl hydrogen absorptions.

1-Acetylbicyclo[3.1.0]hexane (4a). Using the general procedure of Corey,[11] acetylcyclopentene[28] furnished a 84% yield of **4a**: bp 95–96° (34 mm); ir (CCl_4) 1690 cm^{-1} (C=O); NMR (CCl_4) δ 0.8 (m, 1, cyclopropyl H), 1.2–2.0 (m, 7), and 1.99 ppm (s, 3, CH_3C=O).

Anal. Calcd for $C_8H_{12}O$: C, 77.36; H, 9.76. Found: C, 77.31; H, 9.73.

1-Acetylbicyclo[5.1.0]octane (4c). Using the procedure of Corey,[11] acetylcycloheptene[29] furnished a 90% yield of **4c**: bp 49–53° (0.6 mm); ir (CCl_4) 1680 cm^{-1} (C=O); NMR (CCl_4) δ 0.7 (m, 1, cyclopropyl H), 1.1–2.2 (m, 10), and 1.96 ppm (s, 3, CH_3C=O).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.77; H, 10.41.

Preparation of Enol Silanes. Method A. To a solution of chlorotrimethylsilane (0.045 mol) and triethylamine (0.07 mol) in dimethylformamide (20 ml) in a nitrogen atmosphere was added 0.03 mol of cyclopropyl alkyl ketone. The solution was heated under reflux for 20 hr, allowed to cool to room temperature, and then diluted with pentane (150 ml). The organic phase was separated, washed with cold 50% saturated sodium bicarbonate solution (150 ml), and dried ($MgSO_4$), the pentane was removed in vacuo, and the residue was distilled to give product enol silane.

Method B. A tetrahydrofuran solution of lithium diisopropylamide (0.015 mol) was prepared by adding diisopropylamine to *n*-butyllithium at −78°. The solution was stirred for 1 hr after the addition. The cyclopropyl alkyl ketone (0.013 mol) was then added dropwise by syringe to the amide solution and the resulting mixture was stirred for 3 hr. The resulting enolate was quenched with excess chlorotrimethylsilane (0.04 mol) and the mixture was stirred for 1 hr. The excess chloromethylsilane was removed in vacuo and the residue was extracted with pentane. The pentane was removed in vacuo and the residue was distilled to give product enol silane.

1-Trimethylsiloxy-1-cyclopropylethylene (7) was prepared by method A to give 65% of enol silane **7:** bp 74–76° (71 mm); ir (CCl_4) 1650 cm^{-1} (C=C); NMR (CCl_4) δ 0.17 (s, 9, $SiCH_3$), 0.50 (m, 5, cyclopropyl H), 3.76 (d, 1, J = 1 Hz), 4.07 (d, 1, J = 1 Hz).

Anal. Calcd for $C_8H_{16}OSi$: C, 61.48; H, 10.24. Found: C, 61.36; H, 10.38.

1-Trimethylsiloxy-1-(bicyclo[3.1.0]hexan-6-yl)ethylene (8a) was prepared by method A to give a 72% yield of enol silane **8a:** bp 82–83° (8 mm); ir 1650 cm^{-1} (C=C); NMR (CCl_4) δ 0.10 (s, 9, $SiCH_3$), 0.8–2.0 (m, 9), 3.78 (broad s, 1), and 3.86 ppm (broad s, 1).

Anal. Calcd for $C_{11}H_{20}OSi$: C, 67.28; H, 10.27. Found: C, 67.07; H, 10.22.

1-Trimethylsiloxy-1-(bicyclo[4.1.0]heptan-7-yl)ethylene (8b) was prepared by method A to give a 67% yield of enol silane **8b:** bp 42–43° (0.1 mm); ir (CCl_4) 1645 cm^{-1} (C=C); NMR (CCl_4) δ 0.15 (s, 9, $SiCH_3$), 0.9–2.0 (m, 11), 3.84 (d, 1, J = 1 Hz), and 3.92 ppm (d, 1, J = 1 Hz).

Anal. Calcd for $C_{12}H_{22}OSi$: C, 68.48; H, 10.55. Found: C, 68.78; H, 10.84.

1-Trimethylsiloxy-1-(bicyclo[5.1.0]octan-8-yl)ethylene (8c) was prepared by method B to give a 91% yield of enol silane **8c:** bp 84–94° (0.8 mm); ir (CCl_4) 1640 cm^{-1} (C=C); NMR (CCl_4) δ 0.15 (s, 9, $SiCH_3$), 0.7–2.3 (m, 13), 3.81 (broad s, 1), and 3.92 ppm (broad s, 1).

Anal. Calcd for $C_{13}H_{24}OSi$: C, 69.57; H, 10.77. Found: C, 69.56; H, 11.07.

1-Trimethylsiloxy-1-(bicyclo[3.1.0]hexan-1-yl)ethylene (9a) was prepared by method B to give a 78% yield of enol silane **9a:** bp 42–44° (0.7 mm); ir (CCl_4) 1650 cm^{-1} (C=C); NMR (CCl_4) δ 0.17 (s, 9, $SiCH_3$), 0.45 (m, 1, cyclopropyl H), 1.4–2.0 (m, 7), 3.9 (broad s, 1), and 4.02 ppm (broad s, 1).

Anal. Calcd for $C_{11}H_{20}OSi$: C, 67.28; H, 10.26. Found: C, 66.96; H, 10.47.

1-Trimethylsiloxy-1-(bicyclo[4.1.0]heptan-1-yl)ethylene (9b) was prepared by method B to give 80% yield of enol silane **9b:** bp 75–85° (0.1 mm); ir (CCl_4) 1640 cm^{-1} (C=C); NMR (CCl_4) δ 0.18 (s, 9, $SiCH_3$), 0.6 (m, 1, cyclopropyl H), 0.7–2.4 (m, 10), 3.9 (broad s, 1), and 4.3 ppm (broad s, 1).

Anal. Calcd for $C_{12}H_{22}OSi$: C, 68.51; H, 10.47. Found: C, 68.50; H, 10.36.

1-Trimethylsiloxy-1-(bicyclo[5.1.0]octan-1-yl)ethylene (9c) was prepared by method B to give a 80% yield of enol silane **9c:** bp 55–60° (0.3 mm); ir (CCl_4) 1620 cm^{-1} (C=C); NMR (CCl_4) δ 0.17 (s, 9, $SiCH_3$), 0.9–2.6 (m, 10), 4.0 (broad s, 1).

Anal. Calcd for $C_{13}H_{24}OSi$: C, 69.57; H, 10.77. Found: C, 69.31; H, 11.07.

1-Trimethylsiloxy-1-(bicyclo[4.1.0]heptan-7-yl)propylene (14) was prepared by method A to give a 90% yield of enol silanes **14:** bp 99–106° (6 mm); ir (CCl_4) 1668 cm^{-1} (C=C); NMR (neat) δ 0.10 (s, 3, $SiCH_3$), 0.18 (s, 6, $SiCH_3$), 0.7–2.5 (m, 11), 1.43 (d, 2.1, J = 7 Hz), 1.61 (d, 0.9, J = 7 Hz), 4.44 (q, 0.7, J = 7 Hz), and 4.50 ppm (q, 0.3, J = 7 Hz). VPC analysis (3% SE-30, 130°) indicated a 67:33 mixture.

Anal. Calcd for $C_{13}H_{24}OSi$: C, 69.58; H, 10.78. Found: C, 69.98; H, 10.42.

Pyrolysis of Trimethylsilyl Enol Silanes. Method A. The appropriate enol silane (45 mg) in benzene (50 μl) was placed in a base-washed ampoule and then degassed and sealed under high vacuum. The tubes were heated in a furnace at 360° (2 or 3 hr) or at 400° (0.5 or 1 hr) depending on the sample. After cooling the tubes were opened and a solution of 0.04 *N* HCl (50 μl) in methanol was added to the pyrolysis products. This mixture was allowed to stand for 2 hr. An internal standard, cyclohexanone (25 μl), was added and mixture was analyzed on a Varian Aerograph Model 1200 gas chromatograph using 3% SE-30 (10 ft × 1/16 in.) at 100 and 125°, by comparison of retention times of products with known samples.

Method B. The appropriate enol silane (45 or 250 mg), an internal standard, decane (10 or 100 μl), and triethylamine (10 or 100 μl) in benzene (50 or 150 μl) were placed in a base-washed ampoule and then degassed and sealed under high vacuum. Pyrolyses were carried out as indicated in method A. The cooled samples were treated with 4 ml of 0.04 *N* HCl in THF for 10 min. Water (10 ml) and pentane (10 ml) were added and the organic phase was analyzed as described above.

The enol silanes examined by method A were **7, 8a, 8b, 9a,** and **14** and those by method B were **8c, 9b,** and **9c.** The products obtained are given in Table I and these results represent data from three or more individual runs. In general the final reaction mixtures contained ca. 70% products and 30% recovered cyclopropyl ketone. Material balances of 80–95% were obtained for method B; for method A material balances were 50–70%.

Rearrangement products were prepared as indicated: **10a,**[30] **10b,**[31] **10c,**[32] **11a,**[30] **11b,**[31] **12a,**[33] **12c,**[34] **and 13a.**[22]

***cis*-Hexahydroindan-1-one (12b).** A solution of 1-indanone (5.1 g, 0.04 mol) in ethanol (200 ml) containing 5% Rh/C (0.5 g) was hydrogenated at room temperature for 24 hr at 1750 psi. After filtering the solvent was evaporated in vacuo and the residue was distilled to give 2.8 g (52%) of 1-hexahydroindanol, bp 52–55° (0.04 mm). This alcohol was oxidized by the method of Brown[35] to give a 90% yield of **12b,** bp 41–44° (0.5 mm) [lit.[36] bp 82–87° (10 mm)].

1-(Cyclohexen-3-yl)propan-2-one (13b) was prepared from 3-bromocyclohexene[37] and ethyl acetoacetate by the method of Van Tamelen[38] to give a 33% yield of **13b:** bp 98–103° (26 mm); semicarbazone mp 171–173° (lit.[39] mp 170–171°); ir (CCl_4) 1720 cm^{-1}; NMR (CCl_4) δ 0.9–2.1 (m, 7), 2.05 (s, 3), 2.42 (m, 2), and 5.54 ppm (m, 2).

1-(Cyclohepten-3-yl)propan-2-one (13c) was prepared as described for **13b** to give a 30% yield of **13c:** bp 90–95° (18 mm); ir (CCl_4) 1715 cm^{-1}; NMR (CCl_4) δ 0.95–2.0 (m, 9), 2.00 (s, 3), 2.40 (m, 2), and 5.50 ppm (m, 2).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.84; H, 10.74.

***syn*-1-Methyl-*cis*-hydroindan-2-one (15a).** *cis*-Hydroindan-2-one (**10b,** 0.93 g, 6.8 mmol) was added dropwise at 0° to a THF solution (5 ml) of lithium diisopropylamide, prepared from methyllithium (8.8 mmol) and diisopropylamine (1.0 g, 10 mmol). After stirring for 1 hr at 0°, excess methyl iodide (6.9 g, 48 mmol) was added and the mixture was allowed to warm to room temperature. Water was added and the mixture was extracted with ether. The organic phase was dried ($MgSO_4$) and evaporated in vacuo and the residue was distilled to give 0.88 g (88%) of **15a:** bp 55–57° (0.6 mm); ir (CCl_4) 1747 cm^{-1}; NMR (CCl_4) δ 0.99 (d, 3, J = 7 Hz) and 0.9–2.7 ppm (m, 13).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.77, H, 10.62.

Epimerization of 15a. A sample of **15a** (19 mg) was allowed to stand in methanol (4 ml) containing a trace of sodium methoxide. After 4 hr the NMR spectrum showed two methyl group doublets at δ 0.99 (**15a**) and 0.94 (**15b**); VPC analysis indicated a ratio of **15a: 15b** of 4.4:1. This ratio was the same after 20 hr.

***anti*-1-Methyl-*trans*-hydroindan-2-one (16b).** Using the procedure described above for **15a,** *trans*-hydroindan-2-one (**11b,** 0.86 g, 6.2 mmol) gave in 95% yield a mixture of recovered **11b** (15%), monoalkylated product **16b** (80%), and 5% of an unidentified substance. Pure **16b** was obtained by preparative VPC: ir (CCl_4) 1740 cm^{-1}; NMR (CCl_4) δ 0.92 (d, 3, J = 7 Hz) and 0.8–2.5 ppm (m, 13).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.82; H, 10.65.

Epimerization of 16b. A sample of **16b** (20 mg) was treated as described above for **15a.** After 1 hr the NMR spectrum showed two methyl doublets at δ 0.92 (**16b**) and 1.00 ppm (**16a**); after 20 hr VPC analysis indicated a ratio of **16a:16b** of 11:1.

Control Experiments. Treatment of either **15a** or **16b** with methanol-*O*-*d* containing HCl gas for 16 hr did not result in any detectable incorporation of deuterium as judged by NMR (doublet methyl signals remained unchanged).

Registry No.—**3a**, 10330-37-7; **3b**, 10330-36-6; **3c**, 53927-14-3; **4a**, 29773-67-9; **4b**, 2862-90-0; **4c**, 53927-15-4; **7**, 42161-96-6; **8a**, 53927-16-5; **8b**, 53927-17-6; **8c**, 53927-18-7; **9a**, 53927-19-8; **9b**, 53927-20-1; **9c**, 53927-21-2; **10b**, 5689-04-3; **11b**, 16484-17-6; **12b**, 2826-65-5; **13b**, 18955-93-6; **13b** semicarbazone, 53927-22-3; **14a**, 53927-23-4; **14b**, 53927-24-5; **15a**, 28436-04-6; **15b**, 28436-03-5; **16a**, 53927-25-6; **16b**, 53927-26-7; **18**, 53927-27-8; **19**, 53927-28-9; cyclopropyl methyl ketone, 765-43-5; ethyl bicyclo[4.1.0]heptan-7-yl ketone, 53927-29-0; 1-(1-methylcylclohexen-2-yl)propan-2-one, 53927-30-3; chlorotrimethylsilane, 75-77-4; 1-indanone, 83-33-0; 1-hexahydroindanol, 53927-31-4.

References and Notes

(1) Financial support of this research by the Robert A. Welch Foundation is gratefully acknowledged.
(2) R. A. Ellison, *Synthesis*, 397 (1973); P. T. Lansbury, *Acc. Chem. Res.*, **5**, 311 (1972); R. F. Romanet and R. H. Schlessinger, *J. Am. Chem. Soc.*, **96**, 3701 (1974); S. Danishefsky, J. Dynak, E. Hatch, and M. Yamamato, ibid., **96**, 1256 (1974); W. S. Johnson, M. B. Gravestock, R. J. Parry, R. F. Meyers, T. A. Bryson, and D. H. Miles, ibid., **93**, 4330 (1971); J. E. McMurry and T. E. Glass, *Tetrahedron Lett.*, 2575 (1971); E. Wenkert, R. A. Muller, E. J. Reardon, Jr., S. S. Suthe, D. J. Scharf, and G. Tori, *J. Am. Chem. Soc.*, **92**, 7428 (1970); A. I. Meyers and N. Nazarenko, *J. Org. Chem.*, **38**, 175 (1973).
(3) P. L. Fuchs, *J. Am. Chem. Soc.*, **96**, 1607 (1974); J. P. Marino and W. B. Mesbergen, ibid., **96**, 4050 (1974); R. Noyori, K. Yooyama, and Y. Hayakawa, ibid., **95**, 2722 (1973); R. Noyori, K. Yokoyama, S. Makino, and Y. Hayakawa, ibid., **94**, 1772 (1972).
(4) (a) E. J. Corey and S. W. Walinsky, *J. Am. Chem. Soc.*, **94**, 8932 (1972); (b) T. Hiyama, M. Tsakanaka, and H. Nozaki, ibid., **96**, 3713 (1974); (c) H. C. Brown, *Acc. Chem. Res.*, **2**, 65 (1969).
(5) G. Buchi and B. Egger, *J. Org. Chem.*, **36**, 2021 (1971); G. Buchi, U. Hochstrasser, and W. Pawlak, ibid., **38**, 4348 (1973).
(6) B. M. Trost and M. J. Bogdanowicz, *J. Am. Chem. Soc.*, **95**, 5311 (1973); B. M. Trost, *Acc. Chem. Res.*, **7**, 85 (1974).
(7) C. D. Gutsche and D. Redmore, "Advances in Alicyclic Chemistry", Supplement 1, Academic Press, New York, N.Y., 1968, Chapter 9; for a comprehensive bibliography, see ref 18 in Trost and Bogdanowicz.[6]
(8) H. O. House, L. J. Czuba, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, **34**, 2324 (1969).
(9) Enolization of cyclopropyl alkyl ketones *away* from the three-membered ring is well established: H. W. Amburn, K. C. Kauffman, and H. Schecter, *J. Am. Chem. Soc.*, **91**, 530 (1969).
(10) M. K. Jorgenson, *Org. React.*, **18**, 1 (1970).
(11) E. J. Corey and M. Chaykousky, *J. Am. Chem. Soc.*, **87**, 1353 (1965).
(12) Similiar stereoselectivity has been observed in the alkylation of trans γ-butyrolactones: P. A. Grieco and M. Miyashita, *J. Org. Chem.*, **39**, 120 (1974).
(13) R. M. Roberts, R. G. Landolt, R. N. Greene, and E. W. Heyer, *J. Am. Chem. Soc.*, **89**, 1404 (1967); D. L. Garin, *J. Org. Chem.*, **35**, 2830 (1970).
(14) R. G. Bergman and W. L. Carter, *J. Am. Chem. Soc.*, **91**, 7411 (1969).
(15) P. H. Mazzocchi and H. J. Tamburin, *J. Am. Chem. Soc.*, **92**, 7220 (1970), and references cited therein.
(16) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry", Verlag Chemie, Weinheim/Bergstr., Germany, 1970, pp 121–122.
(17) P. D. Bartlett, L. K. Montgomer, and B. Seidel, *J. Am. Chem. Soc.*, **86**, 616 (1964); C. Walling and W. Thaler, ibid., **83**, 3877 (1961); R. Sustmann and H. Trill, ibid., **96**, 4343 (1974).
(18) A. D. Ketley, A. J. Berlin, and L. P. Fisher, *J. Org. Chem.*, **31**, 2648 (1966).
(19) Experimental data to support a diradical mechanism for the rearrangement of more hindered cisoid vinylcyclopropane substrates have been advanced.[15]
(20) K. E. Harding, *Bioorg. Chem.*, **2**, 248 (1973).
(21) Cf. ref 6 and 8 and G. Stork and P. F. Hudrlik, *J. Am. Chem. Soc.*, **90**, 4462, 4464 (1968); H. O. House, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, **36**, 2361 (1971).
(22) Commercially available from Aldrich Chemical Co.
(23) R. T. LaLonde and M. A. Tobias, *J. Am. Chem. Soc.*, **86**, 4068 (1964).
(24) J. Novak, J. Ratusky, V. Sneberg, and F. Šorm, *Chem. Listy*, **51**, 479 (1951); *Chem. Abstr.*, **51**, 10508e (1957).
(25) J. A. Berson and G. S. Hand, *J. Am. Chem. Soc.*, **86**, 1978 (1964).
(26) W. Kirmse and K. H. Pook, *Chem. Ber.*, **98**, 4022 (1969).
(27) R. Jacquier and P. Besinet, *Bull. Soc. Chim. Fr.*, 749 (1956).
(28) P. F. Casals, *Bull. Soc. Chim. Fr.*, 253 (1963).
(29) J. Hanuise and R. R. Smolders, *Bull. Soc. Chim. Fr.*, 2139 (1967).
(30) S. Dev, *J. Indian Chem. Soc.*, **30**, 815 (1953).
(31) A. Kandiah, *J. Chem. Soc.*, 922 (1931).
(32) A. M. Islam and R. A. Raphael, *J. Chem. Soc.*, 3151 (1955).
(33) A. C. Cope and W. R. Schmitz, *J. Am. Chem. Soc.*, **72**, 3056 (1950); A. C. Cope, S. W. Fenton, and C. F. Spencer, ibid., **74**, 5884 (1952); N. Jones and H. T. Taylor, *J. Chem. Soc.*, 4017 (1959).
(34) N. Jones and H. T. Taylor, *J. Chem. Soc.*, 1342 (1961); G. Buchi, W. D. Maclead, Jr., and J. Padilla, *J. Am. Chem. Soc.*, **86**, 4438 (1964).
(35) H. C. Brown and C. P. Gary, *J. Am. Chem. Soc.*, **83**, 2952 (1961).
(36) H. O. House and G. H. Rasmusson, *J. Org. Chem.*, **28**, 31 (1963).
(37) H. J/ Dauben, Jr., and L. L. McCoy, *J. Am. Chem. Soc.*, **81**, 4863 (1959).
(38) G. D. Zuidema, E. van Tamelen, and G. Van Zyl, "Organic Syntheses", Collect. Vol. IV, Wiley, New York, N.Y., 1963, p 10.
(39) A. W. Burgstahler and I. C. Nardin, *J. Am. Chem. Soc.*, **83**, 198 (1961).

A Study of the Enamino Ketone Variant of the Robinson Annelation

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The mechanism of the enamino ketone variant of the Robinson annelation has been clarified. Isomeric enamino ketones **10** and **11** were prepared by methylation of the cross- and fully conjugated enolate anions of cyclic enamino ketone **5**, and both isomers gave the same mixture of dimethyl-3,4,8,8a-tetrahydro-1,6(2*H*,7*H*)-naphthalenediones on reaction with methyl vinyl ketone. The annelation products are derived from a common trione intermediate, **13**. Efforts to alter the mechanistic course of the annelation reaction were unfruitful.

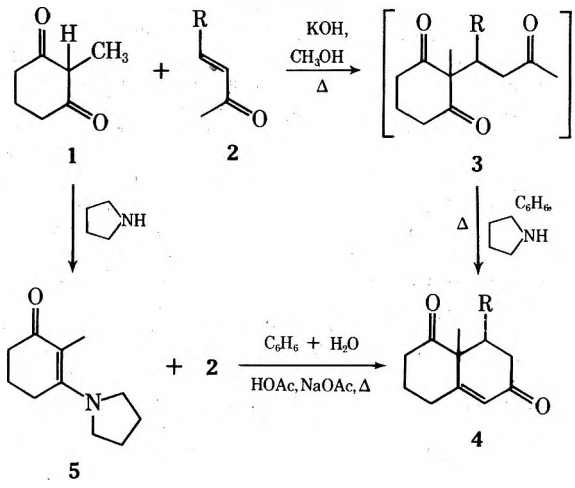
An important class of synthetic intermediates related to the Wieland–Miescher ketone[1] (**4**, R = H) can be prepared by Robinson annelations of 2-methylcyclohexane-1,3-dione with unsaturated ketones like **2**. In the procedure described by Newman and Ramachandran[2] a base-catalyzed Michael reaction generates the triketone **3**, which then undergoes aldol cyclization on treatment with pyrrolidine in benzene. A variant of this approach, developed by Coates and Shaw,[3] uses the monopyrrolidine enamine **5** derived from the 1,3-diketone reactant and employs a heterogeneous reaction medium incorporating a buffered acetic acid catalyst (Scheme I).

Coates and Shaw found that reaction of 3-penten-2-one (**2**, R = CH_3) with **5** gave predominantly the trans diketone **4** (R = CH_3) accompanied by small amounts of the cis isomer. However, by using a more polar solvent such as dimethylformamide or dimethyl sulfoxide, they were able to obtain higher proportions of the cis isomer (e.g., 1:1).

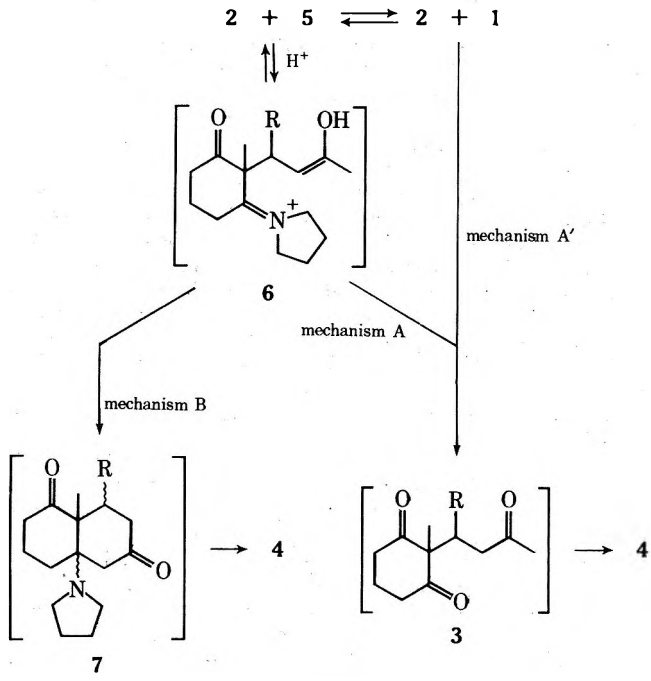
Two distinct mechanisms for this modified annelation procedure can be conceived (Scheme II).

An initial acid-catalyzed Michael addition should generate an intermediate (**6**), which could then be hydrolyzed to **3** followed by pyrrolidine-induced aldol cyclization (mechanism A). Other mechanisms leading to intermediate **3** can also be envisaged (e.g., hydrolysis of **5** to **1** followed by conventional annelation, as in mechanism A′), but for the purposes of this discussion they need not be distinguished from mechanism A. Alternatively, the immonium intermediate **6** could undergo aldol-like cyclization to a nitrogen-containing precursor (**7**) of diketone **4** (mechanism B), as

Scheme I



Scheme II

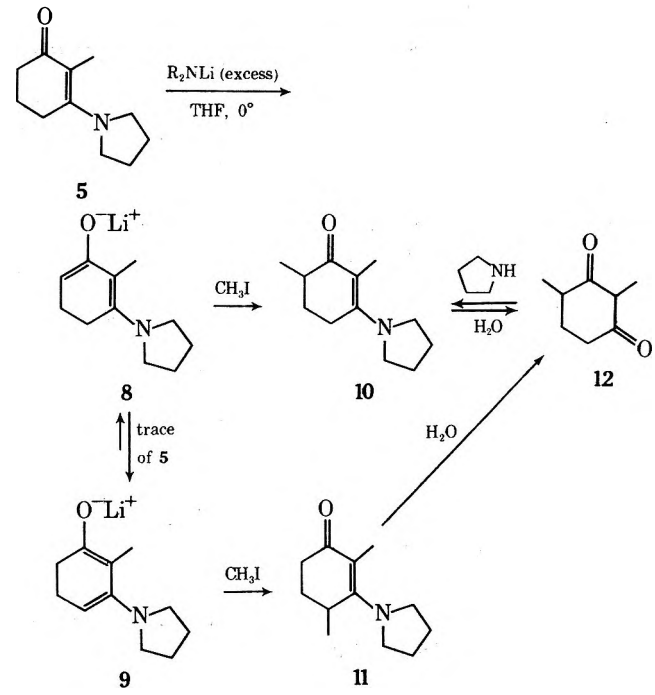


proposed by Stork et al.[10] for the reaction of the pyrrolidine enamine of cyclohexanone with methyl vinyl ketone. In mechanism A the product stereochemistry, when R = CH_3, is determined in the aldol cyclization step (i.e., by the relative rates of reaction at each of the two cyclic carbonyl groups). In mechanism B, however, the configuration of product (4) is determined in the Michael addition step—provided, of course, that the immonium function in 6 dominates the carbonyl group in its reactivity. In either case a solvent effect is needed to explain the results reported by Coates and Shaw.

We have prepared a pair of isomeric methyl homologs of **5**, which not only permit us to distinguish the mechanisms described above, but also offer—in the event mechanism B is operating—the possibility of unprecedented control in synthesizing derivatives of the Wieland–Miescher ketone.

The ability to conduct controlled alkylations of enamino ketone **5** requires selective formation of either the cross-conjugated (8) or fully conjugated (9) conjugate bases of the substrate. Since lithium isopropylcyclohexylamide (Rathke's base[4]) has been effective in preparing the kinetically favored cross-conjugated bases of cyclohexenones[5]

Scheme III



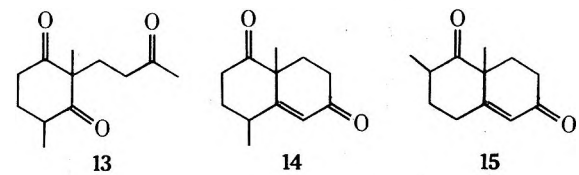
and since Stork[6] has used a similar method to generate the conjugate bases of enol ether derivatives of **1**, our initial efforts were in this direction (Scheme III).

If the amide base is maintained in excess during reaction with **5**, the cross-conjugated intermediate **8** is formed exclusively, and on methylation gives the dimethyl enamino ketone **10**. Alternatively, the presence of a slight excess of **5** during the initial stage allows equilibration of bases **8** and **9**, with the latter predominating. Methylation of **9** then gives the isomeric product **11**.

A similar γ-alkylation of an enamino ketone conjugate base was recently reported by Yoshimoto et al.[7,12] However, these workers used *n*-butyllithium as the initiating base, and our efforts to repeat this aspect of their work failed.

It is not easy to distinguish **10** and **11** by spectroscopic means (see the data in the Experimental Section). Both **10** and **11** yielded the same dimethylcyclohexane-1,3-dione (presumably **12**) on hydrolysis. Reaction of **12** with pyrrolidine was expected to take place at the less hindered carbonyl group, and the product of this reaction was assigned structure **10**.

The use of isomers **10** and **11** to distinguish mechanism A and B is straightforward. Reaction of **10** and **11** with methyl vinyl ketone (**2**, R = H) by mechanism A should yield the same mixture of Wieland–Miescher ketone derivatives **14** and **15**, since the triketone **13** is a common intermediate.

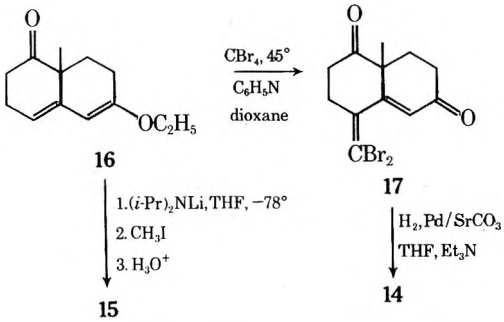


On the other hand, mechanism B predicts that **10** will be selectively transformed to **15** and **11** to **14**.

When these reactions were effected under the conditions specified by Coates and Shaw, both **10** and **11** gave the same 1:5 mixture of **14** and **15**. In the case of the reaction of methyl vinyl ketone with **11**, a small amount of another product, tentatively identified as the triketone **13** by ir and

mass spectrometry, was also obtained. Assignment of structures **14** and **15** to these products was achieved by direct comparison of these isomers with authentic samples prepared by unambiguous syntheses.

Compound **14** was prepared by reaction of the dienol ether **16**[8] with carbon tetrabromide in pyridine, followed by hydrogenation of the resulting dibromomethylene derivative **17** using a 2% $Pd/SrCO_3$ catalyst. This synthetic method is based on the work of Liisberg et al.[9] in the preparation of 6-methyl-Δ^4-3-keto steroids.



Methylation of **16**, using lithium diisopropylamide and methyl iodide, afforded **15** after hydrolysis of the intermediate methylated dienol ether.

The experiments described here clearly show that this annelation proceeds by mechanism A under the reaction conditions defined by Coates and Shaw. Nevertheless, it would be very useful to develop conditions for effecting an equivalent annelation by mechanism B, since the regioselective control provided by such a pathway is desirable. However, efforts to effect an acid-catalyzed reaction of enamino ketone **5** with methyl vinyl ketone, in a variety of anhydrous solvents ranging in polarity from benzene to hexamethylphosphoric triamide, were unsuccessful. Even with elevated temperatures and prolonged reaction times, very little reaction occurred, and the amount of Wieland–Miescher ketone in the neutral products was always very small.

Experimental Section

Preparation of 2,6-Dimethyl-3-(1-pyrrolidyl)-2-cyclohexen-1-one (10). A. To a chilled (0°) solution of 0.31 ml (2.2 mmol) of diisopropylamine in 1 ml of dry tetrahydrofuran (THF) under dry nitrogen was added 1.0 ml of a 2.15 *M* solution of *n*-butyllithium in hexane. To the resulting solution of lithium diisopropylamide (LDIA) was added a solution of 358 mg (2.0 mmol) of **5** (prepared by the method of Coates and Shaw[3] and recrystallized from ether, mp 37–39°) in 1 ml of THF. This enolate solution was stirred at 0° for 30 min, following which 0.15 ml (2.4 mmol) of methyl iodide was added. The resulting mixture was warmed to room temperature, stirred for 15 min, and then concentrated under reduced pressure. An ethyl acetate solution of the residue was washed with water and brine, dried (Na_2SO_4), and evaporated under reduced pressure to give 351 mg (91%) of **10** as a light brown oil which crystallized when chilled. Several recrystallizations of **10** from ether gave colorless, deliquescent crystals: mp 27–35°; ir (neat) 1540, 1605 cm^{-1}; NMR ($CDCl_3$) δ 1.04 (d, J = 6.5 Hz, 3), 1.2–2.3 (m, 7), 1.86 (s, 3), 2.50 (br t, 2), 3.45 (m, 4); uv max (95% EtOH) 317 nm (ϵ 26,300)

Anal.[11] Calcd for $C_{12}H_{19}NO$: C, 74.57; H, 9.91; N, 7.25. Found: C, 74.66; H, 10.01; N, 7.29.

B. A compound having the same spectroscopic properties as **10** was produced by the reaction of pyrrolidine with dione **12**. A solution of 65 mg of **12** (produced by hydrolysis of 97 mg of **10** or **11** in 5% HCl at 100° for 15 min) in 3 ml of benzene and 0.075 ml of pyrrolidine was refluxed through a Dean-Stark trap for 75 min and then concentrated under reduced pressure. An NMR spectrum of the crude product was superimposable with that of **10** produced by the methylation of **5**.

Preparation of 2,4-Dimethyl-3-(1-pyrrolidyl)-2-cyclohexen-1-one (11). To a solution of 4.6 mmol of LDIA in 2.5 ml of THF under nitrogen at 0° was added a solution of 895 mg (5.0 mmol, 8.7% excess) of **5** and 2.5 ml of dry hexamethylphosphoric triamide in 2.5 ml of THF. The resulting enolate solution was stirred at room temperature for 21 hr and then at 40° for 3 hr. After this solution was cooled to 0°, 0.35 ml (5.6 mmol) of methyl iodide was added, and the mixture was allowed to return to room temperature for 1.5 hr. Work-up as described for the preparation of **10** gave 986 mg of yellow oil. Column chromatography (silica gel, 1:10 methanol–ether) of 748 mg of this oil gave 403 mg (63%) of **11**. Several recrystallizations from ether gave colorless, deliquescent crystals: mp 27–35°; ir (neat) 1540, 1605 cm^{-1}; NMR ($CDCl_3$) δ 1.20 (d, J = 7 Hz, 3), 1.5–2.2 (m, 6), 1.91 (s, 3), 2.36 (br t, 2), 2.55 (m, 1), 3.56 (m, 4); uv max (95% EtOH) 323 nm (ϵ 26,300).

Anal. Calcd for $C_{12}H_{19}NO$: C, 74.57; H, 9.91; N, 7.25. Found: C, 74.56; H, 9.95; N, 7.18.

Preparation of 6-Ethoxy-8a-methyl-3,7,8,8a-tetrahydro-1(2*H*)-naphthalenone (16). The procedure of Boyce and Whitehurst[8] was modified to give better yields. A solution consisting of 35 ml of benzene, 9 ml (54 mmol) of distilled triethyl orthoformate, 15 mg of *p*-toluenesulfonic acid, and 8.9 g (50 mmol) of Wieland–Miescher ketone **4**, R = H, was stirred under nitrogen at room temperature for 4 hr. The reaction mixture was neutralized with three drops of triethylamine, diluted with 35 ml of ether, and extracted successively with 15 ml of 10% $NaHCO_3$, 20 ml of water, and 20 ml of brine. After being dried over Na_2SO_4, the solution was evaporated in vacuo to give a yellow oil which could be used without further purification.

Preparation of 4-Dibromomethylene-8a-methyl-3,4,8,8a-tetrahydro-1,6(2*H*,7*H*)-naphthalenedione (17). A solution containing 618 mg (3.0 mmol) of dienol ether **16**, 2.00 g (6.0 mmol) of carbon tetrabromide, 3 ml of pyridine, and 3 ml of dioxane was maintained at room temperature under nitrogen for 24 hr and then heated at 45° for 24 hr. The resulting dark solution was filtered, concentrated under reduced pressure, acidified, and extracted with ethyl acetate. The organic extract was washed successively with 6 *N* HCl, 10% $NaHCO_3$, and brine before being dried over Na_2SO_4. Evaporation of the solvents in vacuo left 954 mg of a brown semisolid which was chromatographed (silica gel, ether) to yield 514 mg (50%) of brown **17**. Several recrystallizations from methylene chloride–ether gave white needles: mp 85–86°; ir (KBr) 1565, 1610, 1665, 1720 cm^{-1}; NMR ($CDCl_3$) δ 1.36 (s, 3), 1.9–2.8 (m, 8), 6.25 (s, 1); uv max (95% EtOH) 260 nm (shoulder ϵ 5700), 287 (7600),

Anal. Calcd for $C_{12}H_{12}Br_2O_2$: C, 41.41; H, 3.48. Found: C, 41.44; H, 3.38.

Preparation of 4,8a-Dimethyl-3,4,8,8a-tetrahydro-1,6-(2*H*,7*H*)-naphthalenedione (14). To a suspension of 800 mg of 2% $Pd/SrCO_3$ catalyst (saturated with hydrogen) in 6 ml of dry THF was added a solution of 1.740 g (5.0 mmol) of **17** and 1.4 ml (10 mmol) of triethylamine in 8 ml of THF. The mixture was stirred vigorously and allowed to absorb 376 ml (15.0 mmol) of hydrogen at atmospheric pressure. After filtration, the catalyst was washed well with THF and the filtrate was concentrated. An ether solution of the residue was extracted with water and brine, dried (Na_2SO_4), and evaporated to give 987 mg of a yellow oil. Column chromatography (silica gel, 30% ethyl acetate–hexane) gave 312 mg (32%) of light yellow **14** as an epimeric mixture, from which the more stable equatorial methyl epimer could be isolated after equilibration of the product in a CCl_4 solution of HCl. Recrystallization from ether–petroleum ether gave white needles: mp 28–34°; ir (KBr) 1605, 1665, 1710 cm^{-1}; NMR (CCl_4) δ 1.18 (d, J = 6.5 Hz, 3), 1.39 (s, 3), 1.5–2.9 (m, 9), 5.60 (d, J = 2 Hz, 1).

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.83; H, 8.31.

Preparation of 2,8a-Dimethyl-3,4,8,8a-tetrahydro-1,6-(2*H*,7*H*)-naphthalenedione (15). To a solution of 0.50 mmol of LDIA in 0.5 ml of THF under nitrogen at −78° was added a solution of 103 mg (0.50 mmol) of dienol ether **16** in 0.7 ml of THF. The resulting solution was stirred at −78° for 20 min and then treated with 0.035 ml (0.60 mmol) of methyl iodide. This solution was stirred at −78° for 10 min and at room temperature for 30 min and finally diluted with water and ether. The organic phase was washed successively with 5% HCl, water, and brine, giving 103 mg of methylated dienol ether after evaporation of the solvent in vacuo. This crude product was hydrolyzed for 3 hr at room temperature in a solution containing 1 ml of THF, 1 drop of 6 *N* HCl, and several drops of water. Work-up as usual gave 83 mg (87%) of **15** which, after purification by GLC (10-ft 4% QF-1, 200°), was obtained as a yellow oil: ir (neat) 1615, 1670, 1710 cm^{-1}; NMR (CCl_4) δ 1.02 (d, J = 6.5 Hz, 3), 1.41 (s, 3), 1.5–3.0 (m, 9) 5.61 (m, 1).

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 75.04; H, 8.40.

Reaction of 10 with Methyl Vinyl Ketone. To a solution consisting of 0.13 ml of water, 0.13 ml of acetic acid, and 62 mg of sodium acetate was added 0.100 ml of methyl vinyl ketone and 215 mg (1.11 mmol) of **10** in 1 ml of benzene. The mixture was refluxed under nitrogen for 4 hr, cooled, diluted with benzene, and extracted with 5% HCl. The organic phase was washed successively with water, 10% $NaHCO_3$, and brine, dried (Na_2SO_4), and evaporated in vacuo to give 179 mg of a yellow oil. GLC analysis of (5-ft 4% QF-1, 175°) of this oil showed **14** and **15** in a ratio of about 1:5 by comparison of the retention times with those of authentic samples.

Reaction of 11 with Methyl Vinyl Ketone. To the same aqueous acetic acid solution used above was added 0.070 ml of methyl vinyl ketone and 193 mg (1.0 mmol) of **11** in 1 ml of benzene. The mixture was refluxed for 4.5 hr and worked up as above to give 142 mg of a yellow oil. GLC analysis of this oil showed **14** and **15** in a ratio of about 1:5, and a small amount of a third component which was isolated by preparative GLC (10-ft 4% QF-1, 190°) and tentatively identified as the trione **13** by its ir [(CCl_4) 1695, 1720 cm^{-1}] and mass spectra (mol wt 210).

Acknowledgment. We thank the National Institutes of Health for their support of this work (Grant 2 R01 AM 10849-08) and Mrs. Lorraine Guile for her assistance in obtaining mass spectra.

Registry No.—**2** (R = H), 78-94-4; **4** (R = H), 42576-97-6; **5**, 53940-63-9; **10**, 53940-64-0; **11**, 53940-65-1; **12**, 20990-14-1; *cis*-**14**, 53940-66-2; *trans*-**14**, 53940-67-3; **15**, 53940-68-4; **16**, 53940-69-5; **17**, 53940-70-8; pyrrolidine, 123-75-1; carbon tetrabromide, 558-13-4.

References and Notes

(1) P. Wieland and K. Miescher, *Helv. Chim. Acta*, **33**, 2215 (1950).
(2) S. Ramachandran and M. S. Newman, "Organic Syntheses," Collect. Vol. V, Wiley, New York, N.Y., 1973, p 486.
(3) R. M. Coates and J. E. Shaw, *J. Am. Chem. Soc.*, **92**, 5657 (1970).
(4) M. W. Rathke and A. Lindert, *J. Am. Chem. Soc.*, **93**, 2318 (1971).
(5) R. A. Lee, C. McAndrews, K. M. Patel, and W. Reusch, *Tetrahedron Lett.*, 965 (1973).
(6) G. Stork and R. L. Danheiser, *J. Org. Chem.*, **38**, 1775 (1973).
(7) M. Yoshimoto, N. Ishida, and T. Hiraoka, *Tetrahedron Lett.*, 39 (1973).
(8) B. C. Boyce and J. S. Whitehurst, *J. Chem. Soc.*, 2680 (1960).
(9) S. Liisberg, W. O. Godtfredsen, and S. Vangedal, *Tetrahedron*, **9**, 149 (1960).
(10) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963).
(11) Microanalyses are by Spang Microanalytical Laboratory, Ann Arbor, Mich.
(12) Note Added in Proof. The general synthetic usefulness of γ-alkylations of enamino ketone conjugate bases has been convincingly demonstrated very recently by T. A. Bryson and R. B. Gammill, *Tetrahedron Lett.* 3963 (1974).

A Novel Chlorination of the Adamantyl System by Silver Salts in Carbon Tetrachloride

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Silver acetate reacts with 1-bromoadamantane in carbon tetrachloride to produce 3-chloro-1-adamantyl acetate as the major product. Silver bromide acts on adamantane in CCl_4 to give a low yield of 1-chloroadamantane. Bromine, phosgene, bromotrichloromethane, and hydrogen chloride are significant by-products. Addition of silver acetate to the silver bromide greatly increases the yield of chlorinated adamantanes. Similar treatment of 1-adamantyl acetate with these same silver salts in CCl_4 gives mainly 3-chloro-1-adamantyl acetate. Silver bromide is the primary initiator of these free-radical chlorinations but, unlike many radical processes, oxygen is a requirement for its propagation. Catalysis by silver acetate was traced to the intermediacy of bromine chloride which can function as an efficient initiator for the carbon tetrachloride chlorination of adamantane.

In connection with concurrent studies in the field of adamantane chemistry, we needed an authentic sample of 1-adamantyl acetate. Although we were aware of its synthesis[2] from the alcohol by treatment with acetic anhydride, production of the acetate from 1-bromoadamantane and silver acetate in carbon tetrachloride appeared to be a feasible alternative to that procedure.

It was observed, however, that after refluxing for 20 hr and standing for 4 days, the principal product was 3-chloro-1-adamantyl acetate (**2**) with the anticipated 1-adamantyl acetate (**3**) forming in considerably smaller amounts (eq 1).

In addition to typical acetate absorptions at 1740 and 1240 cm^{-1} the infrared spectrum of chloroacetate **2** showed a band at 840 cm^{-1} attributable to C–Cl stretching. An nmr spectrum displayed five peaks at τ 7.63, 7.74, 7.93, 8.10, and 8.40 corresponding to 2, 2, 8, 3, and 2 protons, respectively. Structure **2** was further confirmed by a spontaneous positive test toward alcoholic silver nitrate reagent.

Since 1-adamantyl acetate was identified as a product, attention focused on silver acetate or the silver bromide by-product as species which might be involved in the conversion of acetate **3** to the chloroacetate **2**.

A review of the literature did not reveal examples of the direct halogenation of a hydrocarbon by silver acetate initiation in CCl_4. In fact, the tendency for silver acetate to ho-

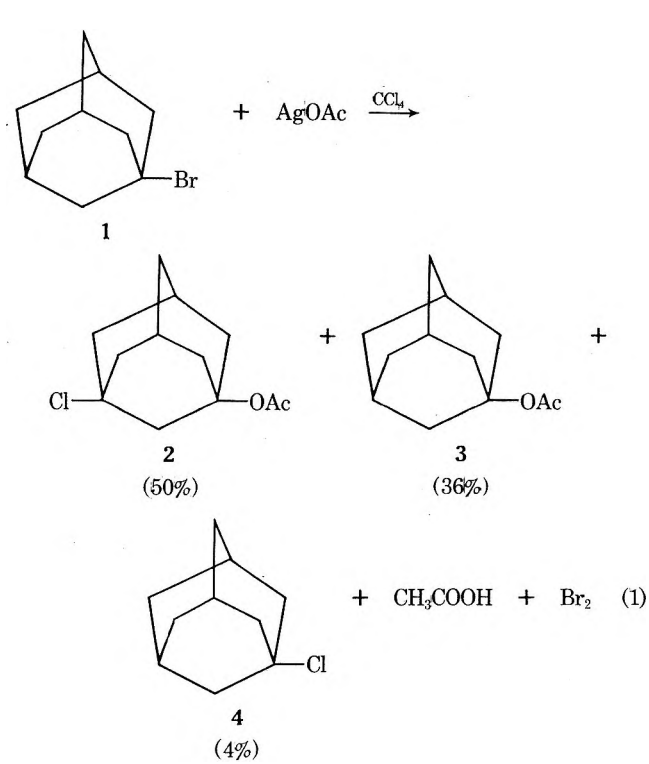
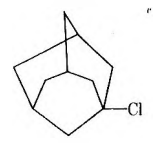
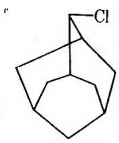
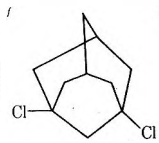
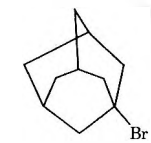


Table I
Products from the Carbon Tetrachloride Chlorination of Adamantane in the Presence of Silver Salt and Halogen Initiators

Initiator	Conditions	% yields of adamantyl products[a]			
					
AgBr[b]	24 hr, 77°; 72 hr, 23°	11	0	0	0
AgBr,[c] AgOAc[d]	24 hr, 77°; 72 hr, 23°	54	9	22	Trace
Br_2	6 days, 23°	40	0	21	2
BrCl	23 hr addition	36	7	22	2
BrCl–AgOAc	26 hr, 23°	46	4	16	Trace
$Br_2 + h\nu$[j]		8	0.5		15 + 2-AdBr[i] (12%)
Benzoyl peroxide[j]		22	3.3		
Di-*tert*-butyl peroxide[j]		43	6		

[a] Based on adamantane. [b] Registry no., 7785-23-1. [c] Reference 7. [d] Registry no., 563-63-3. [e] Registry no., 935-56-8. [f] Registry no., 7346-41-0. [g] Registry no., 16104-50-0. [h] Registry no., 768-90-1. [i] Registry no., 7314-85-4. [j] Reference 11b.

molyze is quite low, since pyrolysis at 400° leads to a 93% yield of acetic anhydride and silver oxide, with the homolysis product, ethane, being detected in a yield of only 1%.[3]

Although the organic chemistry of silver bromide is more obscure than that of the acetate, some examples in which this compound functions as a reagent in a redox or free radical-like capacity can be found.[4-6] A program of research was instituted to study chlorination of adamantane in carbon tetrachloride in the presence of silver acetate and/or silver bromide.

Results and Discussion

Results of reactions of adamantane with silver acetate or silver bromide in carbon tetrachloride are summarized in Chart I. Refluxing a CCl_4 solution of 1-bromoadamantane with silver acetate for 20 hr produces 1-adamantyl acetate as the sole product. Refluxing a carbon tetrachloride solution of adamantane with silver acetate for 20 hr followed by 3 days at room temperature gives only unchanged adamantane. Similar treatment of adamantane with silver bromide does give rise to an 11% yield of 1-chloroadamantane (**4**). An 11% yield of the chloride 4 was produced with 3 days of standing at room temperature, and an additional 8 days caused the yield of 1-chloroadamantane to increase to 31%. In general it was found advantageous to allow time for yields to accrue to values of about 30 in order that important by-products such as bromotrichloromethane, bromine, and hydrogen chloride be identified with greater reliability. Attempts to increase the yields through high temperature or photolysis of reaction mixtures were ineffective.

Chart I
Reactions of Adamantane with Silver Acetate or Silver Bromide in Carbon Tetrachloride

$$\mathrm{AdH + AgOAc + CCl_4} \xrightarrow[\text{2. 3 days at room temp}]{\text{1. reflex 20 hr}} \text{no reaction}$$

$$\mathrm{AdH + AgBr + CCl_4} \xrightarrow[\text{2. 3 days at room temp}]{\text{1. 24 hr reflex}} \mathrm{AdCl}\ (11\%) \qquad (2)$$

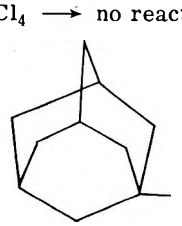
$$\mathrm{AdH + AgBr + CCl_4} \xrightarrow[\text{room temp}]{\text{11 days}} \mathrm{AdCl}\ (31\%) + \mathrm{BrCCl_3}\ (13\%) + \mathrm{HCl} + \mathrm{Br_2} + \mathrm{Cl_2C{=}O}\ (17\%) \qquad (3)$$

$$\mathrm{AdH + AgBr + CCl_4} \xrightarrow[140^\circ]{48\ \text{hr}} \mathrm{AdCl}(10\%) \qquad (4)$$

$$\mathrm{AdH + AgBr + CCl_4} \xrightarrow[20\ \text{hr}]{h\nu} \mathrm{AdCl}(8\%) \qquad (5)$$

$$\mathrm{AgBr + CCl_4} \xrightarrow{h\nu} \mathrm{BrCCl_3 + Br_2}$$

$$\mathrm{AdH + CCl_4} \longrightarrow \text{no reaction}$$

Ad = 

Products and yields of the carbon tetrachloride chlorination of adamantane are summarized in Table I. While silver bromide can initiate chlorination of adamantane, the presence of an equivalent quantity of silver acetate increaed the yield of the chloroadamantanes to as much as 90%.

Like adamantane, 1-adamantyl acetate underwent chlorination by treatment with silver bromide and silver acetate in CCl_4. After 1 day of refluxing and another standing at room temperature a 38% yield of chloroacetate 2 was realized; after an additional 10 days, this figure rose to 62% (eq 6).

The quality or age of silver bromide affected the yield of the chloro compounds.[7] Optimum results were achieved with freshly prepared material, and consistent results were obtained when the salt was generated in situ.

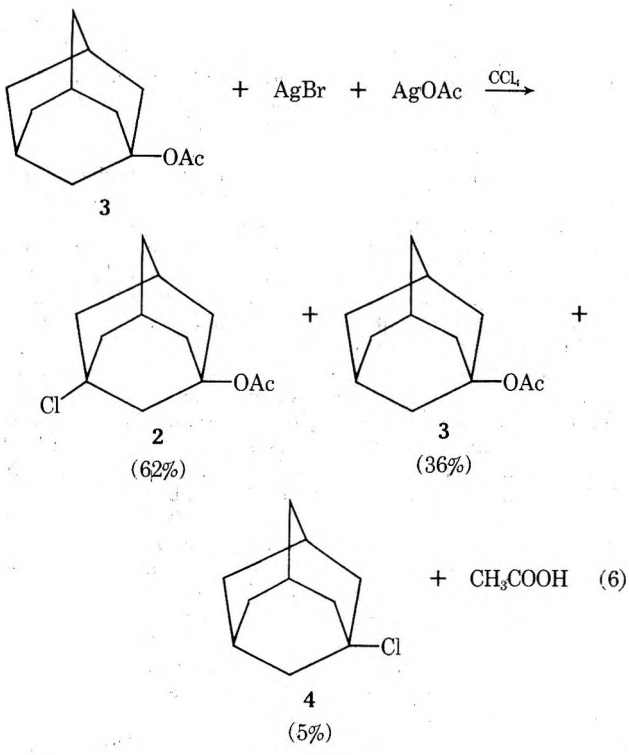
Product ratios and yields of by-products from the carbon tetrachloride chlorination of adamantane in the presence of various silver salt and halogen initiators are summarized in Table II.

Evidence for Free-Radical Chlorination by the Carbon Tetrachloride Solvent. Isolation of 2-chloroadamantane, chloroform, and bromotrichloromethane suggests a free-radical chlorination of the adamantyl nucleus by the solvent. Adamantane reactions which proceed via ionic intermediates give substitution at the bridgehead positions almost exclusively.[8] Chloroform and bromotrichloro-

Table II
Product Ratios and Yields of By-Products Produced from the Carbon Tetrachloride Chlorination of Adamantane in the Presence of Various Silver Salt and Halogen Initiators

Initiator	Conditions	Total yield adamantyl products, %	1-Chloro-adamantane[a] / 2-Chloro-adamantane	Absolute yields, %			
				$BrCCl_3$[b]	$CHCl_3$[b]	CH_3COOH[c]	$Cl_2C{=}O$[b]
AgBr	10 days, 23°	31	7.6	13	0		17
AgBr–AgOAc	24 hr, 77°; 4 days, 23°	72	5.2			66	
AgBr–AgOAc[d]	24 hr, 77°; 7 days, 23°	85	5.4	7	33	78	9
AgBr–AgOAc	72 hr, 77°	95	9.4			10	
Br_2	6 days, 23°	95	∞	8	0		0
BrCl	8 hr addition, 23°	81	5.4	30	0		0
BrCl	24 hr addition, 23°	92	5.1	10	0		0
BrCl–AgOAc	8 hr addition, 23°	81	11.0	18	0	101	0

[a] Based on GLC peak areas. [b] Based on adamantane. [c] Based on silver acetate. [d] Same as above with an additional 3 days at 23°.

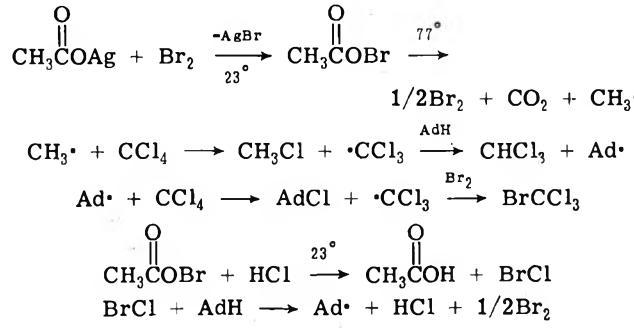


methane both can be regarded as trapped manifestations of trichloromethyl radicals, produced when the adamantyl radical abstracts chlorine from CCl_4. For more complex reasons chloroform does not always accompany free-radical CCl_4 chlorinations of adamantane, but in the thermal decomposition of *tert*-butyladamantane percarboxylate, Razuvajev[9,10] did observe, in addition to extensive chlorination of the adamantyl system, production of substantial quantities of chloroform. Owing to the low selectivity of the 1-adamantyl radical, free-radical reactions of adamantane which are initiated in CCl_4 often yield predominantly 1-chloroadamantane, even in the presence of other highly reactive halogenating agents such as bromine and NBS[11] (also see Table I). Furthermore, in the course of our investigations 1-:2-chloroadamantane ratios of 5–10 were obtained from various experiments. Such values fall comfortably within the range of what one would consider diagnostic of a free-radical process, especially when compared with other known radically initiated CCl_4 chlorinations of adamantane[11a-c] (Tables I and II).

Since bromine[12] was produced in the chlorination reactions, bromine-initiated carbon tetrachloride chlorination of adamantane was investigated. Although the reaction required 6 days for completion there was, nevertheless, a total dissipation of the bromine color. The results derived from this reaction somewhat parallel the silver bromide initiated reaction (see Tables I and II) in that scavenging of the trichloromethyl radical by bromine preferentially leads to the formation of bromotrichloromethane. In both reactions chloroform could not be detected,[13] but by comparing the yields of adamantyl products it appears unlikely that the sole hydrogen abstractors in the silver bromide reaction could have been bromine, since the 1-:2-chloroadamantane ratios differ so greatly for the two reactions.

Silver Acetate Catalysis. Chlorination of Adamantane Initiated by Bromine Chloride and Acetyl Hypobromite. For the silver bromide initiated chlorination reaction of adamantane as catalyzed by silver acetate, we propose a mechanism which is depicted in Chart II. We believe

Chart II
Proposed Mechanism for the Silver Bromide Initiated Chlorination of Adamantane in CCl_4 as Catalyzed by Silver Acetate



that bromine, produced as a result of the silver bromide chlorination process, is responsible for the catalytic activity of silver acetate. Bromine reacts rapidly with silver acetate, producing acetyl hypobromite.[14] Acetyl hypobromite, in the presence of HCl, would be expected to yield acetic acid and the interhalogen molecule, bromine chloride. Formation of halogens from acyl hypohalites and hydrohalic acids[15] has been known for some time and more recently Bunce and Tanner[16] showed that molecular chlorine is generated from benzoyl hypochlorite and hydrogen chloride. Thus, the bromine is converted to the highly efficient initiator, bromine chloride. Speier[17] demonstrated that bromine chloride, via hydrogen chloride formation, functions as a potent reagent for the halogenation of various types of

aliphatic hydrocarbons. In this study bromine chloride effectively halogenated cyclohexane under conditions for which bromine was unable to foster any such reaction.

In support of the above mechanism, we found that bromine chloride reacted with adamantane in CCl_4 to produce good yields of chloroadamantanes in addition to bromotrichloromethane and hydrogen chloride (Tables I and II). Approximately 20 min is required for the adamantane solution to discolor a portion of bromine chloride as opposed to the 6 days required for complete discoloration of bromine. Also, the 1-chloroadamantane:2-chloroadamantane ratio derived from this reaction is the same as that derived from the silver acetate–silver bromide chlorination (Table II) and shows that bromine chloride is possibly the major hydrogen-abstracting species in the latter case as well. The interpretation of the 1-:2-chloroadamantane ratio may be somewhat clouded by the conversion of 4 to 1,3-dichloroadamantane, but an inspection of Table II reveals that even as the total yield of the AgBr–AgOAc reaction was increased by 13% this ratio increased by only 0.2%. Production of disproportionately larger yields of 1,3-dichloroadamantane from the BrCl reaction may only reflect a larger concentration of the reagent in that case.

Further evidence in support of the intermediacy of acetyl hypobromite comes from the experimental verification of acetic acid, which according to Chart II is a necessary counterpart to bromine chloride formation. Bunce and Tanner[16] reported a 60% yield for the chlorination of 2,3-dimethylbutane by benzoyl hypochlorite. By a product ratio determination these workers demonstrated that chlorine, produced from the action of hydrogen chloride on the hypochlorite, was responsible for the hydrogen abstraction processes and their sequence was further substantiated by the identification of benzoic acid.

In the silver acetate–silver bromide initiated chlorination of adamantane, acetic acid is isolated in 80% yields when the reaction is run at ambient temperatures, but only in 10% yield when the reaction is carried out at the CCl_4 reflux temperature. Such a trend reflects the more rapid decomposition of the acetyl hypohalite at the higher temperature and it is conceivable that decomposition may be of sufficient rapidity so as to preclude attack by hydrogen chloride.

The reactivity trend being described here for acetyl hypobromite parallels that of benzoyl hypochlorite, which gave in benzene a moderate yield of phenyl benzoate at 3° but little at reflux.[18]

Since acetic acid and bromine chloride should be produced in equimolar quantities (Chart II), lower acetic acid yields reflect lower bromine chloride production and hence at elevated temperatures the major part of the propagation effort would have to be effected by the acetyl hypobromite decomposition products and the trichloromethyl radicals. Propagation by these less potent and thus more discriminating hydrogen abstractors,[19] as expected, causes an increase in the 1-:2-chloroadamantane ratio (Table II).

It was possible to identify methyl chloride, and though the yields of this product were not rigorously quantified, they increased notably at the higher reaction temperature. It is also significant that, whereas chloroform could not be identified in those reactions initiated merely by silver bromide, it has been detected in the silver acetate catalyzed chlorinations (Table II). This data can be rationalized by assuming that the bromine produced from the preliminary silver bromide interactions is rapidly consumed by AgOAc as soon as it is formed, and therefore is not available for scavenging of trichloromethyl radicals.

The significantly higher 1-:2-chloroadamantane ratio for the bromine chloride chlorination carried out in the presence of silver acetate (Table II) indicates that in this case the halogen is being converted to less potent hydrogen abstractors before it attacks adamantane.

Experimental Section[20]

Silver Bromide. An aqueous solution of sodium bromide was added with stirring and exclusion of light to an equivalent quantity of a silver nitrate solution. The resulting yellow precipitate was permitted to digest for 0.5 hr, isolated by filtration, and then successively washed with water, methanol, and acetone. Drying of the product was accomplished at 0.03 nm and room temperature.

General Analytical Procedures. Reaction of Adamantane with Silver Bromide and Silver Acetate in Carbon Tetrachloride. To a solution of adamantane (1.2 g, 9 mmol) in 31 ml of CCl_4 was added a finely pulverized mixture of silver bromide (1.7 g, 9 mmol) and silver acetate (1.5 g, 9 mmol). The mixture was stirred at reflux for 24 hr and then permitted to stand for an additional 5 days. At this point yields were determined on the supernatant liquid directly. Volatile by-products were determined by the use of quantitative external standards. Successive gas chromatographic injections reproduced peak areas with a precision of ±1%. Methyl chloride, phosgene (9%), and chloroform (33%, elution order) were determined at a column temperature of 23°; programming to 45° was necessary in order to determine the yield of bromotrichloromethane (8%). Acetic acid (78%, column B[20]) was determined at 70° and its identity as well as chloroform's was established by collection and comparison of the spectra with those of the authentic materials. The odor of phosgene was immediately apparent but its identity could be more rigorously established by the presence of its carbonyl absorption at 1828 cm^{-1} in the infrared spectrum of the supernatant. Following bromotrichloromethane analysis the column was programmed to 120°, whereby analysis of the adamantyl products was carried out over a programming range of 40° as a product ratio. The yield of unchanged adamantane as deduced from this ratio was in excellent agreement with the figure arrived at from a quantitative external standard evaluation. Identification of products was rigorously established, after isolation from the column, by comparison of the spectra with those of the authentic sample. Yields were as follows (elution order): adamantane (15%), 1-chloroadamantane (40%), 2-chloroadamantane (7%), 1,3-dichloroadamantane (15%), unidentified products (23%). Bromine was confirmed according to ref 12 and hydrogen chloride was determined by extracting the carbon tetrachloride solution with water (3 × 20 ml) and precipitating silver chloride by the addition of silver nitrate solution. This precipitate was pure white, turned purple on exposure to light, and was readily soluble in ice-cold 6 *N* NH_4OH. As a control and to show that the precipitate did not arise from hydrogen bromide, silver bromide was precpitated from an authentic HBr solution. This precipitate was distinctly yellow, turned green on exposure to light, and was insoluble in 6 *N* NH_4OH. The presence of hydrogen chloride also was obvious by the presence of a fuming acidic gas emanating from the reaction flask. An infrared spectrum of the silver salt mixture revealed that silver acetate was not present. If silver acetate and silver bromide are refluxed in carbon tetrachloride without adamantane, the mixture darkens considerably but silver acetate is not consumed.

3-Chloro-1-adamantyl Acetate (2). Method A. Reaction of 1-Bromoadamantane with Silver Acetate in Carbon Tetrachloride. A mixture of bromide 1 (1.0 g, 5 mmol), silver acetate (1.1 g, 7 mmol), and carbon tetrachloride (25 ml) was stirred at reflux for 24 hr. After an additional 4 days of standing the yields of adamantyl products were determined directly on the supernatant liquid as described in the preceding section (in order of elution): 1-chloroadamantane (4%), 1-adamantyl acetate (36%), 3-chloro-1-adamantyl acetate (**2**, 50%), unidentified products (10%). The yield of acetic acid was 82% and the other by-products such as $CHCl_3$, $BrCCl_3$, Br_2, and HCl were qualitatively identified. Washing of the CCl_4 solution with aqueous sodium carbonate, drying ($MgSO_4$), and removal of solvent afforded 1.0 g of a light yellow liquid from which the adamantyl products were isolated by preparative gas chromatography. Chloroacetate **2** initially elutes as an oil which crystallizes upon standing. Its spectral properties have been described in the introductory section.

Anal. Calcd for $C_{12}H_{17}ClO_2$: C, 62.90; H, 7.49; Cl, 15.46. Found: C, 62.91; H, 7.43; Cl, 15.55.

Method B. Reaction of 1-Adamantyl Acetate with Silver Bromide and Silver Acetate in Carbon Tetrachloride. A mix-

ture of 1-adamantyl acetate (**3**, 1.5 g, 8 mmol), silver acetate (1.3 g, 8 mmol), and silver bromide (1.5 g, 8 mmol) in 25 ml of carbon tetrachloride was stirred at reflux for 30 hr and then allowed to stand for an additional 10 days. At this point a 77% yield of acetic acid was determined from the supernatant liquid directly. Phosgene, methyl chloride, chloroform, and bromotrichloromethane were identified qualitatively. The adamantyl products were isolated by preparative gas chromatography in the following yields (elution order): 1-chloroadamantane (5%), 1-adamantyl acetate (22%), 3-chloro-1-adamantyl acetate (**2**, 62%), unidentified products (11%).

Reaction of Adamantane with Silver Bromide in Carbon Tetrachloride. Adamantane (1.0 g, 7 mmol) in 30 ml of carbon tetrachloride was stirred at reflux in the presence of 2.0 g (11 mmol) of silver bromide for 24 hr. After standing for an additional 3 days an 11% yield of 1-chloroadamantane was computed. At this point the gas chromatography peaks due to 2-chloroadamantane and 1,3-dichloroadamantane were too small to be reliably evaluated. It was, however, possible to identify bromine[12] and after an additional 7 days of standing it was possible to reliably compute the yields of all products reported as follows: phosgene (17%), bromotrichloromethane (13%). A quantitative external standard served to establish a 61% yield of unchanged adamantane while the ratio of adamantyl products was 1-chloroadamantane:2-chloroadamantane:1,3-dichloroadamantane, 76:10:19. Hydrogen chloride and bromine were also identified.

Chlorination of Adamantane with Bromine in Carbon Tetrachloride. To a solution of adamantane (1.2 g, 9 mmol) in 42 ml of carbon tetrachloride was added with stirring over a period of 27 hr a solution of bromine (0.8 g, 5 mmol) in 50 ml of carbon tetrachloride. After 6 days of stirring at room temperature the bromine color dissipated completely and at this point gas chromatographic analysis of the solution revealed the following yields: adamantane (6%), 1-chloroadamantane (40%), 1-bromoadamantane (2%), 1,3-dichloroadamantane (21%), unidentified products (31%).

Chlorination of Adamantane with Bromine Chloride. A 10% (w/v) solution of bromine chloride in carbon tetrachloride was prepared by adding bromine (11.80 g, 7.4 mmol) to a solution of chlorine (5.24 g, 7.4 mmol) in 90 ml of CCl_4.[21] With additional solvent the volume of solution was brought up to 170 ml. A uv spectrum of the solution displayed a single λ_{max} at 374 nm.

A 14-ml aliquot of the bromine chloride solution (12 mmol of BrCl) was diluted with additional CCl_4 to give a total volume of 40 ml and this was added with stirring over a period of 8 hr to a solution of adamantane (1.6 g, 12 mmol) in 30 ml of carbon tetrachloride. It took approximately 20 min for the last traces of halogen color to fully discharge. After an additional 20 hr of stirring the product yields were determined on the solution directly: bromotrichloromethane (30%), adamantane (19%), 1-chloroadamantane (25%), 2-chloroadamantane (5%), 1-bromcadamantane (5%), 1,3-dichloroadamantane (19%), unidentified products (27%). The solution was twice extracted with water and 1.0 g of silver chloride was precipitated by treating the washings with silver nitrate solution (60% yield of HCl). Hydrogen bromide could not be detected.

Chlorination of Adamantane with Bromine Chloride in the Presence of Silver Acetate. The procedure here was carried out in the exact manner as the one described above except that silver acetate (2.0 g, 12 mmol) was initially suspended in the adamantane solution before the addition of halogen was begun. After a 6-hr addition and 20 hr of stirring the following yields were determined from the supernatant liquid directly: adamantane (16%), 1-chloroadamantane (46%), 2-chloroadamantane (4%), 1-bromoadamantane (trace), 1,3-dichloroadamantane (16%), unidentified products (18%), bromotrichloromethane (18%), acetic acid (101%).

Registry No.—**2**, 53906-99-3; **3**, 19066-22-9.

References and Notes

(1) Taken in part from the Doctoral Thesis of Arthur L. Schwartz, Adelphi University, Jan 1973.
(2) F. N. Stepanov and L. E. Stolyarov, *Zh. Vses. Khim. Ova.*, **13**, 713 (1968).
(3) A. D. Kirschenbaum, A. G. Streng, and M. Hauptschein, *J. Am. Chem. Soc.*, **75**, 3141 (1953).
(4) C. H. DePuy and K. L. Rinehart, Jr., "Introduction to Organic Chemistry", Wiley, New York, N.Y., 1967, p 110.
(5) M. A. Aleksankin, L. I. Fileleeva, and P. I. Gragerov, *Zh. Org. Khim.*, **4**, 1439 (1968).
(6) H. H. Anderson, *J. Am. Chem. Soc.*, **79**, 4913 (1957).
(7) Some variation in yields derived from comparative reaction carried out under similar conditions will be observed throughout this paper. As described above, this phenomenon can be attributed to the activity or quality of the silver bromide.
(8) R. C. Fort and P. v. R. Schleyer, *Chem. Rev.*, **64**, 277 (1964).
(9) G. A. Razuvajev, L. S. Boguslavskaya, V. S. Etlis, and G. V. Brovkina, *Dokl. Akad. Nauk. SSSR*, **183**, 1124 (1968).
(10) G. A. Razuvajev, Z. S. Boguslavskaya, V. S. Etlis, and G. V. Brovkina, *Tetrahedron*, **25**, 4925 (1968).
(11) (a) G. J. Gleicher, J. L. Jackson, P. H. Owens, and J. D. Unruh, *Tetrahedron Lett.*, 833 (1969); (b) I. Tabushi, J. Hamuro, and R. Oda, *J. Am. Chem. Soc.*, **89**, 7127 (1967); (c) I. Tabushi, Y. Aoyama, S. Kojo, J. Hamuro, and Z. Yoshida, ibid., **94**, 1177 (1972); (d) C. Ruchardt, K. Herwig, and S. Eichler, *Tetrahedron Lett.*, 421 (1969).
(12) In addition to the easily observable color of bromine, the presence of the halogen was further confirmed by its immediate discoloration with 1-hexene and its uv maximum at 413 nm displayed by the supernatant. An authentic solution of Br_2 in CCl_4 also has a λ_{max} at 413 nm. For the same solution λ_{max} at 410 nm has been reported by M. Anbar and I. Dostrovsky, *J. Chem. Soc.*, 1105 (1954).
(13) There have been other reports where trichloromethyl radicals could have abstracted hydrogen atoms but were instead scavenged by bromine: W. G. Dauben and H. Tilles, *J. Am. Chem. Soc.*, **72**, 3185 (1950); F. W. Baker, H. D. Holz, and L. M. Stock, *J. Org. Chem.*, **28**, 514 (1963).
(14) C. V. Wilson, *Org. React.*, **9**, 332 (1957).
(15) W. Bockemuller and F. W. Hoffman, *Justus Liebigs Ann. Chem.*, **519**, 1657 (1935).
(16) N. J. Bunce and P. P. Tanner, *J. Am. Chem. Soc.*, **91**, 6096 (1969).
(17) J. L. Speier, *J. Am. Chem. Soc.*, **73**, 826 (1951).
(18) N. J. Bunce and L. B. Urban, *Can. J. Chem.*, **19**, 821 (1971).
(19) J. March, "Advanced Organic Chemistry", McGraw-Hill, New York, N.Y., 1968, p 531.
(20) Melting points were measured on a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were determined on a Perkin-Elmer 257 grating spectrophotometer in CCl_4 or CS_2 in cavity cells. Uv spectra were recorded on a Perkin-Elmer 202 ultraviolet–visible recording spectrophotometer. A Varian A-60 spectrophotometer was used to record nmr spectra in CCl_4 using tetramethylsilane as an internal standard. Yields were determined by gas chromatography on a Hewlett-Packard 720 dual-column gas chromatograph. With the exception of acetic acids all products were determined on a 4 ft × 0.25 in. column of 20% SE-30 on Chromosorb W (column A). For acetic acid a 2 ft × 0.25 in. column of 20% DEGS on Chromosorb W, AW (column B) gave good results. Helium flow rates of 30–40 ml/min were found optimal. Elemental analyses were carried out by Spang Microanalytical Laboratory, Ann Arbor, Mich.
(21) R. Villotte, H. J. Ringold, and C. Djerassi, *J. Am. Chem. Soc.*, **82**, 5699 (1960).

Allowed and Forbidden Sigmatropic Pathways in the Stevens Rearrangement of a Phenacylammonium Ylide

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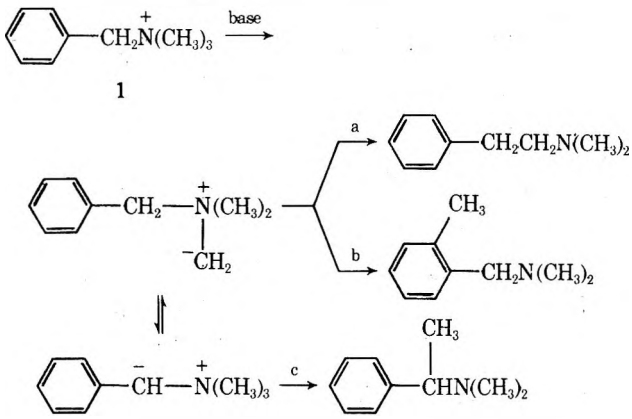
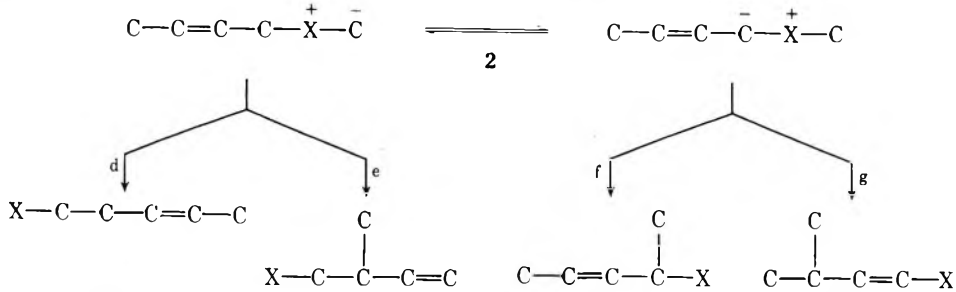
The possibility that the Stevens rearrangement of benzyldimethylphenacylammonium ylide (3) could proceed by a two-step allowed [1,4] and forbidden [1,3] sigmatropic pathway rather than the one-step [1,2] forbidden process has been investigated. The proposed enamine enol ether intermediate (5) was synthesized and shown *not* to rearrange to the Stevens product under typical Stevens rearrangement conditions. The conversion can be accomplished at elevated temperatures. No evidence for the involvement of the enamine enol ether intermediate in this example of the Stevens rearrangement was found. Comparison of this phenacylammonium ylide with related allylic and phenacylsulfonium ylides is considered.

The molecular rearrangements of ylides derived from ammonium and sulfonium salts have received considerable interest in regard to orbital symmetry consideration. Such considerations have provided theoretical support for the suggestion that the Stevens rearrangement—formally a [1,2] sigmatropic process—involves a stepwise rather than a concerted mechanism.[2] In the case of benzylammonium **1**[3] (and related sulfonium)[4] salts the base-promoted reactions can proceed by two different pathways. The theoretically less favorable [1,2] Stevens rearrangement (paths a and c) and the more favorable [2,3] Sommelet–Hauser rearrangement (path b) are generally both observed. It has

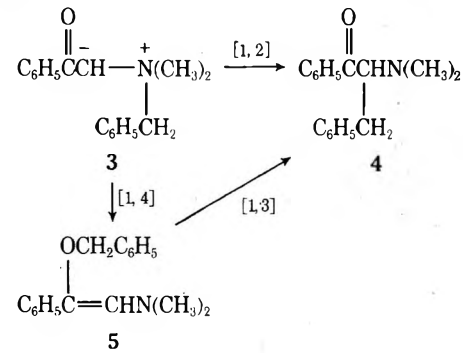


been suggested by ourselves[5] and others[3,6] that the marked dependence of these competing reactions on experimental parameters is explicable in terms of orbital symmetry considerations.

Related to the above are the competitive pathways available to allylic onium ylides **2**. Again either [1,2] (path d) and [2,3] (path e) or [1,2] (path f) or [1,4] (path g) are observed depending on the precursor ylide.[7] Ollis has suggested that the nature of the onium atom plays a part in directing the rearrangement.[7c]



Phenacyl-stabilized ylides are electronically analogous to allylic ylides. Thus similar rearrangement pathways are feasible and products from these pathways have been observed. In regard to the Stevens rearrangement of phenacylammonium ylides the "allylic" [1,4] pathway could provide the first step as an alternative to the [1,2] process as outlined below for the benzyldimethylphenacylammonium ylide (**3**). Our question was, is the two-step **3** to **5** (allowed)



and **5** to **4** (forbidden) pathway more favorable energetically than the one-step **3** to **4** (forbidden) sequence? In the following we report our results in the study of this alternate rearrangement pathway.

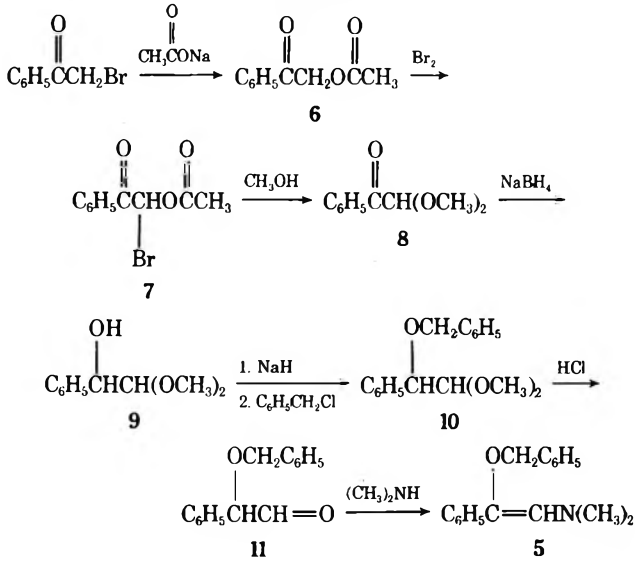
Results and Discussion

The formation of ylide **3** either in situ or as its stable hydrate and subsequent rearrangement to **4** has been investigated by ourselves and others.[8] To test for the involvement of the alternate rearrangement pathway we have synthesized the enamine enol ether **5** and studied its conversion to the Stevens rearrangement product **3**.

Initial attempts to prepare **5** through benzylation of the enolate anion of dimethylphenacylamine provided only **4**. From this result it was not clear whether the proposed intermediate **5** formed and rapidly rearranged to **4**, or if **4** was directly formed by C-benzylation. The desired compound **5** was ultimately obtained as outlined in Scheme I.

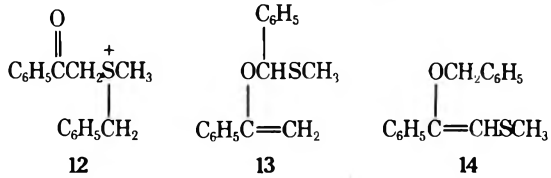
Various attempts to convert **5** to the rearrangement product **4** were carried out. Heating in water, chloroform, or methanol converted **5** back to the aldehyde **11**, while heating in hot benzene or toluene yielded only a small

Scheme I



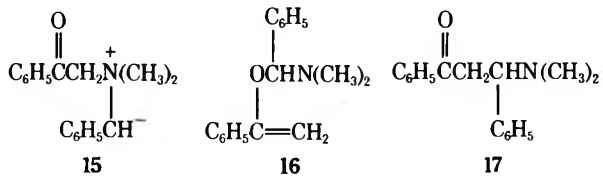
amount of rearrangement product **4**. Use of methanol–sodium methoxide to duplicate our typical Stevens rearrangement conditions resulted in little change at room temperature, while almost complete conversion of **5** to **4** occurred in 2–3 hr at 70°. In marked contrast to this result the rearrangement of **3** to **4** is complete in 1–2 min at 70°. It seems clear that the enamine enol ether **5** is not involved in the Stevens rearrangement of **3** to **4**.

It is of interest to compare our results on the ammonium ylide **3** with those observed in related sulfonium ylides. Ruiz[9] as well as Ratts and Yao[10] observed that phenacyl-stabilized sulfur ylides could undergo "allylic" type rearrangements involving the carbonyl oxygen atom as well as the normal Stevens rearrangement.[11] Thus sulfonium salt **12** could be converted to the enol ether **13** with base. Note that this transformation must involve the benzyl rather than the more favorable phenacyl ylide anion. More recently Baldwin[12] has reported a small yield of the sulfur analog **14** of our enol ether (**5**) from **12**. Schöllkopf has further



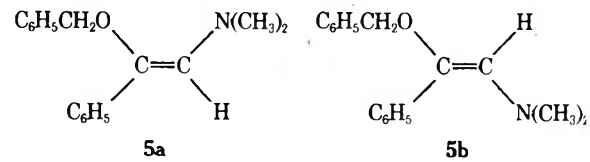
considered this system and finds that the phenacyl anion ylide derived from **12** rearranges to the normal Stevens rearrangement product in aprotic solvents while **13** is produced in the protic solvent methanol.[13] This solvent effect was attributed to the ability of methanol to aid in the formation of the requisite benzyl ylide precursor to **13**.

In our ammonium system **3** we have found no evidence for enol ether intermediate **16** or rearrangement product **17**



derived from the benzyl ylide **15**. This is not surprising, since the acidifying effect of the sulfonium atom is much greater than that of the ammonium atom. Thus it is expected that the formation of the benzylic anion from **12** in methanol–methoxide is considerably more favorable than with the ammonium salt. Ratts[14] has reported the pK_a of similar phenacylsulfonium salts to be approximately 7 while our observations suggest that the ammonium salts have a pK_a near 14.

One final consideration related to the possible involvement of **5** in the Stevens rearrangement is stereochemical. The enamine enol ether could exist as two geometrical isomers, **5a** or **5b**. If our synthesis had provided the "wrong"



isomer then our experimental results could be invalid. However, we believe that the desired isomer is **5a** and that this is what we have synthesized. Models suggest that nonbonded repulsions favor isomer **5a**. We see only one set of peaks in the NMR spectrum of **5** suggesting that only one isomer is present. The ultraviolet spectrum (λ_{max} 308 nm) suggests trans coplanarity between the phenyl and dimethylamino groups in this styrene system.[15] Calculation of the expected NMR chemical shift position for the olefinic hydrogen atom[16] is also more consistent with the **5a** structure. Finally, we believe that **5a** would have been the isomer formed during the reaction of **3** if this were the pathway for the migration of the benzyl group to the oxygen atom. The transition state would involve a five-membered ring for this concerted [1,4] process.

Thus we conclude that the direct conversion of **3** to **4** is energetically more favorable than the two-step pathway **3** to **5** to **4**. This conclusion is similar to that reached by Baldwin[12] in a related sulfur ylide. It is important to note, however, that this work does not answer the question of whether the conversion of **3** to **4** involves a symmetry-forbidden [1,2] sigmatropic rearrangement[17] or a dissociation–recombination ion-pair or radical-pair pathway.

Our results further demonstrate that a rapid reversible [1,4] sigmatropic conversion between ylide **3** and enol ether **5** does not take place. The question of why the carbonyl oxygen atom becomes involved in many carbonyl-stabilized sulfur ylide reactions but not in similar nitrogen ylide reactions must await further results and speculations.

Experimental Section

Phenacyl Acetate (6). A mixture of 10 g of phenacyl bromide, 10 g of sodium acetate, and 20 ml of methanol was refluxed for 1 hr, then poured into 300 ml of ice water and extracted with chloroform. Drying and evaporation of the solvent gave a yellow oil which was not purified further: NMR (CCl_4) δ 2.1 (s, 3), 5.1 (s, 2), 7.2–7.8 (m, 5).

α-Bromophenacyl Acetate (7). The crude acetate **6** was dissolved in carbon disulfide and bromine was added dropwise with stirring, under nitrogen, until the brown color persisted (ca. 3 ml). Evaporation of the solvent under vacuum (without heating) gave a brown oil: nmr (CCl_4) δ 2.1 (s, 3), 7.3 (s, 1), 7.2–8.1 (m, 5).

Phenylglyoxal Dimethyl Acetal (8). The crude bromoacetate **7** was dissolved in 30 ml of methanol and the solution was refluxed for 1 hr. Evaporation of the solvent under vacuum gave a viscous liquid which was not further purified: NMR (neat) δ 3.3 (s, 6), 5.3 (s, 1), 7.2–8.1 (m 5).

2-Hydroxy-2-phenylethanal Dimethyl Acetal (9). The crude acetal **8** was dissolved in 70 ml of absolute ethanol: then 3 g of sodium borohydride was carefully added. After stirring for 2 hr at room temperature the solvent was evaporated under vacuum. The hard, foamy residue was dissolved in water and extracted with ether. Drying with $MgSO_4$ and evaporation gave a pale yellow oil which was not further purified: NMR (CCl_4) δ 2.5 (s, 1), 3.1 (s, 3), 3.3 (s, 3), 4.0 (d, J = 6 Hz, 1), 4.4 (d, J = 6 Hz, 1), 7.1 (broad s).

2-Benzoxy-2-phenylethanal Dimethyl Acetal (10). The crude hydroxy acetal **9** was dissolved in dry THF; then 2 g of sodi-

um hydride was carefully added with stirring and cooling. Excess benzyl chloride (20 g) was added, and the solution was refluxed for 3 hr and then left at room temperature overnight. Excess hydride was destroyed by careful addition of methanol; then water was added and the product was recovered by ether extraction. The crude product (6 g) was purified by chromatography on grade II neutral alumina using petroleum ether (bp 60–70°) and then 10% ethyl ether in petroleum ether to give 3.5 g of pure liquid product: NMR (CCl_4) δ 3.15 (s, 3), 3.35 (s, 3), 4.24 (s, 2), 4.35 (AB, 2), 7.20 (s, 5), 7.25 (s, 5).

2-Benzoxy-2-phenyl-*N,N*-dimethylethenylamine (5). The acetal ether (0.1 g) was dissolved in 9 ml of acetonitrile and 3 ml of 4 *N* HCl, heated to 60–65° for 20 min, then added to 10 ml of cold water and rapidly extracted with chloroform. The colorless oil recovered was about 25% acetal ether **10** and 75% aldehyde ether **11**: NMR (CCl_4) δ 4.55 (s, 2), 4.63 (d, J = 2 Hz, 1), 7.20 (s, 5), 7.25 (s, 5), 9.45 (d, J = 2 Hz, 1). Attempts to more effectively hydrolyze the ketal gave undesirable side products. The crude aldehyde ether was dissolved in 20 ml of benzene and 5 ml of dimethylamine was added. After 15 min at room temperature, the solvent was evaporated under vacuum without heating to give a light yellow oil: NMR (CCl_4) δ 2.7 (s, 6), 4.6 (s, 2), 5.6 (s, 1), 6.9–7.4 (m, 10); methiodide mp 159–160° (chloroform).

Anal. Calcd for $C_{18}H_{22}NOI$: C, 54.69; H, 5.61; N, 3.54. Found: C, 54.87; H, 5.60; N, 3.33.

Conversion of Enol Ether 5 to Rearrangement Product 4. Freshly prepared enol ether (0.1 g, 4 × 10^{-4} mol) was dissolved in 0.5 ml of 1 *N* $NaOCH_3$–CH_3OH. The nmr spectrum taken at room temperature showed no change. The NMR probe temperature was raised to 70° and the change followed. After 2 hr essentially all of the enol ether was converted to rearrangement product. The product could be recovered as a light yellow solid: NMR (CCl_4) δ 2.38 (s, 6), 2.8–3.5 (m, 2), 4.2–4.5 (m, 1), 7.1–7.4 (m, 8), 7.8–8.0 (m, 2).

Registry No.—**4**, 30669-80-8; **5a**, 53907-31-6; **5a** methiodide, 53907-32-7; **6**, 2243-35-8; **7**, 53907-33-8; **8**, 6956-56-5; **9**, 21504-23-4; **10**, 53907-36-1; **11**, 38968-65-9.

References and Notes

(1) Support from the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the National Science Foundation is gratefully acknowledged.
(2) (a) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry," Academic Press, New York, N.Y., 1970, p 131; (b) S. H. Pine, *J. Chem. Educ.*, **48**, 99 (1971); (c) S. H. Pine, *Org. React.*, **18**, 403 (1970); (d) U. Schöllkopf, *Angew. Chem., Int. Ed. Engl.*, **9**, 763 (1970).
(3) A. R. Lepley and R. H. Becker, *J. Org. Chem.*, **30**, 3888 (1965).
(4) C. R. Hauser, S. W. Kantor, and W. R. Brasen, *J. Am. Chem. Soc.*, **75**, 2660 (1953).
(5) S. H. Pine, E. M. Munemo, T. R. Phillips, G. Bartolini, W. D. Cotton, and G. C. Andrews, *J. Org. Chem.*, **36**, 984 (1971).
(6) (a) J. E. Baldwin, J. E. Brown, and R. W. Cordell, *Chem. Commun.*, 31 (1970). (b) For an early approach see H. E. Zimmerman in "Molecular Rearrangements," P. de Mayo, Ed., Wiley, New York, N.Y., 1963, pp 387–391.
(7) (a) J. E. Baldwin and R. E. Hackler, *J. Am. Chem. Soc.*, **91**, 3646 (1969); (b) R. W. C. Cose, A. M. Davies, W. D. Ollis, C. Smith, and I. O. Sutherland, *Chem. Commun.*, 293 (1969); (c) R. W. Jemison and W. D. Ollis, *ibid.*, 294 (1969); (d) R. Paul and S. Tchelitcheff, *Bull. Soc. Chim. Fr.*, 1289 (1967); (e) G. Wittig and H. Sommer, *Justus Liebigs Ann. Chem.*, **594**, 1 (1955).
(8) (a) T. S. Stevens, E. M. Creighton, A. B. Gordon, and M. MacNicol, *J. Chem. Soc.*, 3193 (1928); (b) G. Wittig, R. Mangold, and C. Felletschin, *Justus Liebigs Ann. Chem.*, **560**, 116 (1948); (c) U. Schöllkopf, U. Ludwig, G. Ostermann, and M. Patsch, *Tetrahedron Lett.*, 3415 (1969); (d) R. W. Jemison, S. Mageswaran, W. D. Ollis, S. E. Potter, A. J. Pretty, I. O. Sutherland, and Y. Thebtaranonth, *Chem. Commun.*, 1201 (1970).
(9) E. B. Ruiz, *Acta Salmant. Cienc.*, 2, No. 7 (1958); *Chem. Abstr.*, **54**, 7623 (1960).
(10) K. W. Ratts and A. N. Yao, *J. Org. Chem.*, **33**, 70 (1968).
(11) T. Thomson and T. S. Stevens, *J. Chem. Soc.*, 69 (1932).
(12) J. E. Baldwin, W. F. Erickson, R. E. Hackler, and R. M. Scott, *Chem. Commun.*, 576 (1970).
(13) U. Schöllkopf, J. Schossig, and G. Ostermann, *Justus Liebigs Ann. Chem.*, **737**, 158 (1970).
(14) K. W. Ratts, *J. Org. Chem.*, **37**, 848 (1972).
(15) A. I. Scott, "Ultraviolet Spectra of Natural Products," MacMillan, New York, N.Y., 1964.
(16) U. E. Matter, C. Pascual, E. Pretsch, A. Pross, W. Simon, and S. Sternhell, *Tetrahedron*, **25**, 691 (1969).
(17) M. J. S. Dewar and C. A. Ramsden, *J. Chem. Soc., Perkin Trans. 1*, 1839 (1974).

Electronic and Steric Effects in Nucleophilic Aromatic Substitution. Reaction by Phenoxides as Nucleophiles in Dimethyl Sulfoxide

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Kinetics of reactions of X-substituted sodium phenolates with *p*-nitrohalogenobenzenes at 25° and 2,6-dimethyl-4-nitrohalogenobenzenes at 50° in DMSO are reported. The electronic effects in the nucleophile, as revealed by ρ values, are large and may depend on the leaving halogen. For these reasons the ratios k_F/k_{Cl} are not a direct measure of the dependence of steric effects on the leaving halogen. Ortho substitution in phenolate shows steric effects which depend on the size of the leaving halogen, the following order of steric effect being observed: F < Cl < Br < I.

Steric effects in nucleophilic aromatic substitutions appear to be an open question mainly as far as steric interaction between the entering and the leaving groups is concerned.

In reactions with 2,4-dinitrohalogenobenzenes, it was established long ago[1,2] that primary and secondary amines reveal differences in rate correlated with interference by alkyl groups branching from the nitrogen atom or adjacent carbons. This behavior is displayed also by anionic nucleophiles such as mercaptides,[3] alkoxides,[4] and phenolates.[5] In all cases the observed steric retardation is also dependent on the size of the leaving halogen.

Moreover, Pietra, studying substitutions on halogenonitrobenzenes by α-alkyl piperidines,[6,7] primary, secondary, or tertiary aliphatic amines in aprotic solvents,[8] and alkoxides,[9] attributed steric retardation to interactions between the nucleophile and the benzene ring carbons and hydrogens in the transition state, rejecting previous ideas[3,5] of steric interactions between entering and leaving groups.

These contrasting interpretations probably result because the data available do not provide good correlation of expected effects with rates of reaction. Also they do not take into account the electronic changes which are operative when the substituents of the nucleophile or the leaving group of the substrate must be changed.

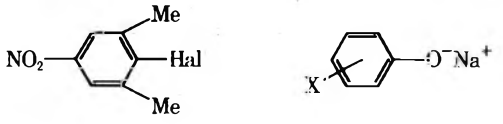
We have investigated the reactions of substituted phenoxides with *p*-nitrohalogenobenzenes and with 2,6-dimethyl-4-nitrohalogenobenzenes in order to evaluate both steric and electronic effects in a more meaningful way.

Results

The reaction rates were measured in dimethyl sulfoxide.

In order to minimize association phenomena low concentrations of phenolates (<10^{-2} *M*) were employed. Under

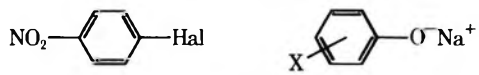
Table I
Experimental Rate Constants[a] for Reactions of 2,6-Dimethyl-4-nitrohalogenobenzenes with X-Substituted Sodium Phenoxides in DMSO at 50°



	X[c]				
Hal[b]	H	o-CH_3	p-CH_3	p-Cl	m-CH_3
F	0.49	0.20	1.45	0.12	0.63
Cl	0.0021	0.00087	0.0082	0.00044	
Br	0.0040	0.0011	0.012	0.00067	

[a] k, mol^{-1} l. sec^{-1}. [b] Registry no. are, respectively, 1736-85-2, 38560-96-2, 53906-84-6. [c] Registry no. are, respectively, 139-02-6, 4549-72-8, 1121-70-6, 1193-00-6, 3109-89-4.

Table II
Experimental Rate Constants[a] for Reaction of p-Nitrophalogenobenzenes with X-Substituted Sodium Phenoxides in DMSO at 25°



	X			
Hal[b]	H	o-CH_3	p-CH_3	2,6-$(CH_3)_2$[c]
F	0.52	0.18	1.9	0.13
Cl	0.0020	0.00051	0.0060	0.00022
Br	0.0034		0.0091	0.00028
I	0.00095		0.0036	0.00015

[a] k, mol^{-1} l. sec^{-1}. [b] Registry no. are, respectively, 350-46-9, 100-00-5, 586-78-7, 636-98-6. [c] Registry no., 16081-16-6.

these conditions the rate coefficients (Tables I and II), calculated by second-order plots, remained constant over a range of nucleophile concentration.

The expected substitution products were obtained in almost quantitative yields, except in the cases of 2,6-dimethyl-4-nitroiodobenzene, which showed a very consistent side process of reductive dehalogenation which is analogous to that reported by us some years ago for some heteroaromatic[10] and aromatic[11] halogeno derivatives. For this reason no kinetic data for the 2,6-dimethyl-4-nitroiodobenzene are reported here.

Discussion

Pietra has argued that the bulk of the leaving group does not affect the reactivity of reactants of increasing steric hindrance, on the grounds that for the 1-halogeno-2,4-dinitrobenzenes the ratio k_{ArF}/k_{ArCl} varies in a random way with increase in steric requirement of reacting amine.

Some published data and some ratios k_{ArF}/k_{ArCl} related to the change of the bulk of the nucleophile are reported in Table III. These data show a clear increase of the ratio k_{ArF}/k_{ArCl} on changing steric requirement of the nucleophile, except with 2,4-dinitrohalogenobenzenes reactions with piperidines in benzene.

On the other hand, the use of k_{ArF}/k_{ArCl} ratios to evaluate steric effects may be criticized on the basis of an important factor recently pointed out by Fava and coworkers.[12] This is the change of effective electronegativity of the reaction center due to the variation in leaving halogen, which can bring about differences in the sensitivity to polar effects of the substituent on the nucleophile.

For this reason the k_{ArF}/k_{ArCl} ratio is not sufficient for the evaluation of steric interactions between entering and leaving groups.

For the reactions between 2,6-dimethyl-4-nitrohalogenobenzenes and phenolates, indeed differences in the k_{ArF}/k_{ArCl} values going from the unsubstituted phenolate to the o-methyl phenolate might lead one to the conclusion that the size of the leaving halogen is not important in determining steric retardation (for phenolate k_{ArF}/k_{ArCl} = 233, for o-methyl phenolate k_{ArF}/k_{ArCl} = 230).

Moreover, substituent variations on the nucleophile allow one to calculate ρ values which (though rough because of the limited number of substituents used) display a remarkable sensitivity of the system being intestigated to polar effects of the substituent on the nucleophile. This sensitivity differs from the fluoro to he chloro derivative (ρ_F = −2.66, ρ_{Cl} = −3.19); therefore the k_{ArF}/k_{ArCl} might be ambiguous in our case.

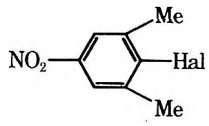
However, a steric retardation free from polar effects can be obtained by kinetic data reported in Table I. If the polar effect of a methyl group is the same in the ortho or para position, as suggested by Taft,[13] then the $k_{p\text{-cresolate}}/k_{o\text{-cresolate}}$

Table III
Values of the Ratios k_F/k_{Cl} in Nucleophilic Substitution Reaction between Aromatic Substrates and Nucleophiles

	Nucleophile				
Substrates and solvent	Piperidine	2-Methylpiperidine	2,6-Dimethylpiperidine		Ref
Fluorodinitrobenzene and chlorodinitrobenzene in benzene	6.86	35.3	25.0		6
Fluorodinitrobenzene in DMSO; chloronitrobenzene in benzene	7240	10,100	27,000		7
Fluorodinitrobenzene and chlorodinitrobenzene in benzene	*n*-Butylamine 410	*sec*-Butylamine 568[a]	*tert*-Butylamine 1050		8
2-Halogenobenzothiazoles in methanol	Methyl mercaptide 107	Ethyl mercaptide 137	Isopropyl mercaptide 180	*tert*-Butyl mercaptide 384	3
2-Halogenobenzothiazoles in the respective alcohols	Methoxide 1036	Ethoxide 1161	Isopropoxide 2941	*tert*-Butoxide 5333	4

[a] Pietra calculated erroneously a value of 1800, but reported k_F = 0.023, $k_{Cl} = 4.05 \times 10^{-5}$; hence k_F/k_{Cl} = 568.

Table IV



Hal	ρ(r)	$k_{p\text{-Me}}/k_{o\text{-Me}}$
F	−2.66 (0.996)	7.2
Cl	−3.19 (0.999)	9.3
Br	−3.17 (0.998)	11

ratio, calculated for each halogeno derivative, will be independent of polar effects.

A comparison of $k_{p\text{-cresolate}}/k_{o\text{-cresolate}}$ values for each halogeno derivative shows now (Table IV) a clear correlation with the size of the leaving halogen; $k_{p\text{-cresolate}}/k_{o\text{-cresolate}}$ increases in the order F < Cl < Br.

The differences seen in the above sequence are significant in that they reflect the differences in size of the leaving halogen mainly as far as chloro and fluoro are concerned; therefore they strengthen the hypothesis of a steric interaction between entering and leaving group (possibly along with steric interactions between other nonbonded atoms in the transition state).

Similar conclusions can be drawn in the case of reactions of *p*-nitrohalogenobenzenes with 2,6-dimethyl phenolate. The following steric retardations (53:82:87:91 for fluoro, chloro, bromo, and iodo derivative, respectively) are obtained if we regard the contribution from the polar accelerating effect of the two methyls in ortho positions as twice the effect of methyl in the para position. The above sequence is clearly correlated with expected increase of steric requirement in the order F ≪ Cl < Br < I.

Experimental Section

Materials. 2,6-Dimethyl-4-nitrohalogenobenzenes were prepared from 2,6-dimethyl-4-nitroaniline (I) via diazonium salt as described by Wepster[14] for the bromo derivative.

2,6-Dimethyl-4-nitrochlorobenzene, mp 102–104° (Anal. Calcd for $C_8H_8ClNO_2$: C, 51.8; H, 4.3; N, 7.5; Cl, 19.1. Found: C, 51.6; H, 4.4; N, 7.6; Cl, 18.9.) was obtained in the same way as the bromo derivative.

2,6-Dimethyl-4-nitroiodobenzene was prepared by adding the diazonium salt of I to a vigorously stirred solution of KI (1 mol of KI for each mole of I used) in H_2O. The precipitated product was filtered and crystallized from ethanol, mp 132–133°. Anal. Calcd for $C_8H_8INO_2$: C, 34.7; H, 2.9; N, 5.1; I, 45.8. Found: C, 34.5; H, 2.9; N, 4.9; I, 45.5.

2,6-Dimethyl-4-nitrofluorobenzene was prepared by adding the diazonium salt of I directly to a HBF_4 solution. The diazonium fluoroborate was filtered and, after washing with cold methanol, was mixed with NaF and thermally decomposed. The pure material was separated by silica gel column chromatography and crystallized from methanol, mp 55.5–56.5°. Anal. Calcd for $C_8H_8FNO_2$: C, 56.8; H, 4.8; N, 8.3; F, 11.2. Found: C, 56.9; H, 5.1; N, 8.2; F, 11.3.

All the 2,6-dimethyl-4-nitroalogenobenzenes prepared, and *p*-nitrohalogenobenzenes (commercial products), were recrystallized several times from methanol or ethanol.

Sodium phenolates were synthesized by the method reported by Kornblum.[15]

The substitution products (aryl ether) were obtained in almost quantitative yields by reactions performed under the same conditions as kinetic runs and were characterized by usual analytical methods.

DMSO was refluxed over calcium hydride and fractionally distilled under a N_2 atmosphere.

Kinetics. All the kinetic reactions were performed in DMSO under a N_2 atmosphere.

In the case of fluoro derivatives the kinetics were determined by following the disappearance of the base. For this, a known excess of HCl added to each portion of the reaction mixture was titrimetrically determined.

In the other cases the appearance of the halide ion was followed via potentiometric titration by $AgNO_3$. The organic substrate was extracted with carbon tetrachloride or chloroform before titration.

The kinetic coefficients were calculated from second-order plots which exhibited a good linear correlation as far as 30%. At higher percent, conversion rate constants were found to decrease into agreement with those found by Berge and Ugelstad.[16]

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Registry No.—2,6-Dimethyl-4-nitroiodobenzene, 53906-85-7.

References and Notes

(1) O. L. Brady and F. R. Cropper, *J. Chem. Soc.*, 507 (1950).
(2) G. S. Hammond and L. R. Parks, *J. Am. Chem. Soc.*, **77**, 340 (1955).
(3) G. Bartoli, L. Di Nunno, and P. E. Todesco, *Tetrahedron Lett.*, 2369 (1968).
(4) L. Di Nunno, S. Florio, and P. E. Todesco *Boll. Sci. Fac. Chim. Ind. Bologna*, **27**, 75 (1969).
(5) G. Bartoli, A. Latrofa, and P. E. Todesco, *Boll. Sci. Fac. Chim. Ind. Bologna*, **27**, 79 (1969).
(6) F. Pietra and F. Del Cima, *Tetrahedron Lett.*, 1925 (1966).
(7) F. Pietra and F. Del Cima, *J. Org. Chem.*, **33**, 1411 (1968).
(8) F. Pietra and D. Vitali, *J. Chem. Soc. B*, 1200 (1968).
(9) F. Pietra, D. Vitali, F. Vitali, F. Del Cima, and G. Cardinali, *J. Chem. Soc. B*, 1659 (1970).
(10) P. E. Todesco and P. Vivarelli, *Gazz. Chim. Ital.*, **94**, 435 (1964).
(11) M. Bosco, L. Forlani, and P. E. Todesco, *Gazz. Chim. Ital.*, **97**, 1954 (1967); M. Bosco, V. Calo', F. Ciminale, L. Forlani, L. Lopez, E. Nonnis, and P. E. Todesco, ibid., **101**, 685 (1971).
(12) L. Senatore, E. Ciuffarin, A. Fava, and G. Levita, *J. Am. Chem. Soc.*, **95**, 2918 (1973).
(13) R. W. Taft, Jr., in M. S. Neumann, Ed., "Steric Effects in Organic Chemistry", Wiley, New York, N.Y., 1956, Chapter 13.
(14) P. Van Berk, J. O. M. Van Langen, P. E. Verkade, and B. M. Wepster, *Recl. Trav. Chim. Pays-Bas*, **75**, 1137 (1956).
(15) N. Kornblum and A. P. Lurie, *J. Am. Chem. Soc.*, **81**, 2705 (1959).
(16) A. Berge and J. Ugelstad, *Acta Chem. Scand.*, **19**, 742 (1965).

Electrochemical Characterization of Salicylaldehyde Anils[1]

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The polarographic half-wave potential in a series of 14 salicylaldehyde anils is a linear function of σ_x^- (except for the *m*- and *p*-NO_2 compounds in which the nitro group is electroactive); analyses of potential as a function of the currents indicate a one-electron process. The half-wave oxidation potential is directly proportional to σ_x^+ (except for *m*- and *p*-NMe_2 compounds in which the dimethylamino group is electroactive). Cyclic voltammetry reveals that the reduction process is irreversible. Oxidative cyclic voltammetry demonstrates that with the exception of the nitro and dimethylamino compounds the initial irreversible one-electron oxidation product undergoes chemical transformation to a tertiary product that forms a reversible one-electron couple; the average of the peak potentials, i.e., the half-wave potential, of the couple is directly proportional to the normal Hammett substituent constant, σ. In addition to the anils, the half-wave reduction and oxidation potentials of the isoelectronic series stilbene, benzaldehyde anil, and azobenzene were linearly correlated to the calculated energies of the lowest unoccupied and highest occupied molecular orbitals, respectively. The effects of anil substituent and intramolecular hydrogen bonding are rationalized on this basis.

The electrochemical behavior of Schiff bases[1c] has been extensively studied by polarography in both aqueous and nonaqueous solutions. Under aqueous conditions reduction has been shown[2] to consist of a two-electron, two-proton transfer which converts the C=N linkage to a CHNH group. In keeping with this, the half-wave potential of the first reduction wave shows a pronounced dependence on pH.[2-4] Such studies are complicated, however, by the hydrolysis of the azomethine compound into its constituent amine and carbonyl compounds.[2,3]

While hydrolysis is not a problem when electrochemical studies are carried out in nonaqueous solvents, the results of such studies have shown the possibility of a number of electrochemical mechanisms. Thus, the two reduction waves seen in dimethylformamide (DMF) were attributed by Scott and Jura[5] to two one-electron transfers followed by irreversible protonation of the dianion formed.

$$\text{First wave: } ArCH{=}NAr' + e \rightleftharpoons Ar\dot{C}H{-}\dot{N}Ar'$$

$$\text{Second wave: } Ar\bar{C}H{-}\dot{N}Ar' + e \longrightarrow Ar\bar{C}H{-}\bar{N}Ar'$$

$$\text{Chemical reaction: } Ar\bar{C}H{-}\bar{N}Ar' + 2BH \longrightarrow ArCH_2NHAr' + 2B^-$$

Remarkably, Bezuglyi and coworkers[6] concluded that the first reduction wave in azomethine compounds in DMF involves an irreversible two-electron transfer, although both these and the former workers used diffusion current constants and the Nernstian slope to reach their differing conclusions.

The results of single sweep voltammetry studies,[7] however, indicate that the reduction of anils in aprotic media proceeds via reversible one-electron transfer followed by an irreversible one-electron transfer and chemical reaction, in agreement with Scott and Jura. Cyclic voltammetry was used by Andrieux and Saveant[8] to study the reduction of several imines in both DMF and acetonitrile (AN). Depending on the solvent and the compound, it was possible to observe either a two-electron wave leading to the saturated amine or two one-electron waves associated with dimerization. In either case the reduction is irreversible.

Studies by Fry and Reed[9] on several imines in DMF indicated that reduction of these compounds occurs by way of an irreversible two-electron transfer. It was postulated on the basis of polarography and cyclic voltammetry that the overall two-electron reduction in fact consists of a one-electron transfer followed by rapid proton transfer and a second rapid electron transfer. It was further found that the stereochemistry of the electrochemical reduction product was the same as that obtained upon reduction with sodium–ethanol.

Shifts in the reduction potential caused by changes in the Ar groups attached to either side of the C=N bond have been discussed in terms of Huckel molecular orbital theory for aromatic rings of different size.[3,5] The effect of substituents on the half-wave potential follows the Hammett relationship, reduction being facilitated by electron-withdrawing substituents.[4,10,11] The presence of an intramolecular hydrogen bond, as would be present in the condensation product of an ortho-hydroxy aldehyde with an amine, was found to facilitate reduction by 0.2–0.3 V.[12,13]

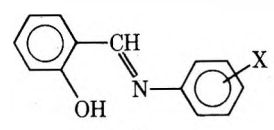
The electrochemical oxidation of imines has been less well studied. The results of linear sweep voltammetry studies[14] on a number of aromatic imines in AN indicated that anodic oxidation occurs via two one-electron steps with the loss of a proton accompanying the second charge transfer.

$$Ar{-}CH{=}\dot{\overset{+}{N}}{-}Ar' \longrightarrow e + Ar{-}CH{=}\overset{+}{N}{-}Ar'$$

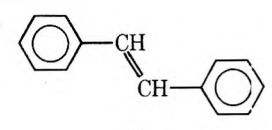
$$Ar{-}CH{=}\dot{\overset{+}{N}}{-}Ar' \longrightarrow H^+ + e + Ar{-}C{\equiv}\overset{+}{N}{-}Ar'$$

The use of anils in liquid crystal display devices has given fresh impetus to studies of their electrochemical behavior, and a number of reports on just this aspect have recently appeared.[15-17]

Our own interest in the electrochemistry of anils arises from studies of substituent effects on molecular orbital energies[18] and the relationship between solution and solid state charge exchange.[19,20] This report, then, is less concerned with electrochemical pathways than with trends in reduction and oxidation potentials caused by substitution and deviations from the general trends. Polarography and cyclic voltammetry were used to study the electrochemistry in AN of 14 salicylaldehyde anils (**1**) bearing various substituents on the aniline ring. In addition, the effect of the bridging group was also examined in the series stilbene (**2**), benzaldehyde anil (**3**), and azobenzene (**4**).



1



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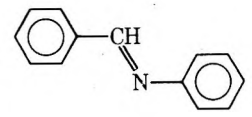

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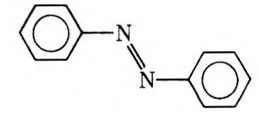

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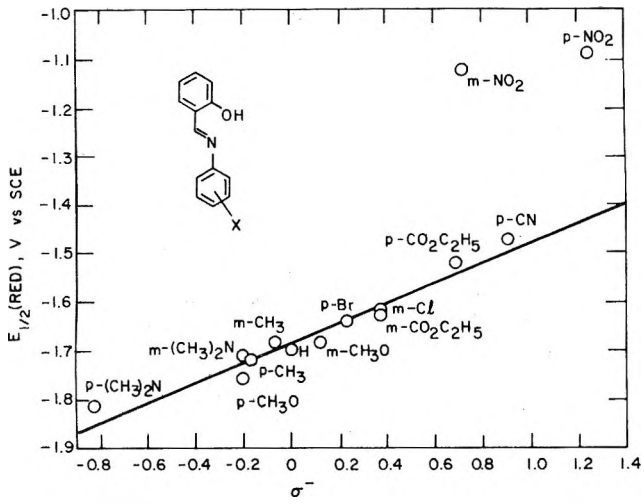

Figure 1. Half-wave reduction potentials of a series of salicylaldehyde anils (1) vs. nucleophilic substituent constant, σ^-.

Results and Discussion

Reduction at the Dropping Mercury Electrode (DME). The polarography of the salicylaldehyde anils (1) was performed at sample concentrations of 4×10^{-4} *M*, since at higher concentrations the reduction waves are distorted by maxima. Typically the polarograms consist of two waves, the first at about −1.7 V vs. a saturated calomel electrode (SCE) and the second at about 0.6 V more negative potential. The height of the second wave is typically 1–1.5 times that of the first. Beyond this observation, our attention focused mainly on the first reduction process, however.

The polarographic half-wave potentials, $E_{1/2}$ (redn), for the first reduction wave of the 14 salicylaldehyde anils vary from −1.81 V vs. SCE for the *p*-dimethylamino compound to −1.09 V for the *p*-nitro compound. Zuman has shown[21] that the effect of a substituent in a given series on the position of the half-wave potential is given by a relationship analogous to the Hammett equation.

$$\Delta E_{1/2} = E_{1/2,X} - E_{1/2,H} = \rho\sigma$$

A plot of the reduction potentials for the present series against the corresponding substituent constants[22] σ^- is shown in Figure 1. With the exception of the *m*- and *p*-NO_2 compounds, an excellent correlation (R = 0.967) of the form $\Delta E_{1/2} = (0.20 \pm 0.02)\sigma^-$ is obtained. It was found that a better fit was obtained with σ^-, the value appropriate to reactions in which electron density is released to the substituent, than with the ordinary σ constant.

The shape of the polarographic reduction waves may be described in terms of the so-called "log plot",[23] i.e., a plot of E against log $[i/(i_d - i)]$ where i is the current at potential E and i_d is the diffusion limited current. The slopes of the log plots, with the exception of the two nitro compounds, are in the range −0.045 to −0.056 V, close to the value of −0.059 V expected for a one-electron process.[23] The *m*- and *p*-nitro compounds have log plot slopes of −0.040 and −0.029 V, respectively.

The polarograms of the two nitro compounds are characterized by a well-defined wave at −1.1 V, followed by a very broad, ill-defined wave which leads into a second well-defined wave near −1.6 V. Evidently the reduction of the two nitro compounds is quite complex and distinct from that occurring with the other members of the series. Based on the deviation of the half-wave potentials from the Hammett plot and the essential identity of the first reduction potentials for both compounds with that of nitrobenzene (−1.15 V vs. SCE in AN),[24] it seems reasonable to consider that in these examples the nitro group is the electroactive moiety responsible for the observed reduction wave rather than the azomethine group.

Oxidation at the Rotating Platinum Electrode (RPE). The oxidative behavior of the salicylaldehyde anils (1) is characterized without exception by a single wave located at about +1.2 V vs. SCE. Plots of E vs. log $[(i_d - i)/i]$ have slopes in the range −0.061 to −0.086 V, in satisfactory agreement with that expected for a one-electron process. The slope for the cyano compound (−0.108 V) is unexpectedly large, but its voltammetry is otherwise undistinguished. Those of the *p*- and *m*-dimethylamino compounds (−0.058 and −0.050 V, respectively) are lower than for the series as a whole and, as will be seen, are reflective of a difference in the mechanism of oxidation.

The half-wave oxidation potentials, $E_{1/2}$ (oxidn), range from +0.70 V for the *p*-dimethylamino compound to +1.32 V for the *p*-nitro compound. The trend in $E_{1/2}$ (oxidn) with substituent may be expressed by the least-squares expression (R = 0.981) $\Delta E_{1/2} = (0.12 \pm 0.01)\sigma^+$. This is illustrated in Figure 2, where it is seen that the two nitro compounds fit the correlation, but the two dimethylamino compounds are oxidized at less anodic potentials than would have been expected. However, the similarity of the $E_{1/2}$ (oxidn) values to that of *N,N*-dimethylaniline in AN (+0.68 V vs. SCE)[25] suggests that it is the amino nitrogen atom which is the electroactive center rather than the azomethine group.

It may be noted that a better correlation of $E_{1/2}$ (oxidn) values was obtained using σ^+, the value appropriate for reactions requiring large electron demand from the substituent, than that obtained using ordinary σ constants. Furthermore, the ρ value for oxidation is smaller than that for reduction, in agreement with an observation made in a similar study of substituted azo compounds.[19]

Cyclic Voltammetry. A. Reduction. For all of the anils investigated except the two nitro compounds the cyclic voltammetry (CV) curves consist of a single cathodic peak; no anodic peak is seen on reversal of the potential scan, thereby demonstrating that the reduction is irreversible under these conditions. The development of a yellow layer next to the cathode was observed during each CV experiment and was undoubtedly due to the irreversibly formed products. The peak potentials become more negative on increasing scan rate, with an average cathodic shift of 40 mV/tenfold increase in scan rate, as expected[26] for an irreversible charge transfer process.

As indicated from the polarographic results, the two nitro compounds do not fit the general pattern for reduction, and this difference is clearly seen in their CV behavior. Thus, the CV curve of the *m*-NO_2 anil (Figure 3) is characterized at high scan rates by a reduction peak at −1.18 V which undergoes a cathodic shift of 19 mV per decade increase in scan rate. No additional peaks are seen on scanning out to −1.8 V. On reversal of the scan the corresponding anodic peak is seen at −1.09 V, the separation in peak potentials being in agreement with a reversible one-electron transfer. However, on repetitive scan a new cathodic peak at −1.27 V appears together with its corresponding anodic peak at −1.17 V. The sequence of events is thus

$$1,\ X = m\text{-}NO_2 \underset{-e}{\overset{e}{\rightleftharpoons}} A \longrightarrow B \underset{-e}{\overset{e}{\rightleftharpoons}} C$$

That is, we have two reversible electrochemical steps separated by an irreversible chemical step. The time required for a detectable amount of species B to be formed from reduced species A is 0.5–1.0 sec.

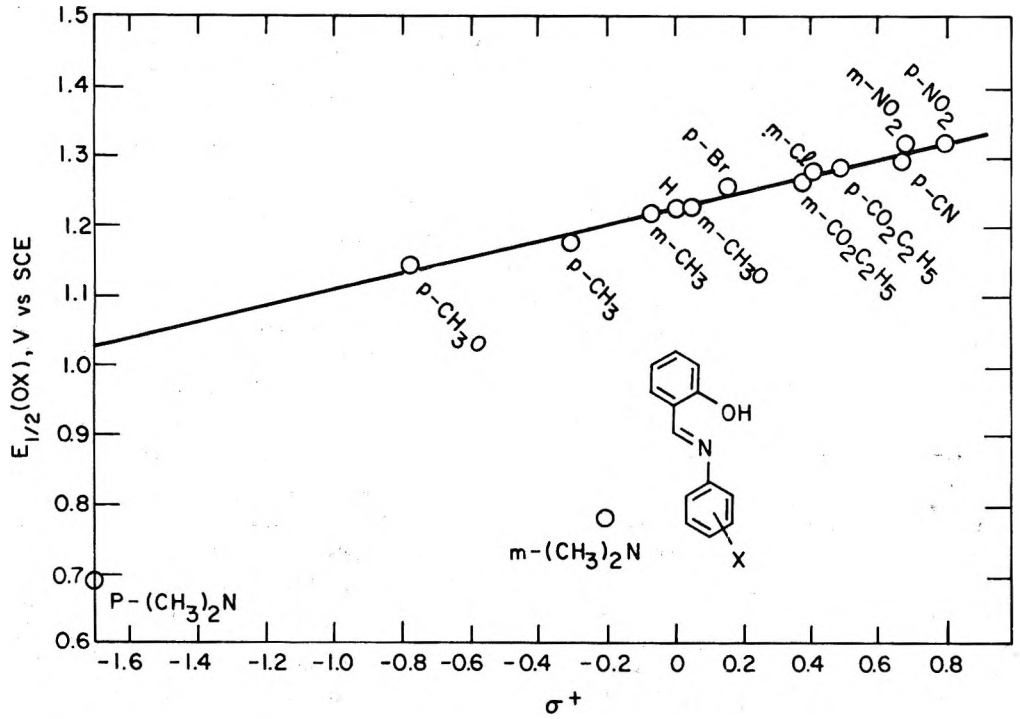

Figure 2. Oxidation half-wave potentials of a series of salicylaldehyde anils (1) vs. electrophilic substituent constant, σ^+.

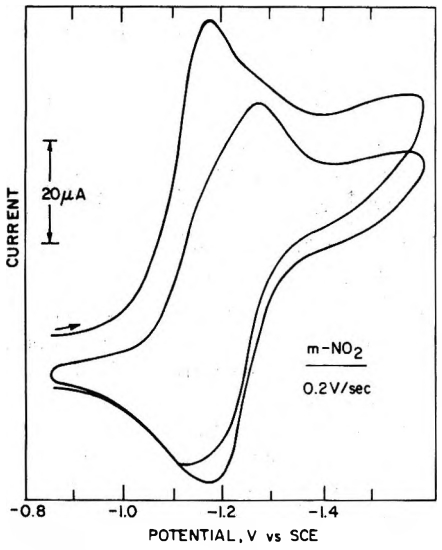

Figure 3. Cyclic voltammogram of salicylaldehyde *m*-nitroanil (1, X = *m*-NO_2) at 200 mV sec^{-1}.

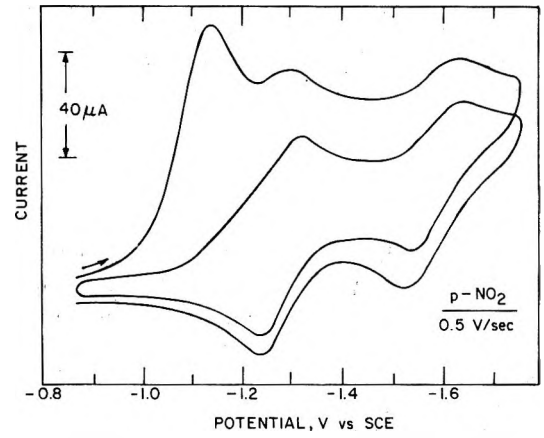

Figure 4. Cyclic voltammogram of salicylaldehyde *p*-nitroanil (1, X = *p*-NO_2). Sweep rate 500 mV sec^{-1}.

The CV behavior of the *p*-NO_2 compound is illustrated in Figure 4. Here again the initial reduction (E_{pc} = −1.12 V) is followed by the irreversible formation of a new electroactive species but at rate much greater than observed for the *m*-NO_2 compound. The events observed in Figure 5 may be represented by the following sequence.

$$\underset{\text{a}}{\text{1, X = } p\text{-NO}_2 \xrightarrow{e} \text{D}} \longrightarrow \underset{\text{b}}{\text{E} \overset{e}{\rightleftharpoons} \text{F}} \underset{\text{c}}{\overset{e}{\rightleftharpoons} \text{G}} \qquad (1)$$

The initial reduction (eq 1, step a) is not reversible on the time scale employed for these experiments and a detectable amount of species E is found to be present as soon as 0.1 sec after initial reduction of 1, X = *p*-NO_2. The product of the irreversible chemical reaction is found to undergo two reversible one-electron transfers characterized by peak potentials (on the second scan) of E_{pc} = −1.31 V and E_{pa} = −1.23 V for the first (eq 1, step b) and E_{pc} = −1.64 V and E_{pa} = −1.51 V for the second step (eq 1, step c).

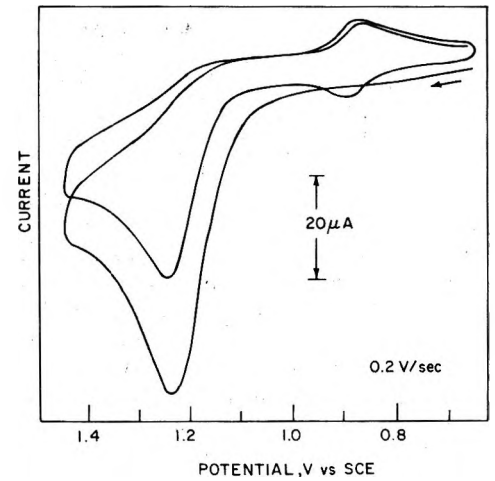

Figure 5. Cyclic voltammogram of salicylaldehyde anil (1, X = H). Sweep rate 200 mV sec^{-1}.

B. Oxidation. The oxidative behavior of the anils, with the exception of the two nitro compounds and the two dimethylamino compounds, is typified by the CV curve

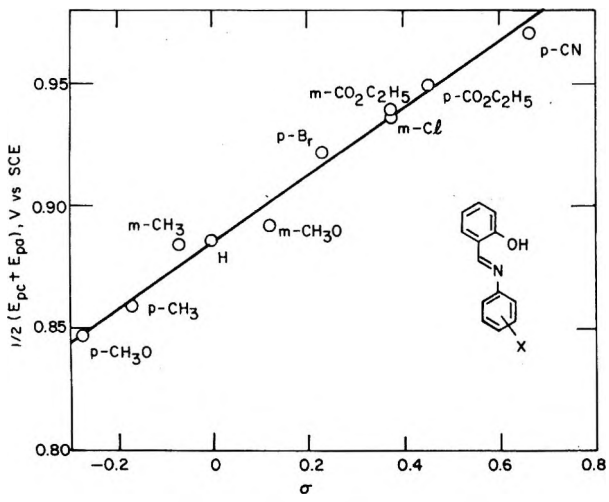

Figure 6. Average of peak potentials for reversible couple formed following CV oxidation of salicylaldehyde anils (1) vs. Hammett σ.

shown in Figure 5. The anodic peak potentials undergo an average positive shift of 32 mV per tenfold increase in scan rate and there is no corresponding cathodic peak seen on reversal of the scan direction. These observations characterize the oxidation as an irreversible one-electron charge transfer. The oxidized species apparently undergoes chemical reaction to form an electroactive product whose reversible redox couple is seen between 0.8 and 1.0 V in the reverse portion of the first scan and in both forward and reverse portions of the second scan. The processes occurring are then

$$1 \xrightarrow{-e} H \longrightarrow I \underset{e}{\overset{-e}{\rightleftharpoons}} J \qquad (2)$$
$$\text{a}$$

The initial oxidation undoubtedly involves the nitrogen atom and hence H = ArCH=$\dot{N}^+$Ar′ in accord with previous findings.[14] This intermediate could then lose a proton to form I, which is a neutral radical stabilized by resonance interaction between O and N. Species I is involved in the redox couple with J, which is presumably a resonance-stabilized cationic species. The mean separation of the peak potentials for the reversible couple (eq 2, step a) produced after initial oxidation is 0.05 V. The average of these $\frac{1}{2}(E_{pc} + E_{pa})$, may be taken as being equal to the half-wave potential for the system of eq 2, step a. As shown in Figure 6, $\frac{1}{2}(E_{pc} + E_{pa})$ shows a linear dependence (R = 0.981) on the Hammett substituent constant σ, the actual relationship being $\Delta(E_{pc} + E_{pa})/2 = 0.14\sigma$. It will be noted that in the case of this reversible charge transfer the best correlation was found with the ordinary σ constant.

The two nitro compounds do not show the presence of the reversible couple following their initial irreversible oxidation. The same is true for the two dimethylamino compounds, but here there is an additional feature of interest. At low scan rates the initial oxidation of the *p*-dimethylamino anil is irreversible, but as the scan rate increases a cathodic peak appears corresponding to the anodic peak of the forward scan. At 0.5 V/sec the separation between the two peaks is 0.09 V. The *m*-dimethylamino anil behaves similarly, so that the observed CV curves correspond to the following processes.

$$1,\ X = N(CH_3)_2 \underset{e}{\overset{-e}{\rightleftharpoons}} K \longrightarrow L$$

The Effect of the Bridging Group. Additional information regarding the nature of the charge transfer process in anils may be obtained by consideration of the isoelectronic series stilbene (2), benzaldehyde anil (3), azobenzene (4), in which methine groups of the bridge are successively replaced by more electronegative nitrogen atoms. Half-wave potentials for reduction (DME) and oxidation (RPE) for these compounds are given in Table I.

Table I
Reduction and Oxidation Half-Wave Potentials in the Isoelectronic Series Stilbene, Benzaldehyde Anil, Azobenzene Together with Hückel Frontier Orbital Energies

Compd	$E_{1/2}$ (redn)[a]	$E_{1/2}$ (oxidn)[a]	Energy of LUMO[b]	Energy of HOMO[b]
2	−2.32	+1.45	−0.544	+0.544
3	−1.96	+1.58	−0.447	+0.642
4	−1.38	+1.72	−0.301	+0.701

[a] AN solution. Potentials vs. SCE. [b] Energies in β units. The following parameters were used: h_N = 0.5, k_{CX} = 0.9 for the bond connecting the phenyl ring to the bridging group, all other h_X = 0, k_{XY} = 1.0.

The results of the electrochemical investigation may be compared with the results of Huckel molecular orbital (HMO) calculations. It is usually assumed[27] that the energy of the lowest unoccupied molecular orbital (LUMO) and highest occupied molecular orbital (HOMO) may be linearly related to the electrochemical reduction and oxidation potentials, respectively. This is borne out for the present series by the data in Table I, which lead to the excellent correlation (R = 0.999)

$$E_{1/2}(\text{redn}) = 3.88E_{\text{LUMO}} - 0.22$$

where E_{LUMO} is the energy of the LUMO expressed in β units. A similar relation is obtained for the oxidation potentials, described by the equation (R = 0.987)

$$E_{1/2}(\text{oxidn}) = 1.68E_{\text{HOMO}} + 0.53$$

Since examination of the eigenvectors obtained in the HMO calculation reveals that both LUMO and HOMO are concentrated on the bridging moiety, it is not surprising that increasing the electronegativity of the atoms located there should have a pronounced effect on the reduction and oxidation potentials in this series. Furthermore, since the effect of hydrogen bonding may be considered to be due in large extent to an increase in the effective electronegativity of the acceptor atom,[28] one might expect similar shifts in half-wave potentials upon comparison of benzaldehyde anil (3, no H bond) with salicylaldehyde anil (1, X = H; internal OH···N bond). Indeed, the presence of an ortho OH group is found to shift the reduction potential, $E_{1/2}$ (redn), 0.26 V more positive, in agreement with the findings of Bezuglyi and coworkers.[12,13] At the same time the oxidation potential, $E_{1/2}$ (oxidn), is shifted 0.28 V, also in the positive direction. It will be noted that the shifts in $E_{1/2}$ (redn) and $E_{1/2}$ (oxidn) (0.26–0.28 V) are the same magnitude as the hydrogen bond energy obtained from a variety of chemical situations.[29]

Mechanisms. Thus, both reduction and oxidation of salicylaldehyde anils occur by charge transfer involving molecular orbitals centered on the bridge between the two rings. The energies of these MO's may in turn be perturbed by altering the effective electronegativity of the bridging group atoms (as by internal hydrogen bonding), and (as demonstrated in the preceding section) by transmission of electronic effects from substituents located distant from the azomethine bridge.

Beyond this, an attempt to elucidate the details of the electrochemical mechanism on the basis of our voltammetric studies was not made. The present results do indicate,

however, that the initial reduction of salicylaldehyde anils in AN takes place by an irreversible one-electron step (a second reduction step not being examined in any detail), in contrast to the conclusions of both Scott and Jura[5] and Bezuglyi et al.[6] Further, in contrast to the results of Martinet, Simonet, and Tendil,[14] however, only a single irreversible one-electron step was observed for the initial oxidation, followed by a chemical reaction whose product forms a reversible redox couple. If the chemical reaction involves loss of a proton from a phenolic group, this would be expected to occur at a rate greater than loss from a methine group as postulated in earlier work.[14]

The exceptions to the general pattern and the deviations from the Hammett plots occur for the reduction of the nitro anils and the oxidation of the dimethylamino anils. In these cases the effect of substitution can no longer be considered as a simple perturbation of the MO's of the azomethine group, and charge transfer now involves orbitals centered on the substituents themselves. The fate of the products of the initial charge transfer is then undoubtedly similar to that of aromatic nitro and amino compounds in general.[30]

Experimental Section

Chemicals. Elemental analyses are by Spang Microanalytical Laboratory, Ann Arbor, Mich. Melting points are corrected. *trans*-Stilbene, zone refined from Aldrich, was used without further purification. Azobenzene (Eastman) was recrystallized from hexane before use. Benzaldehyde anil (mp 52°, lit.[31] mp 53°) was prepared by the condensation of benzaldehyde and aniline and recrystallized from low-boiling petroleum ether. The salicylaldehyde anils were synthesized by condensation of equimolar amounts of salicylaldehyde and substituted anilines in refluxing absolute ethanol for 2 hr. The crude products, which precipitated in 57–100% yields on cooling or after concentration of the solutions, were brought to analytical purity by several (at least three) recrystallizations from ethanol or ethanol–benzene. *p*-$N(CH_3)_2$: mp 135.0–136.0° (reported[32] 137°). Anal. Calcd for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71, N, 11.66. Found: C, 75.17; H, 6.99; N, 11.80. *m*-$N(CH_3)_2$: mp 69–72° (reported[33] 72°). *p*-OCH_3: mp 82.0–83.5° (reported[34] 83–84°). *m*-OCH_3: mp 59.0–60.1° (reported 60°,[32] 61–62° [34]). *p*-CH_3: mp 90.0–91.5° (reported 94°,[32] 97° [34]). *m*-CH_3: bp 161 (1.2 mm), mp 39.0–40.5° (reported[34] 42°). H: mp 49.2–50.4° (reported[34] 49–50°). *p*-Br: mp 108.5–109.7° (reported[34] 110–111°). *m*-Cl: mp 94.0–96.5° (reported[34] 89.0–90.0°). *m*-$COOC_2H_5$: mp 70.0–71.0°. Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.16; H, 5.68; N, 5.16. *p*-$COOC_2H_5$: mp 85.0–86.5° (reported[35] 83°). *p*-CN: mp 122.5–124.0°. Anal. Calcd for $C_{14}H_{10}N_2O$: C, 75.66; H, 4.54; N, 12.61. Found: C, 75.53; H, 4.57; N, 12.54. *m*-NO_2: mp 127.0–128.0° (reported[34] 128°). *p*-NO_2: mp 158.5–159.0° (reported[34] 153°). The solvent for the electrochemical measurements was acetonitrile (Burdick & Jackson, distilled in glass) dried over 4-Å molecular sieves and percolated through a 55-cm column of grade I neutral alumina into a volumetric flask containing sufficient tetraethylammonium perchlorate (Southwestern Analytical Chemicals, dried for 16 hr under vacuum) to produce a 0.1 *M* solution of supporting electrolyte.

Electrochemistry. All measurements were made using the Princeton Applied Research Model 170 Electrochemistry System in the three-electrode mode. The working electrode for reduction was a DME using a 1-sec drop timer. For oxidations a Beckman RPE was used, while for cyclic voltammetry a stationary platinum disk electrode (Beckman) served for both reduction and oxidation studies. An isolated platinum wire was used as the auxiliary electrode, and potentials are referred to a SCE. All runs were made after a 15-min purge with purified nitrogen and within 30 min of preparing the solutions.

Acknowledgment. The syntheses of the salicylaldehyde anils were carried out by Mr. F. C. Bailey, to whom the authors express thanks. Discussion with Professor P. Zuman also proved helpful.

Registry No.—1 [X = *p*-$N(CH_3)_2$], 959-74-0; 1 [X = *m*-$N(CH_3)_2$], 788-19-2; 1 (X = *p*-OCH_3), 889-08-7; 1 (X = *m*-OCH_3), 889-29-2; 1 (X = *p*-CH_3), 782-76-3; 1 (X = *m*-CH_3), 952-81-8; 1 (X = H), 779-84-0; 1 (X = *p*-Br), 886-34-0; 1 (X = *m*-Cl), 886-32-8; 1 (X = *m*-$COOC_2H_5$), 54120-01-3; 1 (X = *p*-$COOC_2H_5$), 3246-76-2; 1 (X = *p*-CN), 33721-67-4; 1 (X = *m*-NO_2), 959-68-2; 1 (X = *p*-NO_2), 788-25-0; 2, 103-30-0; 3, 538-51-2; 4, 103-33-3; benzaldehyde, 100-52-7; aniline, 62-53-3.

References and Notes

(1) (a) Presented in part at the 167th National Meeting of the American Chemical Society, Los Angeles, Calif., April 1974, ORGN 107. (b) This contribution is part III of Linear Free Energy Relationships by H. W. G.; for part II, see *Tetrahedron*, **30**, 2043 (1974). (c) The literature contains several ways of naming compounds of general structure RR'C=NR'' obtained from the condensation of an aldehyde or ketone with ammonia or a primary amine. "Schiff base" refers to the general class of compounds and is used interchangeably with "imine". An "anil" is a Schiff base derived from aniline or a substituted aniline. "Azomethine compounds" are also imines, but the azomethine "group" CH=N is contained not only in imines, but also in such compounds as oximes, hydrazones, and the like.
(2) H. Lund, *Acta Chem. Scand.*, **13**, 249 (1959).
(3) E. Paspaleev and A. Pavlova, *C. R. Acad. Bulg. Sci.*, **18**, 533 (1965).
(4) V. N. Dmitrieva, L. V. Kononenko, and V. D. Bezuglyi, *Teor. Eksp. Khim.*, **1**, 456 (1965).
(5) J. M. W. Scott and W. H. Jura, *Can. J. Chem.*, **45**, 2375 (1967).
(6) L. V. Kononenko, V. D. Bezuglyi, and V. N. Dmitrieva, *Zh. Obshch. Khim.*, **38**, 2153 (1968).
(7) P. Martinet, J. Simonet, and J. Tendil, *C. R. Acad. Sci., Ser. C*, **268**, 303 (1969).
(8) C. P. Andrieux and J. M. Saveant, *J. Electroanal. Chem.*, **33**, 453 (1971).
(9) A. J. Fry and R. G. Reed, *J. Am. Chem. Soc.*, **91**, 6448 (1969).
(10) V. D. Bezuglyi, L. V. Kononenko, A. F. Forunova, V. N. Dmitrieva, and B. L. Timan, *Zh. Obshch. Khim.*, **39**, 1680 (1969).
(11) V. N. Dmitrieva, N. A. Rozanel'skaya, L. V. Kononenko, B. I. Stepanov, and V. D. Bezuglyi, *Zh. Obshch. Khim.*, **41**, 60 (1971).
(12) V. N. Dmitrieva, V. B. Smelyakova, B. M. Krasovitskii, and V. D. Bezuglyi, *Zh. Obshch. Khim.*, **36**, 405 (1966).
(13) N. F. Levchenko, L. Sh. Afanasiadi, and V. D. Bezuglyi, *Zh. Obshch. Khim.*, **37**, 666 (1967).
(14) P. Martinet, J. Simonet, and J. Tendil, *C. R. Acad. Sci., Ser. C*, **268**, 2329 (1969).
(15) G. Briere, R. Herino, and F. Mondon, *Mol. Cryst. Liq. Cryst.*, **19**, 157 (1972).
(16) A. Lomax, R. Hirasawa, and A. J. Bard, *J. Electrochem. Soc.*, **119**, 1679 (1972).
(17) A. Denat, B. Gosse, and J. P. Gosse, *Chem. Phys. Lett.*, **18**, 235 (1973).
(18) H. W. Gibson, *Can. J. Chem.*, **51**, 3065 (1973).
(19) P. J. Cressman, G. C. Hartmann, J. E. Kuder, F. D. Saeva, and D. Wychick, *J. Chem. Phys.*, **61**, 2740 (1974).
(20) H. W. Gibson and J. E. Kuder, to be published.
(21) P. Zuman, "Substituent Effects in Organic Polarography," Plenum Press, New York, N.Y., 1967.
(22) Hammett substituent constants are taken from C. D. Ritchie and W. F. Sager, *Prog. Phys. Org. Chem.*, **2**, 323 (1964).
(23) L. Meites, "Polarographic Techniques", 2nd ed, Wiley-Interscience, New York, N.Y., 1965.
(24) A. H. Maki and D. H. Geske, *J. Chem. Phys.*, **33**, 825 (1960).
(25) V. Dvorak, I. Menec, and J. Zyka, *Microchem. J.*, **12**, 99 (1967).
(26) R. S. Nicholson and I. Shain, *Anal. Chem.*, **36**, 706 (1964).
(27) G. Briegleb, *Angew. Chem., Int. Ed. Engl.*, **3**, 617 (1964).
(28) B. Pullman and A. PULLMAN= "Quantum Biochemistry", Wiley-Interscience, New York, N.Y., 1963, Chapter 3.
(29) L. Pauling, "The Nature of the Chemical Bond", 3rd ed, Cornell University Press, Ithaca, N.Y., 1960, Chapter 12.
(30) C. K. Mann and K. K. Barnes, "Electrochemical Reactions in Nonaqueous Systems", Marcel Dekker, New York, N.Y., 1970, Chapters 9 and 11.
(31) E. Heilbronner, J. N. Murrell, F. Gerson, and J. Schulze, *Helv. Chim. Acta*, **44**, 428 (1961).
(32) French Patent 1,427,102 (1966); *Chem. Abstr.*, **65**, 9069*f* (1966).
(33) B. M. Krasovitskii, B. M. Bolotini, and N. Nurmukhametov, *Zh. Obshch. Khim.*, **34**, 3786 (1964).
(34) E. W. Gooden, *Aust. J. Chem.*, **18**, 637 (1965).
(35) M. D. Cohen, G. M. J. Schmidt, and S. Flavian, *J. Chem. Soc.*, 2041 (1964).

Chemistry of Sulfoacetic Acid Derivatives. III.[1] Reactions of Derivatives of Sulfoacetic Acid, Benzoylmethanesulfonic Acid, and *p*-Nitrophenylmethanesulfonic Acid with Salicylaldehydes

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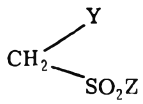
Diphenyl sulfoacetate (**1a**), sulfoacetic acid dianilide (**1b**), and carbophenoxymethanesulfonanilide (**1c**) react with salicylaldehydes under the conditions of the Knoevenagel reaction to form products characterized as coumarins (**2**). Phenyl *N*-phenylcarbamylmethanesulfonate (**1d**), phenyl benzoylmethanesulfonate (**1e**), and phenyl *p*-nitrophenylmethanesulfonate (**1f**) condense with salicylaldehydes to form sultones (**4**) by mechanisms involving nucleophilic transesterification at a sulfophenoxy sulfonyl group. The transesterification, hydrolysis, and anilinolysis reactions of **1f** and the conversion of **1d**, **1e**, and **1f** to sultones appear to proceed analogously via sulfene intermediates.

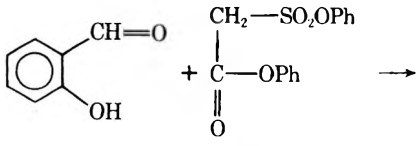
In a previous communication,[1a] we have demonstrated that diphenyl sulfoacetate (**1a**) undergoes a number of classical reactions at its central methylene group (in its anionic form) and nucleophilic substitution reactions at both the carbophenoxy and the sulfophenoxy groups. The unusual reactivity of the sulfophenoxy group toward nucleophiles was noted and was attributed to its proximity to the electron-withdrawing carbophenoxy group and its ability to form a sulfene intermediate ($>C{=}SO_2$)[2] under the basic conditions of the reactions studied.

We now wish to summarize another series of related reactions performed with **1a**, with the dianilide (**1b**) and phenyl ester anilide (**1c**, **1d**) derivatives of sulfoacetic acid, and with phenyl esters (**1e**, **1f**) of other similar negatively substituted methanesulfonic acids indicated generally by structure **1**.

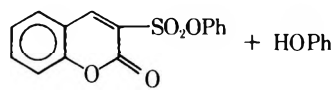


1a, Y = CO_2Ph; Z = OPh
b, Y = CONHPh; Z = NHPh
c, Y = CO_2Ph; Z = NHPh
d, Y = CONHPh; Z = OPh
e, Y = COPh; Z = OPh
f, Y = *p*-$O_2NC_6H_4$; Z = OPh

The members of this series of compounds react rapidly and in high yields with salicylaldehydes to form cyclic condensation products. For example, **1a** condenses with salicylaldehyde to produce a material that has been characterized as phenyl 3-coumarinsulfonate (**2a**).[3] A number of



1a

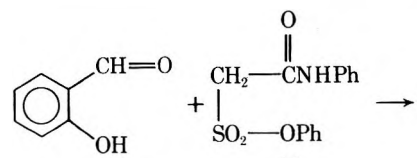


2a

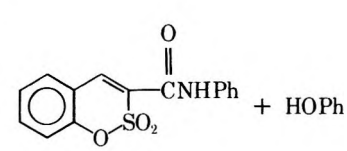
such coumarins (Table I) have been derived from variously substituted salicylaldehydes and **1a**, **1b**, and **1c**. In a parallel study, it was found that diphenyl malonate could be converted with the same salicylaldehydes to a series of previously unknown 3-carbophenoxycoumarins (**3**) (see Table II).

The formation of coumarin derivatives from **1a**, **1b**, **1c**, and diphenyl malonate is catalyzed by piperidine, the usual Knoevenagel reaction catalyst.[4] A variety of other basic agents, such as pyridine, potassium carbonate, sodium acetate, potassium fluoride, and the hydroxy, carbonate, and acetate forms of Dowex 1X4 anionic exchange resin,[4,5] all proved to be as effective as piperidine in promoting the reaction. Diphenyl malonate is generally more reactive with salicylaldehyde than **1a** under the same experimental conditions.[6] Both diphenyl malonate and **1a** failed to react with *o*-hydroxyacetophenone under all conditions attempted.

1a fails to react with benzaldehyde or *p*-nitrobenzaldehyde under the usual conditions of the Knoevenagel reaction.[4] Its facile condensation with salicylaldehydes is apparently dependent upon the formation of the stable lactone structure of the coumarin (**2**) by a transesterification occurring, as a crucial step, at the carbonyl portion of the carbophenoxy group in **1a**. A nucleophilic displacement of the phenoxide ion at the sulfonyl portion of the sulfophenoxy group is apparently not favored in this case and therefore no sultone (**4**) is formed. Similarly, the dianilide (**1b**) and carbophenoxymethanesulfonanilide (**1c**), in condensing with salicylaldehyde, both form *N*-phenyl-3-coumarinsulfonamide (**2i**) by mechanisms involving nucleophilic attack at the carbonyl groups in **1b** and **1c**. In contrast, the isomer of **1c**, phenyl *N*-phenylcarbamylmethanesulfonate (**1d**), forms sultones **4a** and **4b** (see Table I) when treated



1d

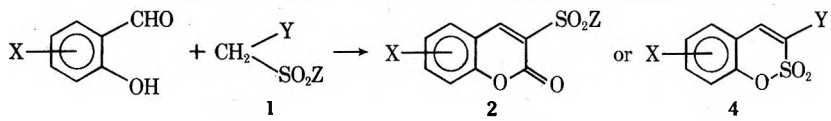


4a

with salicylaldehyde and 3-nitrosalicylaldehyde by mechanisms which must involve nucleophilic transesterification at the sulfonyl group in **1d**. In an analogous manner, phenyl benzoylmethanesulfonate (**1e**) and phenyl *p*-nitrophenylmethanesulfonate (**1f**) both form the corresponding sultones (**4c–f** and **4g–j**).[7]

As reported previously for **1a**,[1a] compounds **1e** and **1f** both react in refluxing pyridine with aniline to form the

Table I
Cyclization Reactions of Compounds 1a–f with Salicylaldehydes

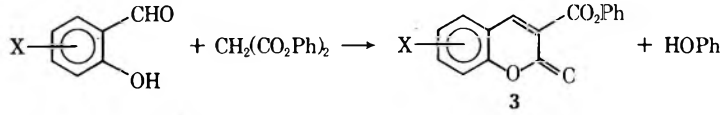


1 2 4

Salicylaldehyde		Substituent							
Registry no.	Substituent, X	Compd	Y	Z	Conditions[a]	Product	Formula[b]	Yield, %	Mp, °C[c]
90-02-8	H	1a	CO_2Ph	OPh	B	2a	$C_{15}H_{10}O_5S$	77	138–139
89-55-4	5-Br	1a	CO_2Ph	OPh	B[d]	2b	$C_{15}H_9BrO_5S$	100	182–183
321-14-2	5-Cl	1a	CO_2Ph	OPh	B	2c	$C_{15}H_9ClO_5S$	98	174–175
85-38-1	3-NO_2	1a	CO_2Ph	OPh	B	2d	$C_{15}H_9NO_7S$	40	138–139
96-97-9	5-NO_2	1a	CO_2Ph	OPh	B	2e	$C_{15}H_9NO_7S$	93	201–202
95-01-2	4-OH	1a	CO_2Ph	OPh	C	2f	$C_{15}H_{10}O_6S$	58	173–174
148-53-8	3-OCH_3	1a	CO_2Ph	OPh	B	2g	$C_{16}H_{12}O_6S$	91	185–186
708-06-5	2-Hydroxy-1-naphthaldehyde[e]	1a	CO_2Ph	OPh	B	2h	$C_{19}H_{12}O_5S$	93	186–187
	H	1b	CONHPh	NHPh	A	2i	$C_{15}H_{11}NO_4S$	42	200–200.5
	H	1c	CO_2Ph	NHPh	A	2i	$C_{15}H_{11}NO_4S$	48	200–200.5
	H	1d	CONHPh	OPh	B	4a	$C_{15}H_{11}NO_4S$	35	173–174
	3-NO_2	1d	CONHPh	OPh	A	4b	$C_{15}H_{10}N_2O_6S$	57	212–214
	H	1e	COPh	OPh	A	4c	$C_{15}H_{10}O_4S$	65	142–143
	5-Br	1e	COPh	OPh	D	4d	$C_{15}H_9BrO_4S$	58	159–160
	5-NO_2	1e	COPh	OPh	A[f]	4e	$C_{15}H_9NO_6S$	30	139–140
	2-Hydroxy-1-naphthaldehyde[e]	1e	COPh	OPh	A[f]	4f	$C_{19}H_{12}O_4S$	69	208–209
	H	1f	p-$O_2NC_6H_4$	OPh	A	4g	$C_{14}H_9NO_5S$	54	220–221
	5-Br	1f	p-$O_2NC_6H_4$	OPh	D	4h	$C_{14}H_8BrNO_5S$	82	238–239
	5-Cl	1f	p-$O_2NC_6H_4$	OPh	D	4i	$C_{14}H_8ClNO_5S$	50	220–221
	5-NO_2	1f	p-$O_2NC_6H_4$	OPh	D	4j	$C_{14}H_8N_2O_7S$	60	213–214

[a] See Experimental Section. [b] Satisfactory analytical data (±0.3% for C, H, N) were reported for all new compounds listed in the table. [c] Determined (uncorrected) on a Fisher-Johns apparatus. [d] Conditions C gave 67% yield. [e] A. Russell and L. B. Lockhart, "Organic Syntheses", Collect. Vol. III, Wiley, New York, N.Y., 1955, p 463. [f] Room temperature.

Table II
Reactions of Diphenyl Malonate with Salicylaldehydes



3

Salicylaldehyde Substituent, X	Compd	Formula[a]	Yield, %	Mp, °C[b]	Registry no.
H	3a	$C_{16}H_{10}O_4$	51	158–159[c]	53992-24-8
5-Br	3b	$C_{16}H_9BrO_4$	91[d]	233–234	53992-25-9
5-Cl	3c	$C_{16}H_9ClO_4$	80	228–229	53992-26-0
3-NO_2	3d	$C_{16}H_9NO_6$	21	235–236	53992-27-1
5-NO_2	3e	$C_{16}H_9NO_6$	67	250–251	53992-28-2
3-OCH_3	3g	$C_{17}H_{12}O_5$	76	148–149	53992-29-3
2-Hydroxy-1-naphthaldehyde[e]	3h	$C_{20}H_{12}O_4$	69	193–194	53992-30-6

[a] Satisfactory analytical data (±0.3% for C, H) were reported for all new compounds listed in the table. [b] Determined (uncorrected) on a Fisher-Johns apparatus. [c] Mp 156° reported by P. M. Bhargava and S. H. Zaheer, *J. Chem. Soc.*, 311 (1952). [d] See ref 6. [e] See footnote *e*, Table I.

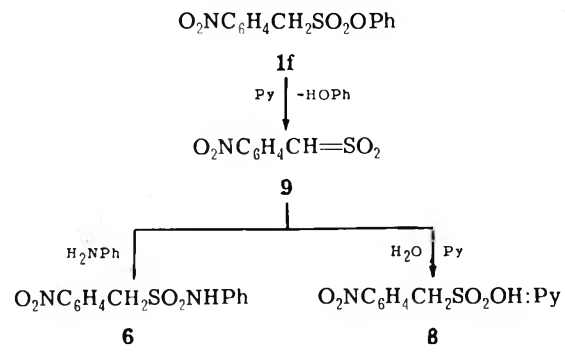
corresponding anilides (**5** and **6**) and with water to form with corresponding sulfonic acids, isolated as their pyridine salts (**7** and **8**) (see Table III). It seems quite likely that these reactions occur by way of a sulfene intermediate (**9**) generated in the basic medium by the elimination of phenol, followed by the addition of aniline or water to the sulfene.[1a,2]

It is tempting to rationalize the cyclization of **1d, 1e,** and **1f** with salicylaldehydes to form sultones in terms of a reaction mechanism involving a sulfene intermediate. If a sulfene is involved, structure **10,** which would result from a simple Knoevenagel reaction of salicylaldehyde with **1f** and which, like phenyl benzenesulfonate, is incapable of forming a sulfene, cannot be an intermediate in the cyclization reaction. In support of this conclusion, it was found that under the conditions (piperidine in refluxing benzene or hot pyridine) used for the reactions of **1f** with salicylaldehydes to form sultones (**4g–j**), **1f,** like **1a,** does not react with benzaldehyde or *p*-nitrobenzaldehyde.[8] When heated under the same conditions (hot pyridine) with a 3-molar

Table III
Products of the Anilinolysis and Hydrolysis of 1e and 1f

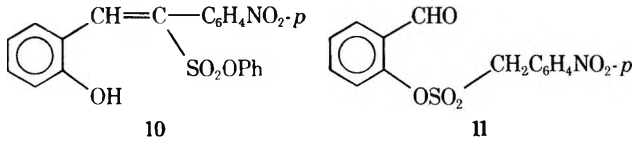
Compd	Structure[a]	Yield, %	Mp, °C[b]	Registry no.
5	$PhCOCH_2SO_2NHPh$	74	109–110	7117-22-8
6	$O_2NC_6H_4CH_2SO_2NHPh$	83	125–126	53992-31-7
7	$PhCOCH_2SO_2OH{:}Py$	56	109–110	53992-32-8
8	$O_2NC_6H_4CH_2SO_2OH{:}Py$	80	157–161	53992-34-0

[a] Satisfactory analytical data (±0.2% for C, H, N) were reported for all new compounds listed in the table, with the exception of 7 (±0.4% for C). [b] Determined (uncorrected) on a Fisher-Johns apparatus.



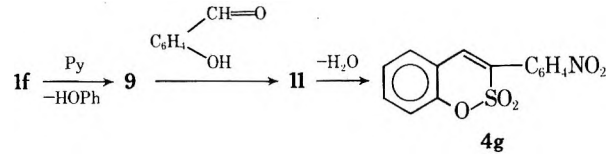
excess of *p*-chlorophenol, **1f** is converted by transesterification to the corresponding *p*-chlorophenyl ester in approximately 35% yield (by NMR analysis of the resulting ester mixture), a reaction which is analogous to the anilinolysis and hydrolysis of **1f** described above.

These results provide compelling support for structure **11**, rather than **10**, as the initially formed intermediate in



10 11

the cyclization of **1f** with salicylaldehyde to form the sultone **4g** and for the possibility that in the overall cyclization reactions of **1d**, **1e**, and **1f** with salicylaldehydes, transesterification, via a sulfene, precedes the Knoevenagel elimination of water.



4g

In the general formation of sultones (**4**) under the rather mild conditions of the reactions that we have described, the facile replacement of a phenoxide ion at a sulfonyl group is remarkable in view of the well-known inertness of other phenyl sulfonate esters, such as phenyl methanesulfonate and phenyl benzenesulfonate, toward nucleophilic agents under considerably more strenuous conditions.[1a] The present work suggests that reactions of this type may eventually have greater synthetic utility than is now generally recognized.

Experimental Section

Reactions of 1 and Diphenyl Malonate with Salicylaldehydes. The phenyl ester or anilide represented by structure **1** or diphenyl malonate and an equimolar quantity of a salicylaldehyde were dissolved in a reagent-grade solvent, approximately a 0.1 molar equiv quantity of the basic agent was added, and the resulting mixture was stirred and/or heated. The various conditions employed may be summarized as follows: A, benzene, piperidine, reflux 4–8 hr; B, acetone, K_2CO_3, or the carbonate form of Dowex 1X4 (J. T. Baker Chemical Co.) anionic exchange resin at room temperature; C, acetone, KF, or $NaC_2H_3O_2$ at room temperature; D, pyridine, steam heat 24 hr. Completeness of the reaction was determined by TLC. The product was isolated by evaporation of the solvent, rinsing with water or with dilute HCl when necessary, and recrystallization from acetone–water or methanol–water mixtures. Products were characterized by melting point, ir, NMR, and by elementary analyses, which were performed by Galbraith Laboratories, Knoxville, Tenn. The reactions, conditions, and the products derived from compounds **1a–f** are summarized in Table I. The new products derived from diphenyl malonate are summarized in Table II.

Preparation of Materials. A. Compounds **1a–d** were prepared by methods described previously in part II of this series.[1a]

B. Phenyl Benzoylmethanesulfonate (1e). $PhOSO_2CH_2CO_2H$ (5 g, 23.1 mmol), obtained by the acidic hydrolysis of **1a**,[1a] was treated with 20 ml of refluxing $SOCl_2$ for 45 min. Excess $SOCl_2$ was removed by evaporation under reduced pressure, last traces being removed by evaporation with a small quantity of anhydrous ethyl ether added to the crude mixture. The residual sulfonyl chloride was taken up in 10 ml of anhydrous benzene, 10 g of anhydrous $AlCl_3$ was added, and the resulting mixture was stirred and warmed at gentle reflux for 45 min. Excess benzene was removed by evaporation and ice and dilute HCl was added to the residual mixture. The crude solid was removed by filtration and was recrystallized from a methanol–water mixture to afford 4.1 g (64%) of product, mp 57–58°.

Anal. Calcd for $C_{14}H_{12}O_4S$: C, 60.85; H, 4.38. Found: C, 61.30; H, 4.29.

C. Phenyl *p*-Nitrophenylmethanesulfonate (1f). A solution of 5.0 g (26.8 mmol) of *p*-nitrobenzyl chloride and 3.69 g (29.3 mmol) of Na_2SO_3 in 150 ml of 50% aqueous acetone was heated at gentle reflux for a period of 10 hr. The resulting clear solution was evaporated to about 35 ml, chilled, and filtered to remove unchanged *p*-nitrobenzyl chloride, rinsing with a small portion of cold water. The clear filtrate was passed through a column of Dowex 50W-X4 cation exchange resin (J. T. Baker Chemical Co.). The strongly acidic eluent was evaporated to a syrupy liquid form of the intermediate *p*-nitrophenylmethanesulfonic acid, which partially crystallized on cooling. To the crude sulfonic acid was added 3.5 g (37.1 mmol) of phenol and 10 ml of $POCl_3$ and the resulting mixture was heated at 75–85° for a period of 8 hr, when evolution of HCl seemed to be complete. The reaction mixture was poured onto ice with stirring. After hydrolysis of excess $POCl_3$ was complete, excess acid was neutralized by adding solid Na_2CO_3. The resulting crude solid was removed by filtration and washed with large volumes of cold water. The wet solid was recrystallized several times from methanol–water mixtures to afford 4.2 g (49% overall) of a flaky, light-gold material: mp 135–136°; NMR (Hitachi Perkin-Elmer R-24) (acetone) δ 4.45 (s, 2 H), 6.65 (br s, 5 H), 7.20, 7.65 (2 d, 4 H, J = 1.5 Hz).

Anal. Calcd for $C_{13}H_{11}NO_5S$: C, 53.23; H, 3.78; N, 4.78. Found: C, 53.40; H, 4.07; N, 4.96.

D. Diphenyl malonate was prepared by an adaption of the method of Auger.[9]

E. The various salicylaldehydes were used as obtained from Eastman Chemicals Co., Rochester, N.Y.

Hydrolysis and Anilinolysis of 1e and 1f. The reactions of **1e** and **1f** with water and aniline were carried out in refluxing pyridine as described in part II of this series.[1a] The products of these reactions are summarized in Table III.

Transesterification of 1f. A solution of 0.5 g (1.7 mmol) of **1f** and 0.66 g (5.1 mmol) of *p*-chlorophenol in pyridine was heated on a steam bath for 24 hr. The mixture was then poured into ice–water and the resulting solid material was removed by filtration. The crude solid was washed repeatedly by stirring with water until the supernatant, according to a $FeCl_3$ test, was free of phenols. After a single recrystallization, TLC indicated the solid to be a mixture. A comparison of the NMR spectrum of the mixture dissolved in acetone with that of **1f** indicated the presence of a new pair of doublets (J = 1.5 Hz) for the *p*-chlorophenoxy group centered at δ 6.65 and superimposed on the aromatic singlet for the original phenyl ester **1f**. Using the CH_2 singlet (δ 4.45) as a reference, the integration of the δ 6.65 signals indicated the mixture to contain approximately 35% of the *p*-chlorophenyl ester and 65% of **1f**. The equilibrium composition of the transesterification mixture was not determined.

Registry No.—**1a**, 53973-62-9; **1b**, 7117-27-3; **1c**, 16753-80-3; **1d**, 16753-81-4; **1e**, 53992-03-3; **1f**, 53992-04-4; **2a**, 53992-05-5; **2b**, 53992-06-6; **1f**, 53992-04-4; **2a**, 53992-05-5; **2b**, 53992-06-6; **2c**, 53992-07-7; **2d**, 53992-08-8; **2e**, 53992-09-9; **2f**, 53992-10-2; **2g**, 53992-11-3; **2h**, 53992-12-4; **2i**, 53992-13-5; **4a**, 53992-14-6; **4b**, 53992-15-7; **4c**, 53992-16-8; **4d**, 53992-17-9; **4e**, 53992-18-0; **4f**, 53992-19-1; **4g**, 53992-20-4; **4h**, 53992-21-5; **4i**, 53992-22-6; **4j**, 53992-23-7; diphenyl malonate, 1969-44-4.

References and Notes

(1) (a) Part II: B. E. Hoogenboom, M. S. El-Faghi, S. C. Fink, E. D. Hoganson, S. E. Lindberg, T. J. Lindell, C. J. Linn, D. J. Nelson, J. O. Olson, L. Rennerfeldt, and K. A. Wellington, *J. Org. Chem.*, **34**, 3414 (1969). (b) Supported by a F. G. Cottrell grant from Research Corporation, Public Health Service Grant GM12153, National Science Foundation Undergraduate Research Participation Grant No. GE-9467, and the Gustavus Adolphus College Research Fund.

(2) G. Opitz, *Angew. Chem., Int. Ed. Engl.*, **6**, 107 (1967).

(3) Phenyl carbethoxymethanesulfonate, $PhOSO_2CH_2CO_2C_2H_5$, derived from $ClSO_2CH_2CO_2C_2H_5$ [R. Vieillefosse, *Bull. Soc. Chim. Fr.*, 351 (1947)], reacts with salicylaldehyde under the same conditions to produce the same product, 2a. Phenyl carboxymethanesulfonate, $PhOSO_2CH_2CO_2H$, is not cyclized to **2a** under the same conditions (piperidine in refluxing benzene) but is instead decarboxylated to form $PhOSO_2CH_3$ in 98% yield.[1a] *N*-Phenylsulfamylacetic acid, $PhNHSO_2CH_2CO_2H$,[1a] is less readily decarboxylated, however, and is cyclized under the same conditions or in refluxing pyridine to form the coumarin (**2l**) in 83% yield.

(4) G. Jones, *Org. React.*, **15**, 204 (1967).

(5) R. W. Hein, M. J. Astle, and J. R. Shelton, *J. Org. Chem.*, **26**, 4874 (1961).

(6) Diphenyl malonate reacts with 5-bromosalicylaldehyde in an acetone solvent without the benefit of an added basic agent to form a high yield (91%) of 6-bromo-3-carbophenoxycoumarin (**3b**, Table II).

(7) The parent sultone is referred to in *Chemical Abstracts* as 1,2-benzoxathiin 2,2-dioxide.

(8) In fact, when water is not carefully excluded from the reaction mixture, the product isolated is the hydrolysis product (**8**). Apparently, once the anion of **1f** is formed, the unimolecular dissociation to form a sulfene (**9**) is faster than the bimolecular reaction with an aldehyde to form the Knoevenagel intermediate addition product, $ArCHOHCHAr'SO_2OPh$.

(9) V. Auger, *C. R. Acad. Sci.*, **136**, 556 (1903).

Thermal Decomposition of *o*- and *p*-Benzenedisulfonyl Azides in Benzene, Cyclohexane, Cyclohexene, and Tetracyclone[1]

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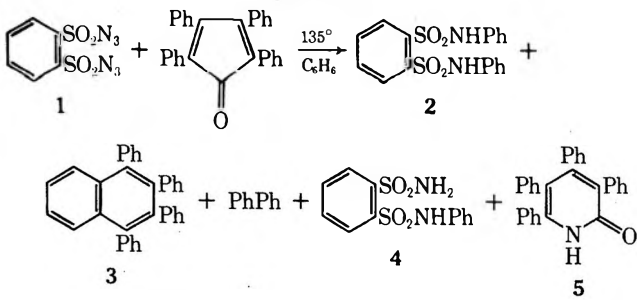
The thermolysis of *o*-benzenedisulfonyl azide in benzene and cyclohexane gives products which can be rationalized as arising from both benzyne and a singlet sulfonyl nitrene. The former can be trapped with tetracyclone whereas the sulfonyl nitrene undergoes aromatic substitution with benzene, C–H insertion into cyclohexane, and addition to tetracyclone. The termolysis of *p*-benzenedisulfonyl azide in benzene, toluene, and cyclohexane leads only to singlet sulfonyl nitrene. Both *o*- and *p*-benzenedisulfonyl azide react readily with cyclohexene to give a diimine or dienamine as the primary product. In the case of the o-diazide, an interesting secondary product was isolated. Formation of the primary product is best explained in terms of a 1,3-dipolar addition mechanism.

The thermal decomposition of monosulfonyl azides in benzene and cyclohexane is known[2] to give singlet sulfonyl nitrene. While disulfonyl azides have been used for the cross-linking of hydrocarbon polymers,[2b] their reactions with aromatic hydrocarbons have not been reported. In this paper we report the thermal decompositions of *o*- and *p*-benzenedisulfonyl azide in benzene, cyclohexane, tetracyclone, and cyclohexene.

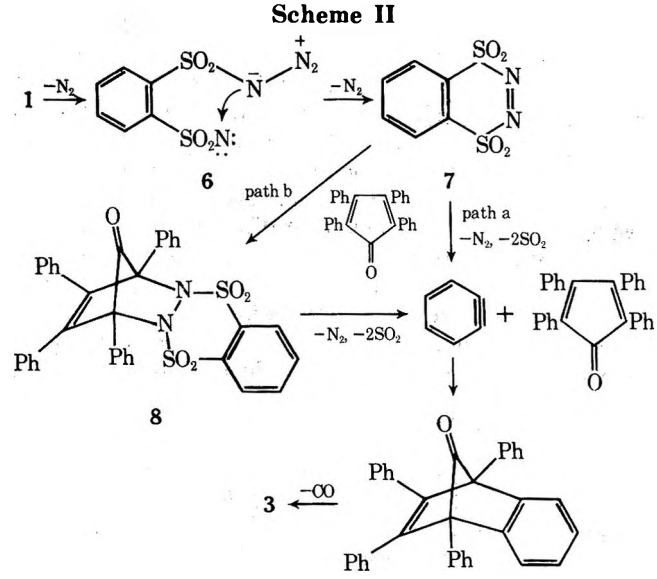
Thermolysis of the *o*-diazide (**1**) in a large excess of benzene at 135° gave the expected nitrene product, o-benzenedisulfonylanilide (**2**, 21%) as the only isolable product. When the same reaction was carried out in the presence of tetracyclone (1.1 molar equiv), an interesting array of products was isolated and these are illustrated in Scheme I.

Scheme I

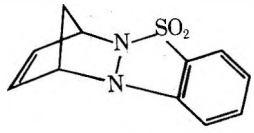


From the nature of the products, it is evident that two different reactive intermediates, likely a benzyne and a sulfonyl nitrene, are being generated from **1** and that at least three mechanisms must be invoked in order to explain the formation of all products. The tetraphenylnaphthalene (**3**, 6%) probably results from the cycloaddition of benzyne to tetracyclone. Possible mechanisms leading to benzyne from **1** are depicted in Scheme II. The electrophilic singlet nitrene (**6**) could cyclize to the unstable cyclic azodisulfone (**7**), which could either eliminate nitrogen and two molecules of sulfur dioxide (path a) or undergo cycloaddition (path b) to tetracyclone to give adduct **8**, and then eliminate nitrogen and sulfur dioxide to give benzyne. Although

Scheme II



the reaction was carried out at 135° and path a would be expected to be a facile process, path b cannot be discounted. It has been observed[3] that 1,2,3-benzothiadiazole 1,1-dioxide reacts with cyclopentadiene to give adduct **9**, which

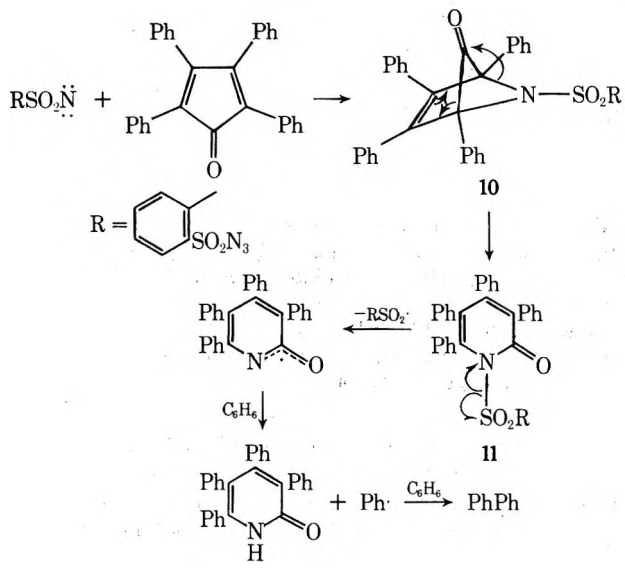


9

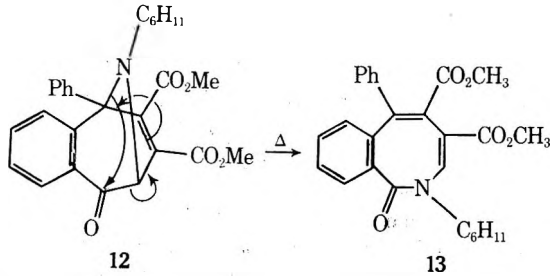
decomposes at 75° to give nitrogen, sulfur dioxide, cyclopentadiene, and benzyne.

o-Benzenedisulfonylanilide (**2**, 9%) and benzenesulfonylanilide-2-sulfonamide (**4**, 5%) are normal aromatic substitution and mixed substitution–hydrogen abstraction products, respectively, of the disulfonyl nitrene. It is not obvious, however, why **4** is formed only in the presence of tetracyclone but not in its absence, but it (or other products or intermediates, e.g., see Scheme III) could probably catalyze the singlet → triplet interconversion in the monosubstituted mononitrene.

Scheme III

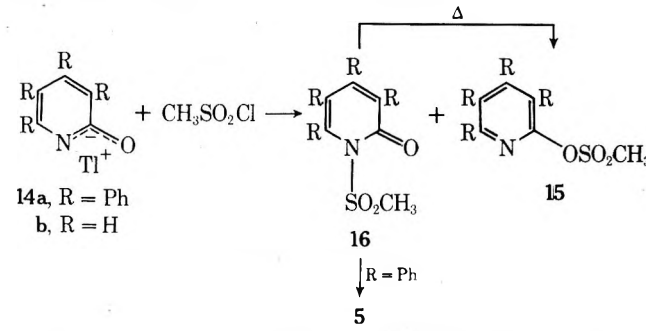


A possible mechanism which could explain the formation of tetraphenyl-2-pyridone (**5**, 13%) and biphenyl is outlined in Scheme III. 1,4-Addition by singlet sulfonyl nitrene to tetracyclone would give the symmetrical intermediate **10** which, on ring expansion, would lead to **11**. Homolytic cleavage of the S–N bond [probably encouraged by the presence of the 6-phenyl substituent in **11** (see below)] followed by hydrogen abstraction from benzene would lead to **5** and a phenyl radical. The latter with benzene would give biphenyl. The ring expansion **10** → **11** has precedent in the known[4] expansion of **12** in boiling toluene to **13**.



12 **13**

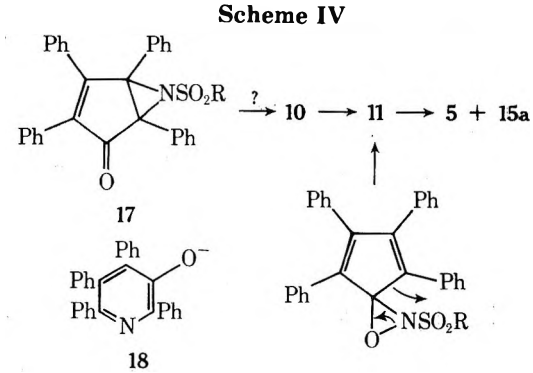
The instability of **11** (or its equivalent) was verified in studies on model compounds. Methanesulfonylation of thallium(I) 2-pyridone (**14b**) in ether at room temperature gave *N*-mesyl-2-pyridone (**16b**, 48%) ($\nu_{C=O}$ 1670 cm^{-1}) and 2-pyridyl methanesulfonate (**15b**, 52%) (no C=O absorption). When **16b** was heated either alone at 175° or in methylene bromide at 135° it rearranged quantitatively to **15b**.[5] On the other hand, methanesulfonation of the thallium(I) salt **14a** in ether (the reaction in other solvents gave similar results) at room temperature (or below) gave **5** (25%) ($\nu_{C=O}$ 1670 cm^{-1}) and 3,4,5,6-tetraphenyl-2-pyridyl methanesulfonate (**15a**, 72%) (no C=O absorption). The *N*-sulfonyl derivative (**16a**) was never detected, even when the reaction was carried out at low temperature. It is undoubtedly formed (**15a** does not hydrolyze to **5** under the reaction conditions or during the isolation procedure; no reaction occurred between **15a** and mesyl chloride) but is unstable (probably owing to steric hindrance by the 6-phenyl group) and either rearranges to **15a** or eliminates methylene sulfene (or its equivalent)[6] to give **5**. With the bulkier ortho-disubstituted benzene elimination probably takes place before any N → O migration can occur (the o-sulfonyl azide function may also play a role in this elimination).



The reaction of sulfonyl azides with tetracyclone appears to have some generality. Thus, methanesulfonyl azide reacts with tetracyclone in methylene bromide at 135° to give **5** (12%), **15a** (12%), and methanesulfonamide (26%). No reaction took place at 80° so that this is not a 1,3-dipolar addition of azide to tetracyclone (such reactions with strained and unstrained double bonds occur at much lower temperature than 135° [7]) but suggests rather that a nitrene is the reactive intermediate.

Three possible modes of addition of a nitrene to tetracyclone can account for the formation of **5** and **15a**: (i) 1,2-addition to give **17** followed by rearrangement to the 1,4 adduct **10** and thence **11**, **5**, and **15a**; (ii) direct 1,4-addition to give **10**; (iii) 1,2-addition to C=O and then rearrangement to **11** (Scheme IV). Precedent for this last possibility

Scheme IV



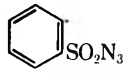
is the known reaction of methylene with acetone to give an oxirane.[8] This was tested by heating methanesulfonyl azide with fluorenone in methylene bromide; an addition to the carbonyl followed by rearrangement would lead to a phenanthridone, while both 1,2- and 1,4-addition to the cyclopentadienone portion are unlikely. In fact, no phenanthri-

done was formed; only a small amount of a monobromo-9-fluorenone was isolated and 9-fluorenone was recovered together with methanesulfonamide (67%) (abstraction from CH_2Br_2). Singlet ethoxycarbonyl nitrene is known[9] to undergo exclusive 1,2-addition to conjugated olefins, but the vinylaziridine so formed rearranges thermally to the apparent 1,4 adduct. On the other hand, its reactions with pyrrole and with 2,5-dimethylthiophene have been formulated as going via the 1,4 adduct.[10] If a 1,2 adduct (**17**) were indeed formed it might have been expected to rearrange to some extent to a betaine **18**. No such product was ever detected, however, which suggests that a direct 1,4-addition may indeed be occurring.

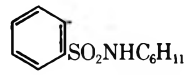
Thermolysis of the *o*-diazide **1** in cyclohexane at 135° gave *N*-cyclohexylbenzenesulfonamide and *N,N'*-dicyclohexyl-*o*-benzenedisulfonamide in 47 and 3% yields, respectively. The most striking feature of this reaction is that a

$$o\text{-}C_6H_4(SO_2N_3)_2 + C_6H_{12} \xrightarrow{\Delta} C_6H_5SO_2NHC_6H_{11} + o\text{-}C_6H_4(SO_2NHC_6H_{11})_2$$

sulfonyl azide moiety is completely lost. It is conceivable that an aryl radical (either **19** or **20**) is formed as an inter-



19



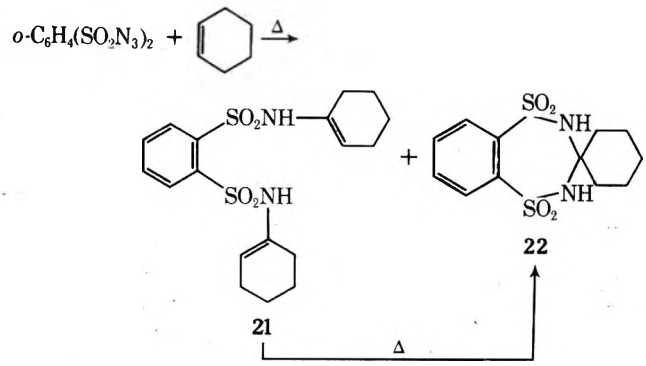
20

mediate which abstracts a hydrogen atom from solvent. Radical-catalyzed losses of SO_2 are well known in sulfonyl azide chemistry[2] and there is precedent for the formation of aryl radicals in the observation that thermolysis of diphenylsulfone-2-sulfonyl azide gave diphenylene sulfone, presumably via a Pschorr-type cyclization of any aryl radical intermediate.[11]

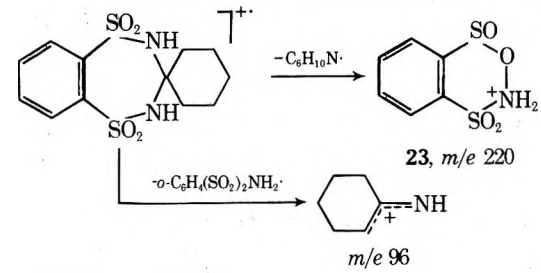
In an effort to find out if **20** was a plausible intermediate the synthesis of *N*-cyclohexylbenzenesulfonamide-2-sulfonyl azide (**21**) was attempted but was unsuccessful. Three different approaches were tried. Treatment of benzene-*o*-disulfonyl chloride with 1 equiv of sodium azide yielded only the disulfonyl azide (43%) and recovered disulfonyl chloride. When the disulfonyl chloride was treated with cyclohexylamine (1 equiv) and then with sodium azide in methanol a mixture of **1** (53%) and *N,N'*-dicyclohexyl-*o*-benzenedisulfonamide (29%) was obtained. Finally, diazotization of *o*-aminobenzenesulfonic acid followed by addition of SO_2 in the presence of $CuCl_2$ only gave the *o*-disulfonic acid and not the sulfonyl chloride *o*-sulfonic acid.

The thermal decomposition of the *o*-diazide (**1**) in cyclohexane containing tetracyclone gave 1,2,3,4-tetraphenylnaphthalene, *N*-cyclohexylbenzenesulfonamide, *N,N'*-dicyclohexyl-*o*-benzenedisulfonamide, and 3,4,5,6-tetraphenyl-2-pyridone in 6, 12, 8, and 18% yields, respectively. This experiment illustrated unequivocally that *o*-benzenedisulfonyl azide is indeed the precursor of benzyne and not the benzene solvent used in the previous thermolysis.

The decomposition of **1** in boiling cyclohexene gave the dienamine **21** as the primary product, and spiro[2*H*-1,5,2,4-benzodithiadiazepine-3(4*H*),1'-cyclohexane-1,1,5,5-tetroxide] (**22**) as a secondary product. Heating **21** in cyclohexene at 135° for 71 hr gave **22** (62%). The structure of **21** (rather than the imine tautomer[7b]) was confirmed by the presence of an NH band (3280 cm^{-1}) in the infrared, by its NMR spectrum [δ 7.23 (NH, 2 H, D_2O exchange) and 5.50 (m, 2 vinyl H)], and by its hydrolysis to cyclohexanone and *o*-benzenedisulfonamide. The spiro compound **22** also exhibited a strong NH absorption in the ir (3265 cm^{-1}) and its NMR and mass spectra were also compatible with the assigned structure. Thus, absorptions were observed at δ

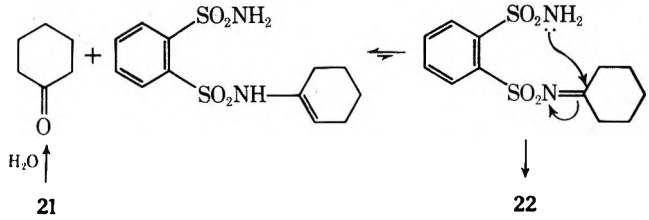


9.72 (NH, 2 H, D_2O exchange), 8.56 (d of d, $J_{3,4}$ = 6.25, $J_{3,5}$ = 3.0 Hz, H_3 and H_6 of aromatic ring), 8.30 (d of d, H_3 and H_5), 2.72–2.48 (m, 4 H, C_2 and C_6 protons of cyclohexane ring), and 2.14–1.92 (m, 6 H). In the mass spectrum, the base peak was at *m/e* 96 ($C_6H_{10}N^+$)[7b] [loss of *o*-$C_6H_4(SO_2)_2NH_2$·], and an intense (83%) fragment at *m/e* 220 could be due to N–S bond cleavage (–$C_6H_{10}N$) to give

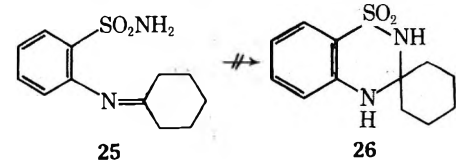


an ion (possibly **23**). Hydrolysis of **22** with aqueous acid gave *o*-benzenedisulfonamide.

There are several pathways by which the transformation of **21** → **22** can occur. If partial hydrolysis of **21** occurred to give *N*-(1-cyclohexenyl)-*o*-benzenedisulfonamide (**24**) and cyclohexanone, nucleophilic cyclization to **22** could follow.



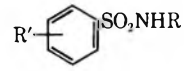
This mechanism is, however, rendered less plausible for a number of reasons. (i) The reaction was carried out in thoroughly dried cyclohexene. (ii) The amino group of a primary sulfonamide is a poor nucleophile. When o-benzenedisulfonamide was heated with cyclohexanone in acetonitrile or cyclohexane, no reaction occurred. Further, attempted cyclization of *N*-cyclohexylidene-*o*-aminobenzenesulfonamide (**25**) (from cyclohexanone and *o*-aminobenzenesulfonamide) to the spiro compound **26** failed. (iii)



When **21** was heated in cyclohexene at 135°, **22** was formed in 62% yield but only a trace of cyclohexanone was detected by gas–liquid chromatography.

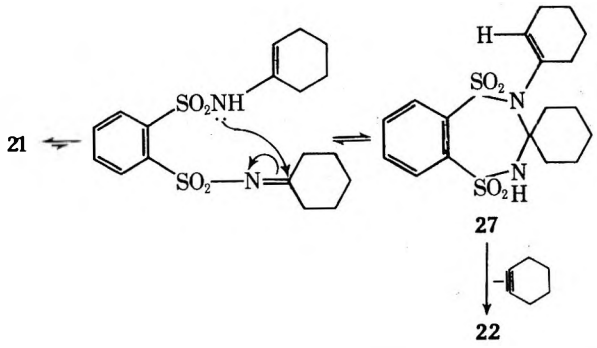
Another possible pathway for the cyclization is illustrated in Scheme V. This intramolecular route, which does not involve a preliminary hydrolysis step, does require, however, the elimination of cyclohexyne (which would be expected to polymerize) or its equivalent. Also, if anything, the sulfonylimino nitrogen might be expected to be even

Table I
Authentic Disubstituted Disulfonamides

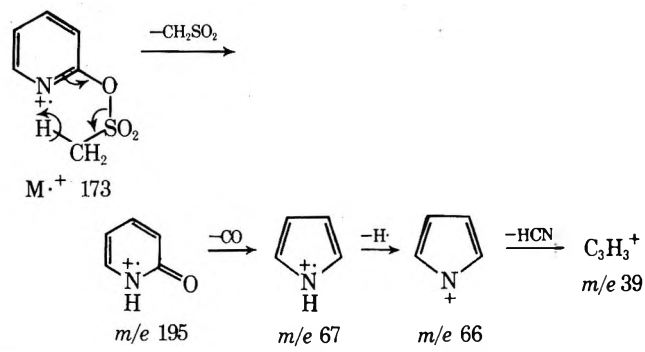


R	R'	Yield, %	Mp, °C	Molecular formula	Found, % C	Found, % H	Calcd, % C	Calcd, % H	Registry no.
C_6H_5	o-($C_6H_5NHSO_2$)	84	249–250	$C_{18}H_{16}N_2O_4S_2$	55.64	4.23	55.65	4.13	
C_6H_5	p-($C_6H_5NHSO_2$)	73	254–255	$C_{18}H_{16}N_2O_4S_2$	55.46	4.20	55.65	4.13	53965-93-8
C_6H_{11}	o-($C_6H_{11}NHSO_2$)	91	126–128	$C_{18}H_{28}N_2O_4S_2$	54.06	7.09	54.00	7.00	53965-94-9
C_6H_{11}	p-($C_6H_{11}NHSO_2$)	77	240–242	$C_{18}H_{28}N_2O_4S_2$	53.92	7.02	54.00	7.00	53965-95-0

Scheme V

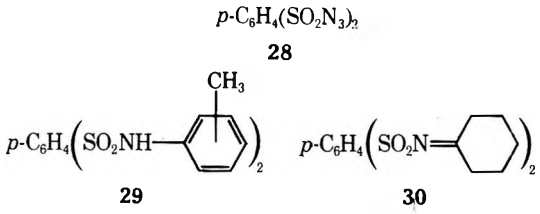


Scheme VI



less nucleophilic in this case. Further work is clearly needed to determine the mechanism of this reaction. Formation of **21** from the azide in unexceptional, however, and the mechanisms of such reactions have already been discussed.[7]

Thermolysis of *p*-benzenedisulfonyl azide (**28**) in benzene gave the *p*-dianilide (55%) as well as some black, intractable material. Thermolysis of the *p*-diazide in toluene at 135° gave a trace of bibenzyl and the isomeric *p*-benzenedisulfonyltoluidides (**29**, 84%). It has been reported[12] that



p-benzyne, generated from *cis*-1,5-hexadiyn-3-ene in toluene, gave diphenylmethane as a major product. No diphenylmethane could be detected by column or gas–liquid chromatography in the present reactions. Thermolysis of **28** in cyclohexane at 135° gave *N,N'*-dicyclohexyl-*p*-benzenedisulfonamide (55%) and *N*-cyclohexylbenzenedisulfonamide (5%) as the only isolable products. The decomposition of **28** in a large excess of an equimolar mixture of cyclohexene–benzene gave *N,N'*-dicyclohexylidene-*p*-benzenedisulfonamide (**30**, 97%) as already reported.[7b]

Nmr and Mass Spectra of *N*- and *O*-Mesyl-2-pyridones. 2-Pyridyl methanesulfonate (**15b**) exhibited a doublet of doublets ($J_{5,6}$ = 5.0, $J_{4,6}$ = 2.0 Hz) at δ 8.32 due to H_6, six lines centered at δ 7.79 ($J_{4,5}$ = $J_{3,4}$ = 8.0, $J_{4,6}$ = 2.0 Hz) due to H_4, a doublet of doublets at δ 7.23 ($J_{3,5}$ < 1.0 Hz) due to H_5, and a quartet at δ 7.08 due to H_3. *N*-Mesyl-2-pyridone (**16**) exhibited an nmr spectrum very similar to that of *N*-methyl-2-pyridone[13] except that the 4 and 6 protons were shifted somewhat downfield as expected and $J_{4,5}$ and $J_{5,6}$ were somewhat larger: δ 7.85 (q, $J_{5,6}$ = 8.0, $J_{4,6}$ = 2.0 Hz, H_6), 7.30 (d of d, $J_{3,4}$ = 9.2, $J_{4,5}$ = 6.8 Hz, H_4), 6.55 (q, $J_{3,5}$ = 1.2 Hz, H_3), and 6.26 (d of d of d, H_5).

The mass spectrum of **15b** showed an $M^{\cdot+}$ peak at *m/e* 173 (13%). The main fragment ions were at *m/e* 95 (100%), 79 (19%), 67 (55%), 66 (16%), and 39 (63%). These may be readily accounted for as in Scheme VI by a McLafferty-type rearrangement of the molecular ion accompanied by the loss of methylene sulfene to give the 2-pyridone radical cation as the base peak. Expulsion of CO would give the *m/e* 67 fragment, which has been formulated as a pyrrole ion.[14] The mass spectrum of **16b** exhibited the parent ion at *m/e* 173 (22%) and the base peak at *m/e* 95. The fragmentation pattern was identical with that of **15b**, as expected if the first step is a McLafferty-type rearrangement.

Experimental Section

Melting points are uncorrected. Nmr spectra were recorded on a Varian Associates Model HA-100 or a Perkin-Elmer Model R-20B spectrometer. Mass spectra were recorded on a C.E.C. Model 21-104 spectrometer at an ionizing voltage of 70 eV. Infrared spectra were recorded on a Perkin-Elmer Model 257 spectrometer. Gas chromatographic analysis was carried out with a Varian Associates Model A-90-P chromatograph with helium as carrier gas. Fischer-Porter pressure tubes, equipped with a degassing valve, were used for the thermolysis at 135°. The initial reaction mixtures were degassed by evacuating the frozen solution and thawing. This procedure was repeated at least three times for each run.

Reagents. Reagent-grade solvents were purified by standard techniques and kept over a drying agent. They were fractionally distilled just prior to use.

Authentic *N,N'*-Dicyclohexylbenzenedisulfonamides and Benzenedisulfonylanilides. These were prepared from the appropriate amine and benzenedisulfonyl chloride with benzene or chloroform as solvent. The properties of the new compounds are given in Table I.

***o*-Benzenedisulfonyl Azide (1).** Powdered sodium azide (5.2 g, 0.080 mol) was added to a stirred solution of *o*-benzenedisulfonyl chloride[15] (8.0 g, 0.029 mol) in distilled methanol (100 ml) over a 0.5-hr period. The reaction mixture was stirred for a further 2 hr at room temperature and poured into ice–water (200 ml) with vigorous stirring, whereupon a white solid precipitated. Recrystallization from methanol gave *o*-benzenedisulfonyl azide (6.9 g, 83%): mp 115–116°; ir (KBr) 2150 (N_3), 1370 (SO_2), and 1175 cm^{-1} (SO_2); NMR ($CDCl_3$) δ 8.30 (d of d, H_3 and H_6, $J_{3,4}$ = 6.0, $J_{3,5}$ = 3.8 Hz) and 7.85 (d of d, H_4 and H_5); MS (70 eV) *m/e* 246 ($M^{\cdot+}$ − 42), 106 (28), 98 (24), 96 (19), 90 (81), 78 (43), 76 (87), 63 (35), 50 (100).

Anal. Calcd for $C_6H_4N_6O_4S_2$: C, 25.00; H, 1.39. Found: C, 25.13; H, 1.48.

***p*-Benzenedisulfonyl Azide (28).** Prepared as described in the literature[16] from *p*-benzenedisulfonyl chloride[17] and sodium azide in methanol, it was obtained in 90% yield and had mp 136–137° (lit.[16] mp 133–134°).

Decompositions of o-Benzenedisulfonyl Azide. A. In Benzene. A thoroughly degassed solution of o-benzenedisulfonyl azide (0.707 g, 2.45 mmol) in dry benzene (20 ml, 0.226 mol) was heated in an oil bath at 135° for 7 days. The reaction mixture was cooled to room temperature, the gas under pressure was released, and a black, shiny material (ca. 0.26 g) was filtered and washed with hot acetonitrile (30 ml). The combined filtrates were chromatographed on silica gel (120 g). Elution with benzene–ether (9:1 v/v, 150 ml) gave a white, crystalline solid (0.199 g, 20.5%) whose ir and NMR spectra were identical with those of authentic o-benzenedisulfonylanilide. No other compounds were detected.

When the decomposition was repeated and the filtrate was analyzed by GLC using a 5 ft × 0.25 in. Apiezon M (15%) on Anakchrom (60–80 mesh) column at an oven temperature of 230°, no biphenyl, benzenesulfonamide, or benzenesulfonylanilide were detected.

B. In Benzene–Tetracyclone. A thoroughly degassed solution of o-benzenedisulfonyl azide (1.027 g 3.57 mmol) and tetracyclone (1.503 g, 3.91 mmol) in dry benzene (20 ml) was heated at 135° for 56 hr. The reaction mixture was worked up as before and the filtrate was chromatographed on silica gel (200 g). The light petroleum fraction (100 ml) gave biphenyl (12 mg, 2%), mp 67–68°, whose ir spectrum was identical with that of authentic material.

Light petroleum–benzene (4:1 v/v, 150 ml) eluted a light yellow oil which solidified on standing. Recrystallization from aqueous acetonitrile gave 1,2,3,4-tetraphenylnaphthalene (0.085 g, 5.5%): mp 204–205° (lit.[18] mp 204.5–205°); NMR ($CDCl_3$) δ 7.75–7.2 (m, 4 H), 7.20 (s, 10 H), and 6.80 (s, 10 H); MS (70 eV) *m/e* 432 ($M^{\cdot+}$, 100).

Light petroleum–benzene (2:1 v/v, 100 ml) and light petroleum–benzene (1:1 v/v, 250 ml) eluted unreacted tetracyclone (0.94 g, 64%). Benzene (150 ml) eluted o-benzenedisulfonylanilide (0.12 g, 8.7%). Benzene–ether (4:1 v/v, 150 ml) eluted an oily solid. Crystallization from chloroform–light petroleum (bp 60–110°) gave **benzenesulfonylanilide-o-sulfonamide (4)** (0.055 g, 5%): mp 208–209°; ir (KBr) 3360 and 3255 (NH_2), 3300 (N–H), 1340 (SO_2), and 1165 cm^{-1} (SO_2); NMR (DMSO-d_6) δ 9.66 (s, NH, 1 H, D_2O exchange), 8.20 (d of d, 1 H, $J_{3,4}$ = 6.5, $J_{3,5}$ = 2.5 Hz, H_3), 8.06–7.68 (m, 3 H), 7.42 (s, NH_2, 2 H, D_2O exchange), and 7.30–6.98 (m, 5 H); MS (70 eV) *m/e* 312 ($M^{\cdot+}$, 39), 295 (31), 278* (312 → 295, $-NH_3$), 93 ($C_6H_5O^+$, 100).

Anal. Calcd for $C_{12}H_{12}N_2O_4S_2$: C, 46.18; H, 3.85. Found: C, 46.18; H, 4.01.

Benzene–ether (3:2 v/v, 250 ml) and ether (200 ml) eluted a white solid. Recrystallization from aqueous acetonitrile gave granular crystals of 3,4,5,6-tetraphenyl-2-pyridone (0.18 g, 12.6%), mp 273–275° (lit.[19] mp 273–275°), whose ir spectrum was identical with that of an authentic sample.

Anal. Calcd for $C_{19}H_{21}NO$: C, 87.18; H, 5.30. Found: C, 87.32; H, 5.35.

C. In Cyclohexane. A degassed solution of o-benzenedisulfonyl azide (0.936 g, 3.25 mmol) in dry cyclohexane (20 ml) was heated in an oil bath at 135° for 72 hr. The reaction mixture was worked up as before and chromatographed on silica gel (150 g). Light petroleum–benzene (1:1 v/v, 100 ml) eluted ***N,N'*-dicyclohexyl-*o*-benzenedisulfonamide** (0.036 g, 2.6%) whose ir spectrum was identical with that of an authentic sample. Benzene–ether (4:1 v/v, 150 ml) eluted a colorless oil which slowly solidified on standing. Recrystallization from aqueous ethanol gave *N*-cyclohexylbenzenesulfonamide (0.368 g, 47.4%) whose ir spectrum was identical with that of an authentic sample prepared from benzenesulfonyl chloride and cyclohexylamine.

D. In Cyclohexane–Tetracyclone. A degassed solution of o-benzenedisulfonyl azide (1.003 g, 3.49 mmol) and tetracyclone (1.44 g, 3.75 mmol) in dry cyclohexane (20 ml) was heated in an oil bath at 135° for 116 hr. The reaction mixture was worked up as before and the product was chromatographed on silica gel (200 g). Light petroleum–benzene (4:1 v/v, 150 ml) eluted 1,2,3,4-tetraphenylnaphthalene (0.089 g, 6%). Light petroleum–benzene (2:1 v/v, 100 ml) eluted unreacted tetracyclone (0.71 g). Light petroleum–benzene (1:1 v/v, 200 ml) eluted *N,N'*-dicyclohexyl-*o*-benzenedisulfonamide (0.092 g, 8%). Benzene (250 ml) gave *N*-cyclohexylbenzenesulfonamide (0.101 g, 12%) and ether (350 ml) eluted 3,4,5,6-tetraphenyl-2-pyridone (0.245 g, 18%).

E. In Cyclohexene. A solution of 1 (0.716 g, 2.49 mmol) in freshly fractionated cyclohexene (bp 82.0–82.5°) (20 ml) was boiled under reflux ($CaCl_2$ drying tube) for 108 hr. The reaction mixture, which contained a white, crystalline material on the wall of the reaction vessel, was cooled to room temperature, filtered, and washed with benzene (15 ml). Recrystallization from acetonitrile–carbon tetrachloride gave **spiro[2*H*-1,5,2,4-benzodithiadiazepine-3(4*H*),1'-cyclohexane 1,1,5,5-tetroxide]** (22, 0.099 g, 13%): mp 240–242°; ir (KBr) 3265 (N–H), 1335 (SO_2), and 1170 cm^{-1} (SO_2).

Anal. Calcd for $C_{12}H_{16}N_2O_4S_2$: C, 45.58; H, 5.06. Found: C, 45.78; H, 5.17.

The filtrate was concentrated carefully under vacuum until an oily solid was left. Addition of anhydrous ether (ca. 15 ml) caused a white, crystalline solid to separate. This was quickly filtered in a drybox and identified as ***N,N'*-di-(1-cyclohexenyl)-o-benzenedisulfonamide** (0.64 g, 65%): mp 162–164°; ir (KBr) 3280 (N–H), 1575 (C=C), 1325 (SO_2), and 1175 cm^{-1} (SO_2); NMR ($CDCl_3$) δ 8.10 (d of d, H_3 and H_6, $J_{3,4}$ = 6.0, $J_{3,5}$ = 3.0 Hz), 7.66 (d of d, H_4 and H_5), 7.23 (N–H, 2 H, D_2O exchange), 5.50 (m, 2 vinyl H), 2.04–1.82 (m, 8 allylic H), and 1.54–1.32 (m, 8 aliphatic H); MS (70 eV) *m/e* 396 ($M^{\cdot+}$, 3), 172 (16), 99 (24), 98 (100), 97 (64).

Anal. Calcd for $C_{18}H_{24}N_2O_4S_2$: C, 54.52; H, 6.06. Found: C, 54.37; H, 6.08.

The ether filtrate was concentrated under vacuum to give an oily solid. Its ir and NMR spectra were identical with those of the above dienamine. This oily solid was dissolved in ethanol–water (1:1 v/v, 10 ml) containing concentrated hydrochloric acid (1.0 ml). As this solution was heated to boiling a white solid precipitated from solution. Filtration gave o-benzenedisulfonamide (0.077 g, 13%): mp >310° (lit.[20] mp 335–338°); ir (KBr) 3360 and 3260 (NH_2), 1330 (SO_2), and 1165 cm^{-1} (SO_2).

Hydrolysis of 22. A solution of **22** (0.197 g) in ethanol–water (1:1 v/v, 20 ml) and concentrated HCl (2.5 ml) was boiled under reflux for 1 hr to give o-benzenedisulfonamide (0.134 g, 91%), mp >310°.

Thermolysis of *N,N'*-Di-(1-cyclohexenyl)-o-benzenedisulfonamide (21). A degassed solution of **21** (0.119 g, 0.300 mmol) in freshly fractionated cyclohexene (10 ml) was heated in an oil bath at 135° for 71 hr and cooled to room temperature and the insoluble spiro compound **22** was filtered (0.060 g, 62%), mp 241–243°. The filtrate was analyzed by GLC on a 10 ft × 0.25 in. column packed with Apiezon L (25%) on Anakchrom ABS (60–70 mesh) at an oven temperature of 200° and a helium flow rate of 60 ml/min. A trace of a compound with the same retention time as cyclohexanone was detected. When a sample of the title compound in anhydrous ether was analyzed under the same conditions, a small peak with the same retention time as cyclohexanone was also observed.

Concentration of the filtrate under vacuum gave an oily solid (ca. 40 mg) whose ir and NMR spectra were identical with those of starting material (no carbonyl absorption at 1680 cm^{-1}).

Attempted Preparation of *N*-Cyclohexylbenzenesulfonamide-2-sulfonyl Azide. Cyclohexylamine (1.8 ml) was added to a stirred solution of o-benzenedisulfonyl chloride (3.18 g) in dry benzene (50 ml). The mixture was boiled under reflux for 1 hr and cooled, and cyclohexylamine hydrochloride was filtered. Methanol (50 ml) was added to the filtrate followed by powdered sodium azide (1.7 g). The mixture was stirred overnight, poured into ice–water (300 ml), and extracted with ether (2 × 500 ml). The dried ($MgSO_4$) extracts were evaporated and the residue was chromatographed on a column of silica gel (250 g). Elution with benzene gave o-benzenedisulfonyl azide (1.64 g). Elution with benzene–ether (4:1 v/v) gave *N,N'*-dicyclohexyl-*o*-benzenedisulfonamide (1.21 g). No other product was detected.

A similar result was obtained when o-benzenedisulfonyl chloride (15.4 mmol) was treated with sodium azide (16.1 mmol) in acetone. Only unchanged disulfonyl chloride (55%) and also disulfonyl azide (1.80 g) were obtained. No monosulfonyl azide could be detected.

Attempted Preparation of *N*-Cyclohexylbenzenesulfonamide-2-sulfonyl Chloride. A suspension of 2-aminobenzenesulfonic acid (7.19 g) in glacial acetic acid (36 ml) and concentrated HCl (6 ml) was heated on a steam bath until the solution became homogeneous, and then cooled to 0–5°. Sodium nitrite (5.4 g) in water (25 ml) was added below 5° and the resulting solution was added to a stirred suspension of $CuCl_2$ (1.4 g) in benzene (130 ml) and glacial acetic acid saturated with SO_2. The mixture was stirred at 5–10° for 2 hr, then at 40° for 3 hr. No benzene-soluble product was formed. From the acidic layer was isolated a solid which, on treatment with thionyl chloride (30 ml) and DMF (1.7 ml) and boiling for 1 hr, gave o-benzenedisulfonyl chloride (8.3 g, 73%), mp 142–143°.

Decompositions of *p*-Benzenedisulfonyl Azide. A. In Benzene. A degassed solution of p-benzenedisulfonyl azide (1.005 g, 3.49 mmol) in dry benzene (20 ml) was heated in an oil bath at

135° for 72 hr. The reaction mixture was worked up as in the case of the ortho derivative and chromatographed on silica gel (100 g). Ether and ether–methanol (2:1 v/v, 100 ml) gave a white solid whose ir and NMR spectra were identical with those of authentic *p*-benzenedisulfonylanilide (0.854 g, 55%), mp 250–252°.

When the reaction was repeated and the filtrate analyzed by GLC using a 5 ft × 0.25 in. Apiezon M (15%) on Anakchrom (60–80 mesh) column at an oven temperature of 230° and a helium flow rate of 60 ml/min no biphenyl, benzenesulfonamide, or benzenesulfonylanilide were detected.

B. In Toluene. A degassed solution of the *p*-diazide (0.815 g, 2.83 mmol) in dry toluene (12.0 ml) was heated in an oil bath at 135° for 60 hr. The reaction mixture was dissolved in hot boiling acetonitrile (80 ml) and filtered and the filtrate was concentrated to ca. 2 ml. This was then analyzed by GLC on a 10 ft × 0.25 in. column packed with Apiezon L (25%) on Anakchrom ABS at an oven temperature of 220° and a helium flow rate of 60 ml/min. One product, with a retention time of 23.4 min, was collected and had a mass spectrum identical with that of authentic bibenzyl. Diphenylmethane was not detected. The concentrated filtrate was chromatographed on silica gel (150 g). Benzene–ether (1:1 v/v, 250 ml) and ether (350 ml) eluted a white, powdery solid (0.99 g, 84%), mp 240–245°. Two recrystallizations from acetonitrile gave granular crystals of a mixture of ***p*-benzenedisulfonyltoluidides:** mp 248–257°; ir (KBr) 3270–3220 (N–H), 1340 (SO_2), and 1165 cm^{-1} (SO_2); NMR (DMSO-d_6) δ 10.39, 9.93, and 9.86 (NH, 2 H, D_2O exchange), 7.89 (s, 4 H), 7.25–6.9 (m, 8 H), 2.24 (s), 2.03 (s), and 1.87 (s) (6 H); MS (70 eV) *m/e* 416 ($M^{\cdot+}$, 8), 107 (15), 106 (100), 79 (11), 78 (6), 77 (15).

Anal. Calcd for $C_{20}H_{20}N_2O_4S_2$: C, 57.67; H, 4.84. Found: C, 57.51; H, 4.68.

C. In Cyclohexane. A degassed solution of the *p*-diazide (1.006 g, 3.49 mmol) in dry cyclohexane (20 ml) was heated in an oil bath at 135° for 62 hr. The reaction mixture was worked up as before and chromatographed on silica gel (175 g). Benzene (50 ml) eluted an oil (0.038 g, 4.5%) which solidified on standing and whose ir, NMR, and mass spectra was identical with those of authentic *N*-cyclohexylbenzenesulfonamide.

Benzene–ether (1:1 v/v, 250 ml) and ether (150 ml) eluted *N,N'*-dicyclohexyl-*p*-benzenedisulfonamide (0.79 g, 55%) whose ir spectrum was identical with that of an authentic sample.

Methanesulfonation of Thallium(I) 3,4,5,6-Tetraphenyl-2-pyridone. Methanesulfonyl chloride (0.108 g, 0.94 mmol) in ether (5 ml) was added dropwise to a stirred heterogeneous solution of the title compound[21] (0.52 g, 0.86 mmol) in anhydrous ether (30 ml) ($CaCl_2$ drying tube). The reaction mixture was stirred at room temperature for 1.5 hr, methylene chloride (125 ml) was added, and the insoluble thallium(I) chloride was filtered. The filtrate was evaporated under vacuum to give a white solid which was chromatographed on silica gel (125 g). Benzene (275 ml) eluted **3,4,5,6-tetraphenyl-2-pyridyl methanesulfonate** (0.30 g, 72%): mp 208–209° (from $CHCl_3$–hexane); NMR ($CDCl_3$) δ 7.40–6.65 (m, 20 H), 3.45 (s, 3 H); MS (70 eV) *m/e* 477 ($M^{\cdot+}$, 92), 398 (100), 370 (8), 293 (23), 267 (27), 265 (31), 89 (10), 79 (12).

Anal. Calcd for $C_{30}H_{23}NO_3S$: C, 75.45; H, 4.85. Found: C, 75.51; H, 5.04.

Benzene–ether (1:1 v/v, 150 ml) and ether (250 ml) eluted 3,4,5,6-tetraphenyl-2-pyridone (0.086 g, 25%), identical with an authentic sample.

Similar results were obtained when the mesylation was carried out in homogeneous solution (dry benzene or $CHCl_3$).

Methanesulfonation of Thallium(I) 2-Pyridone. Methanesulfonyl chloride (0.54 g, 4.68 mmol) in ether (5 ml) was added dropwise to a stirred suspension of thallium(I) 2-pyridone[22] (1.77 g, 5.92 mmol) in anhydrous ether (50 ml). The reaction mixture was stirred at room temperature for 1 hr, and thallium(I) chloride and unreacted starting material were filtered and washed with anhydrous ether (25 ml). The combined filtrates were concentrated under vacuum to give a colorless oil which was chromatographed on silica gel (150 g). Benzene–ether (4:1 v/v, 100 ml) eluted a colorless oil (0.42 g, 52%) which solidified on standing. Recrystallization from ether at −78° gave **2-pyridyl methanesulfonate,** mp 52–53°.

Anal. Calcd for $C_6H_7NO_3S$: C, 41.61; H, 4.08. Found: C, 41.72; H, 4.22.

Benzene–ether (1:1 v/v, 150 ml) eluted a colorless oil (0.39 g, 48%) which crystallized from ether at −78° to give ***N*-methanesulfonyl-2-pyridone:** mp 68–69°; ir (KBr) 1670 (C=O), 1600 and 1580 (C=C), 1350 (SO_2), and 1170 cm^{-1} (SO_2).

Anal. Calcd for $C_6H_7NO_3S$: C, 41.61; H, 4.08. Found: C, 41.62; H, 4.19.

Isomerization of *N*-Mesyl-2-pyridone to 2-Pyridyl Methanesulfonate. A. In CH_2Br_2 at 135°. A solution of *N*-mesyl-2-pyridone (0.152 g) in freshly distilled CH_2Br_2 (10 ml) was heated at 135° for 30 hr. Evaporation gave an oil (0.153 g) which solidified (mp 52–53°) and whose infrared and NMR spectra were identical with those of 2-pyridyl methanesulfonate.

B. In the Absence of Solvent. A similar result was obtained by heating the *N*-mesyl derivative at 170–180° for 50 min, or by two distillations of the *N*-mesyl compound (bp 92° at 0.02 mm). In the first case, pure *O*-mesyl derivative was obtained; in the second, the ratio of *O*-:*N*-mesyl derivatives was 92:8 as indicated by the area ratios of the NMR peaks at δ 3.45 and 3.61.

***N*-Cyclohexylidene-*o*-aminobenzenesulfonamide (25).** A solution of o-aminobenzenesulfonamide[23] (0.505 g, 2.93 mmol) and cyclohexanone (0.52 g, 5.3 mmol) in benzene (25 ml) was boiled under reflux for 15 hr and cooled to room temperature, and the solvent was removed under vacuum to give a light tan solid. Recrystallization from chloroform gave white plates of ***N*-cyclohexylidene-*o*-aminobenzenesulfonamide (25,** 0.69 g, 93%): mp 204–206°; ir (KBr) 3365 and 3220 (NH_2), 1605 (C=N), 1340 (SO_2), and 1165 cm^{-1} (SO_2); NMR ($CDCl_3$) δ 7.42 (d of d, H_3, $J_{3,4}$ = 8.0, $J_{3,5}$ = 1.0 Hz), 7.18 (d of d of d, H_4, $J_{4,5}$ = 7.0, $J_{4,6}$ < 0.5 Hz), 6.74 (d of d, H_6, $J_{5,6}$ = 8.5 Hz), 6.66 (d of d of d, H_5), 6.17 (NH_2, 2 H, D_2O exchange), 2.44–2.1 (m, 2 H), and 1.9–1.2 (m, 8 H); MS (70 eV) *m/e* 252 ($M^{\cdot+}$, 76), 223 (16), 210 (26), 209 (100), 196 (21), 172 (31), 170 (16), 156 (34), 145 (34), 108 (28), 96 (24), 93 (27), 92 (94).

Anal. Calcd for $C_{12}H_{16}N_2O_4S$: C, 57.14; H, 6.35. Found: C, 57.23; H, 6.47.

A solution of **25** (0.633 g, 2.51 mmol) in dry benzene (20 ml) was heated in a pressure tube in an oil bath at 135° for 35 hr. Concentration of the reaction mixture under vacuum gave unchanged starting material (0.63 g).

Attempted Reaction of *o*-Benzenedisulfonamide with Cyclohexanone. A degassed solution of o-benzenedisulfonamide (0.288 g, 0.966 mmol) and cyclohexanone (0.155 g, 1.58 mmol) in freshly fractionated cyclohexene (15 ml) was heated in an oil bath at 135° for 45 hr. Only starting materials were isolated. A similar result was obtained when acetonitrile was used as solvent.

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Registry No.—**1**, 21691-17-8; **2**, 53965-87-0; **3**, 751-38-2; **4**, 53965-88-1; **5**, 51954-59-7; **14a**, 53371-23-6; **14b**, 20877-39-8; **15a**, 53371-21-4; **15b**, 25795-97-5; **16b**, 53371-22-5; **21**, 53965-89-2; **22**, 53965-90-5; **25**, 53965-91-6; **28**, 53965-92-7; **29**, 53965-96-1; benzenamine, 62-53-3; cyclohexanamine, 108-91-8; *p*-benzenedisulfonyl chloride, 6461-77-4; o-benzenedisulfonyl chloride, 6461-76-3; tetracyclone, 479-33-4; *o*-aminobenzenesulfonamide, 3306-62-5; cyclohexanone, 108-94-1; methanesulfonyl chloride, 124-63-0.

References and Notes

(1) Part of this work was the subject of a preliminary communication: R. A. Abramovitch and G. N. Knaus, *J. Chem. Soc., Chem. Commun.*, 238 (1974).
(2) (a) R. A. Abramovitch and R. G. Sutherland, *Fortschr. Chem. Forsch.*, **16**, 1, (1970); (b) D. S. Breslow in "Nitrenes", W. Lwowski, Ed., Interscience, New York, N.Y., 1970.
(3) G. Wittig and R. W. Hoffmann, *Chem. Ber.*, **95**, 2718 (1962).
(4) A. Padwa, P. Sackman, E. Shefter, and E. Vega, *J. Chem. Soc., Chem. Commun.*, 680 (1972).
(5) This contrasts with the benzoylation of the sodium salt of 6-phenanthridone, in which the *N*-benzoyl derivative is the product of thermodynamic, and the *O*-benzoyl derivative the product of kinetic, control: D. Y. Curtin and J. H. Engelmann, *Tetrahedron Lett.*, 3911 (1968).
(6) Methylene sulfene decomposes when warmed above −30°: G. Opitz, M. Kleeman, D. Bucher, G. Waltz, and K. Rieth, *Angew. Chem., Int. Ed. Engl.*, **5**, 594 (1966).
(7) (a) R. A. Wohl, *J. Org. Chem.*, **38**, 3862 (1973); (b) R. A. Abramovitch, G. A. Knaus, M. Pavlin, and W. D. Holcomb, *J. Chem. Soc., Perkin Trans. 1*, 2169 (1974).
(8) J. N. Bradley and A. Ledwith, *J. Chem. Soc.*, 3480 (1963).
(9) A. Mishra, S. N. Rice, and W. Lwowski, *J. Org. Chem.*, **33**, 481 (1968).
(10) K. Hafner and W. Kaiser, *Tetrahedron Lett.*, 2185 (1964).
(11) R. A. Abramovitch, C. I. Azogu, and I T. McMaster, *J. Am. Chem. Soc.*, **91**, 1219 (1969).
(12) R. R. Jones and R. E. Bergman, *J. Am. Chem. Soc.*, **94**, 660 (1972).
(13) P. W. von Ostwalden and J. D. Roberts, *J. Org. Chem.*, **36**, 3792 (1971).
(14) G. Spiteller and M. Spiteller-Friedmann, *Monatsh. Chem.*, **93**, 1395 (1962).
(15) L. R. Buzbee, *J. Org. Chem.*, **31**, 3289 (1966).

(16) J. Goerdeler and H. Ullmann, *Chem. Ber.*, **94**, 1067 (1961).
(17) V. C. Parekh and P. C. Guha, *J. Indian Chem. Soc.*, **11**, 95 (1934).
(18) G. Wittig and E. Knauss, *Chem. Ber.*, **91**, 906 (1968).
(19) J. R. M. Wajon and J. F. Arens, *Recl. Trav. Chim. Pays-Bas*, **76**, 65 (1957).
(20) W. V. Farrar, *J. Chem. Soc.*, 63 (1960).
(21) Prepared in 97% yield from thallous ethoxide and 3,4,5,6-tetraphenyl-2-pyridone, mp 162–164°.
(22) A. McKillop, M. J. Zelesko, and E. C. Taylor, *Tetrahedron Lett.*, 4945 (1968).
(23) M. J. Taglianetti, *An. Fac. Farm. Odontol. Univ. Sao Paulo*, **5**, 17 (1947); *Chem. Abstr.*, **42**, 2587*g* (1948).

Base-Promoted Rearrangement of Arenesulfonamides of N-Substituted Anilines to N-Substituted 2-Aminodiaryl Sulfones[1]

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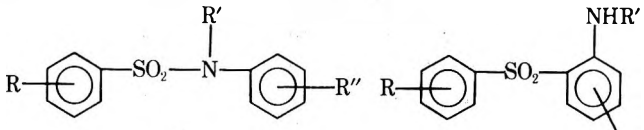
Arenesulfonamides of N-substituted aromatic amines react readily with lithium bases (e.g., methyllithium) in ether solvents to give N-substituted 2-aminodiaryl sulfones in quite respectable yield. The reaction is probably intramolecular, and involves formation of a dianion from the sulfonamide before rearrangement occurs. The immediate product of the rearrangement is a dianion with a carbanionic carbon ortho to the sulfonyl group in the nonamino ring. The reaction would appear to be the method of choice for synthesizing such amino sulfones, particularly when electron-donating groups are present. The NMR spectra of these amino sulfones indicate that the N–H proton is hydrogen bonded to a sulfone oxygen.

While previous work indicated that treatment of arenesulfonamides of unsubstituted anilines or of dialkylamines with strong bases (phenyl- or butyllithium) in THF resulted only in metalation ortho to the sulfonyl group[2] (or, in the case of o-toluenesulfonamides, at the *o*-methyl group),[3] we have observed that treatment of sulfonamides of general structure **1** with excess alkyl- or aryllithium in THF, followed by quenching with water, yields a rearranged material of general structure **2.**



1

2

a, R = R″ = H; R′ = CH_3
b, R = *p*-CH_3; R′ = CH_3; R″ = *p*-CH_3O
c, R = R″ = H; R′ = CH_3CH_2
d, R = *p*-CH_3; R′ = CH_3CH_2; R″ = H
e, R = *p*-CH_3O; R′ = CH_3CH_2; R″ = H
f, R = R″ = H; R′ = C_6H_5
g, R = *p*-$(CH_3)_2N$; R′ = CH_3; R″ = H
h, R = *p*-CH_3O; R′ = CH_3; R″ = H
i, R = *p*-CH_3O; R′ = CH_3; R″ = *p*-CH_3O
j, R = *o*-CH_3; R′ = CH_3; R″ = H
k, R = *p*-CH_3; R′ = CH_3; R″ = H

Initially, reactions were carried out by injecting a 2.5- to threefold excess of *n*-butyllithium (in hexane) into a solution of the sulfonamide in THF at 0°, allowing the mixture to stir for 5–15 min, and then quenching with water. Under these conditions **1a** gave about a 50% yield of **2a** as well as ca. 40% of *N*-methylaniline, presumably resulting from direct attack of the lithium alkyl on the sulfonamide sulfonyl group. Further investigation showed that methyl-, phenyl-, and *tert*-butyllithium, as well as the hindered bases derived from butyllithium and dicyclohexyl- and diisopropylamine, all brought about the rearrangement. Bases examined which did not cause rearrangement were sodium and lithium hydride, sodium amide, lithium metal, and methylmagnesium iodide. Phenylsodium caused very small amounts of rearrangement but its use was not examined in detail. Methyllithium proved to be the most economical and efficient reagent, a 97% yield (by gc) of **2a** being obtainable.

Table I
Yields and Properties of 2-Aminodiaryl Sulfones[a]

Sulfone	Base	Yield, %	Mp, °C	Registry no.
2a	CH_3Li	89	136–137	53973-76-5
2b	CH_3Li	61	150–151	53973-77-6
2c	CH_3Li	40	106–107	53973-78-7
2d	CH_3Li	81	87–88	53973-79-8
2e	CH_3Li	57	110–111	53973-80-1
2f	n-C_4H_9Li	86	79–80	52914-17-7
2g	n-C_4H_9Li	54	152–153	53973-81-2
2h	n-C_4H_9Li	45	144–145	53973-82-3
2i	n-C_4H_9Li	53	164–165	53973-83-4
2j[b]	CH_3Li	50	103–104	53973-84-5
2k	n-C_4H_9Li	52	134–135	53973-85-6

[a] Satisfactory analytical data (±0.4% for C, H) were reported for all compounds in the table. [b] Prepared by methylating dianion of 2a with methyl iodide.

In Table I are given isolated yields and physical properties of the aminosulfones. The reactions with methyllithium were most conveniently carried out at 25°, allowing about 2 hr for reaction before quencing. The sulfones were easily isolated by recrystallization and the progress of the reaction could readily be followed by TLC, all of the aminosulfones exhibiting a characteristic blue fluorescence on excitation by uv. Several of the entries in Table I involve use of butyllithium. The yields in these cases could probably be improved through use of methyllithium.

The major structural requirement of the sulfonamide for rearrangement was that the nitrogen be completely substituted. Sulfonamides of primary anilines merely formed the normal salt and were recovered unchanged. Halogen substituents did not survive, as would be expected, and alkyl groups ortho to the sulfonyl seriously interfered (vide infra).[3]

Proof of the structures of the aminosulfones was established by several means. The least substituted sulfone, **2a**,

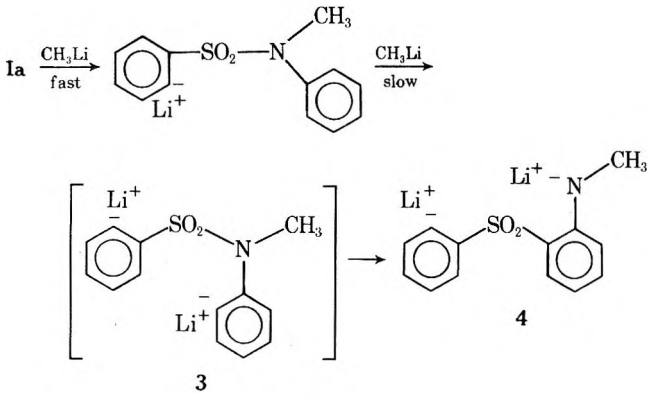
was identical with material prepared after the manner of Halberkann.[4] An NMR study of the **1b–2b** system strongly implied that the sulfonyl group had migrated to an ortho position in the amino ring; **1b** exhibited two AB quartets in the aromatic region, one for the sulfonyl ring centered at 7.22 and 7.48 ppm (J = 8.0 Hz) and one for the amino ring centered at 6.76 and 6.97 ppm (J = 9.0 Hz), while **2b** showed only one AB quartet centered at 7.29 and 7.78 ppm (J = 8.0 Hz) clearly corresponding to a para-substituted sulfonyl ring. The aromatic protons of the amino ring of **2b** appeared as an ABX system, ν_A = 6.60 ppm, ν_B = 7.00 ppm, and ν_X = 7.43 ppm (J_{AB} = 9.0, $J_{AX} \approx 0$, J_{BX} = 3.0 Hz). Finally, all of the sulfones bearing an alkyl group on nitrogen exhibited in the NMR a rather strong coupling ($J \approx 5$ Hz) between the amino proton and the α protons of the alkyl group. This has been noted as being characteristic of alkylamino groups that are intramolecularly hydrogen bonded to nitro groups in the ortho position.[5] For example, in **2a** the methyl group comes at 2.83 ppm (J = 4.9 Hz), while in *N*-methyl-*o*-nitroaniline it comes at 2.93 ppm (J = 5.1 Hz).[5] Exchange of the amino proton of **2a** with acidic D_2O collapses the doublet.

Other methods of effecting the rearrangement of arenesulfonanilides to aminosulfones have usually involved treatment with concentrated sulfuric acid at relatively high temperatures.[4,6] A photochemical rearrangement of *p*-toluenesulfonanilide to 4-methyl 4′-aminodiphenyl sulfone in relatively low yield has also been noted.[7] It would seem that this regiospecific, base-promoted technique for preparing 2-aminodiaryl sulfones from the readily available sulfonamides might have considerably synthetic value.

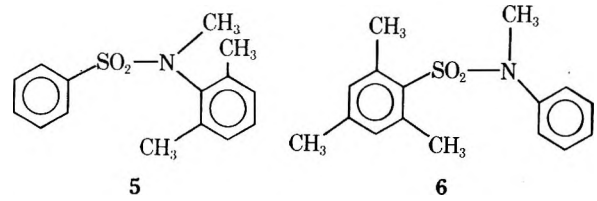
The mechanism of the reaction was shown probably to be intramolecular by treating a mixture of sulfonamides **1i** and **1k** with butyllithium at 25°. Only the expected sulfones, **2i** and **2k**, could be isolated. The possible "cross products", **2b** and **2h**, would have been easily detected by GC and were clearly shown to be absent. Such an experiment does not absolutely rule out an intermolecular pathway, particularly if the rates of reaction of **1i** and **1k** were quite different. However, considering that the two sulfonamides are fairly similar in structure and that the butyllithium reaction is quite rapid at 25° and thus probably not very selective, we feel that the probability that it is intramolecular is quite high.

More information on the mechanism was obtained by observing that 1 equiv or less of alkyllithium did not cause any rearrangement at all even though a rapid reaction, as evidenced by gas evolution (butane or methane) and development of a bright yellow color, ensued. Treatment of such solutions with water or methanol yielded unrearranged sulfonamide (ca. 90% yield) and no trace of rearrangement product. Treatment of the yellow solution so obtained from **1a** with methyl iodide yielded, after work-up, the ortho-methylated sulfonamide, **1j**. Thus, the first stage of the reaction is simple ortho metalation as observed previously.[2] Treatment with larger ratios of alkyllithium resulted in rapid formation of yellow color (quenching at this stage again yielded unrearranged sulfonamide) followed by much slower formation of a red-brown solution. (When **1a** was treated with 3 equiv of methyllithium at 25°, formation of the yellow species was apparently complete in ca. 5 min, while complete rearrangement required about 90 min). Quenching of the red-brown solution with water yielded the corresponding amino sulfone. Quenching of the red-brown solution so obtained from **1a** with methyl iodide yielded a new amino sulfone, mp 103–104°, to which, on the basis of evidence described below, we assign structure **2j**. (Alkylation of the amino anion in these amino sulfones is

Scheme I



apparently very difficult. See Experimental Section.) The overall sequence of steps is depicted in Scheme I. Whether or not dianion **3** has a finite existence is not clear. The proposed second metalation ortho to the amino group seems reasonable on several grounds. First, it is the position to which the sulfonyl group migrates. Second, if these positions are blocked by methyl groups, as in *N*-methyl-*N*-2,6-dimethylphenylbenzenesulfonamide (**5**), rearrangement

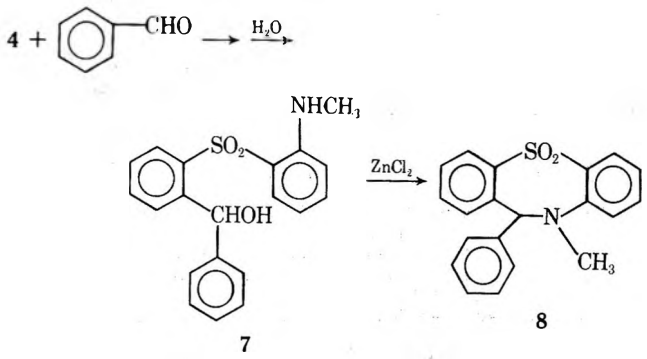


fails. (Instead, a variety of cleavage reactions apparently occur.) Thirdly, chelation of the lithium cation by one of the sulfonyl oxygens via a six-membered ring is feasible at this site,[8] as well as the well-known directing effect of a heteroatom at the adjacent ortho position.[9]

An attempt was made to see whether metalation ortho to the sulfonyl group was a prerequisite for rearrangement by treating *N*-methyl-*N*-phenylmesitylenesulfonamide (**6**) with methyllithium in THF. As in the case of **5**, no rearrangement but rather a variety of cleavage reactions ensued, as inferred from the large number of unidentified, low molecular weight peaks observed on GC analysis of the product mixture. Even one *o*-methyl group in the sulfonyl ring diverted the course of the reaction, as sulfonamide **1j** also yielded only low molecular weight products on treatment with methyllithium rather than the expected **2j**. While no firm evidence is at hand, we suspect that the metalation of the ortho benzylic positions is occurring rapidly,[3] followed by unknown side reactions.

The location of the carbanion in species **4** (Scheme I) was determined as follows. A solution of **4**, obtained by rearrangement of **1a** in usual fashion, was treated with an excess of benzaldehyde. Usual work-up of the mixture yielded a solid product to which, on the basis of ir and NMR evidence, and the result of the next reaction, we assign structure **7**. Refluxing **7** in benzene with toluenesulfonic acid failed to effect any change, but heating it at 110° with zinc chloride for several minutes caused cyclization to 10-methyl-11-phenyldibenzo[*b*,*f*][1,4]thiazepin 5,5-dioxide (**8**), whose structure was readily confirmed by spectroscopic data. In particular, the *N*-methyl group had collapsed to a singlet in the nmr (δ 2.95 ppm) and the parent peak in the mass spectrum was at *m/e* 335. The sequence of reactions is shown in Scheme II. Barring any unusual rearrangement in the zinc chloride reaction, formation of **8** from **4** conclusive-

Scheme II



7 8

ly locates the position of the carbanionic center ortho to the sulfonyl group in the nonamino ring.

Experimental Section

Materials and Equipment. Alkyllithium and phenyllithium solutions were obtained from commercial sources. Tetrahydrofuran (THF) was Matheson Coleman and Bell reagent grade and was dried by distillation from potassium benzophenone ketyl and stored under nitrogen. Elemental analyses were performed by Instranal Laboratory, Inc., Rensselaer, N.Y. Melting points were determined on a Mel-Temp apparatus and are reported uncorrected. Gas chromatographic analyses were performed on a Hewlett-Packard Model 5750 instrument equipped with flame ionization detectors, using a 6 ft × 0.125 in., 10% silicone rubber (UC-W98) on Chromosorb W column. Yields by GC were determined using internal standards and measuring peak areas by cutting and weighing. The NMR spectra were recorded using either a Varian A-60A instrument or an HA-100-D instrument modified by a Digilab FTS-3 Fourier transform system.[10]

Sulfonamides were prepared by standard techniques from commercially available sulfonyl chlorides and amines except in the cases noted. Their physical properties are described in Table II.

***N*-Methyl-*N*-2,6-dimethylphenylbenzenesulfonamide (5).** To 150 ml of water were added 2.0 g of sodium hydroxide, 4.84 g (0.04 mol) of 2,6-dimethylaniline, and 7.48 g (0.04 mol) of benzenesulfonyl chloride and the resulting mixture was stirred for 9 hr. After acidification and usual work-up 1.51 g (15% yield) of white crystals of *N*-2,6-dimethylphenylbenzenesulfonamide was obtained, mp 152–153° (methanol). To 100 ml of water were added 1.43 g (5.5 mmol) of this material, 0.4 g (10 mmol) of sodium hydroxide, and 1.64 g (13 mmol) of dimethyl sulfate.

The mixture was heated at reflux for 45 min, cooled, and the product extracted with ether. After removal of ether the product was recrystallized from methanol, yielding 1.20 g (79%) of **5**.

***N'*-Methyl-*N'*-phenyl-*p*-dimethylaminobenzenesulfonamide (1g).** *N'*-Methyl-*N'*-phenyl-*p*-aminobenzenesulfonamide was prepared by acid hydrolysis of the corresponding *p*-acetamidobenzenesulfonamide, yielding material of mp 141–141.5° (benzene) (lit. mp 138–140°).[11] To 0.524 g (2.0 mmol) of this material in 20 ml of dry THF at 0° was added dropwise 1.25 ml of 1.6 *M* butyllithium in hexane. After stirring for 5 min the red-brown solution was then treated (dropwise) with 0.284 g (0.13 ml, 2.0 mmol) of methyl iodide. After stirring for another 10 min, another 2.0-mmol portion of butyllithium was added slowly as previously. After 5 min another 2.0-mmol portion of methyl iodide was added, and the mixture was stirred for 15 min and then quenched with water. After normal work-up the crude solid was recrystallized from methanol, yielding 0.406 g (70%) of **1g**.

Rearrangement of Sulfonamides with Lithium Bases. The general procedure was to dissolve 1 g of sulfonamide (ca. 4 mmol) in 10 ml of dry THF under a nitrogen atmosphere and then rapidly add, with stirring, ca. 8.5 mmol of lithium base. A water bath was often essential to absorb the heat of the reaction. After stirring for 70–100 min, water was added, and products were separated by ether extraction and isolated in usual fashion. The resulting aminosulfones were recrystallized from methanol or methanol–water mixtures.

Rearrangement of *N*-Methyl-*N*-phenylbenzenesulfonamide (1a) with Sulfuric Acid. The method followed is essentially that of Halberkann.[4] To 5.0 g (0.02 mmol) of **1a** was added 15 g of 98% sulfuric acid and the mixture was stirred and heated at 100° for 2 hr. After cooling, the mixture was poured into ice water and the resulting brown solid was separated by filtration. Two recrystallizations from methanol yielded 0.355 g (7% yield) of white needles, mp 136–137°, of **2a**, identical in all respects (ir, NMR, mass spectrum) with **2a** obtained by reaction of **1a** with methyllithium.

Table II
Properties of Sulfonamides

Sulfonamide	Mp, °C	Lit. mp, °C
1a	79–79.5	79[a]
1b	61–62°	68–69[b]
1c	Liquid[a]	
1d	86–87	88[c]
1e	67–68[d]	
1f	122–123	124[a]
1g	132–133[d]	
1h	106.5–107	109–110[e]
1i	76–77	77[f]
1j	Liquid[g]	
1k	92.5–93.5	94[a]
5	111–112[d]	
6	94–95	95–96[h]

[a] Z. Rappaport, "Handbook of Tables for Organic Compound Identification", 3rd ed, Chemical Rubber Publishing Co., Cleveland, Ohio, 1967, Table XVIII. [b] J. Halberkann, *Ber.*, **54**, 1669 (1921). [c] A. I. Vogel, "Practical Organic Chemistry", Longmans, Green and Co., New York, N.Y., 1948, p 627. [d] Satisfactory analytical data (±0.4% for C, H) were reported for these new compounds. [e] S. Ji, L. B. Gortler, A. Waring, A. Battisti, S. Bank, W. D. Closson, and P. Wriede, *J. Am. Chem. Soc.*, **89**, 5311 (1967). [f] Y. Osawa, *Nippon Kagaku Zasshi*, **84**, 134 (1963). [g] Reaction with an excess of sodium naphthalene in THF resulted in production of 98% of the calculated amount (determined by GC) of *N*-methylaniline. See W. D. Closson, S. Ji, and S. Schulenberg, *J. Am. Chem. Soc.*, **92**, 650 (1970). [h] M. Pezold, R. S. Schreiber, and R. L. Shriner, ibid., **56**, 696 (1934).

Preparation of 2-(*N*-Methylamino)diphenyl Sulfone by Alkylation of 2-Aminodiphenyl Sulfone. 2-Aminodiphenyl sulfone was prepared by the method of Ullman and Pasdermadjian,[12] mp 120–121° (lit.[12] mp 121°). To a stirred solution of 0.233 g (1.0 mmol) of this material in 10 ml of THF at −30° was added 1.3 ml of 1.0 *M* *n*-butyllithium in hexane. This was immediately followed by addition of 0.12 g (1.3 mmol) of dimethyl sulfate, and the reaction mixture was warmed quickly to 50° and stirred at this temperature for 3 min. After quenching with water and usual work-up a brown oil was obtained which was purified by column chromatography, using 40–140 mesh silica gel and chloroform eluent. A pale yellow oil was obtained which crystallized on standing. Several recrystallizations from methanol yielded 0.010 g (4% yield) of white solid, mp 135–137°, which had ir and NMR spectra identical with those of **2a** obtained by the rearrangement reactions. Attempts at alkylation with butyllithium–methyl iodide, or by refluxing the sulfone in trimethyl phosphate, failed to yield any detectable amount of **2a**.

Reaction of *N*-Methyl-*N*-phenylbenzenesulfonamide (1a) with 1 Equiv of Butyllithium. To a stirred solution of 1.0 g (4 mmol) of **1a** in 10 ml of dry THF (at 25°) was slowly added 2.5 ml of 1.6 *M* *n*-butyllithium in hexane. The bright yellow solution was stirred for 5 min and then quenched with water. Analysis by GC showed the presence of only **1a** and no trace of **2a**. Usual work-up resulted in recovery of 0.91 g (91%) of **1a**.

To a similarly prepared solution of the anion derived from **1a** was added 0.61 g (4.3 mmol) of methyl iodide. After stirring for 5 min after disappearance of the yellow color, water was added and the product was isolated by extraction in the usual way, yielding a viscous liquid. This was purified by column chromatography on 40–140 mesh silica gel, using methylene chloride as eluent. The resulting oil, 0.715 g (68%), was identical in spectral properties (ir, NMR) with *N*-methyl-*N*-phenyl-*o*-toluenesulfonamide (**1j**) prepared by the Schotten–Baumann reaction of *o*-toluenesulfonyl chloride and *N*-methylaniline.

Reaction of *N*-Methyl-*N*-phenylbenzenesulfonamide (1a) with 2.5 Equiv of Methyllithium. To a stirred solution of 1.0 g (4.0 mmol) of **1a** in 10 ml of dry THF at 25° was added 5.5 ml (9.2 mmol) of 1.67 *M* methyllithium in ether. The solution was then

stirred for 90 min and then 0.71 g (5 mmol) of methyl iodide was added slowly. After another 5 min of stirring, 50 ml of water was added and the product was isolated in usual fashion. Recrystallization from aqueous methanol yielded 0.515 g (50%) of white crystals: mp 103–104°; NMR ($CDCl_3$) δ 2.49 (s, 3 H, CH_3), 2.79 (d, 3 H, J = 5.0 Hz, NCH_3), 5.9–6.2 (m, 1 H, NH), 6.5–8.1 (m, 8 H, aromatic).

On the basis of this and other evidence the compound is tentatively identified as 2-(*N*-methylamino)-2′-methyldiphenyl sulfone (**2j**).

A similar solution of dianion was prepared from 1.7 g (6.9 mmol) of **1a** in 15 ml of dry THF and treated dropwise with 1.05 g (10 mmol) of benzaldehyde. After stirring for another 15 min the mixture was quenched with water and the product was isolated. The resulting viscous oil was purified by chromatography on silica gel, eluting with carbon tetrachloride–chloroform. This yielded 2.07 g (85%) of clear oil which crystallized on standing: mp 115–116°; NMR ($CDCl_3$) δ 2.63 (d, 3 H, J = 5.0 Hz, NCH_3), 3.57 (broadened d, 1 H, J = 4.0 Hz, OH), 6.05 (broadened d, 1 H, J = 4.0 Hz, C-H), 6.4–7.9 (m, 14 H, aromatic and NH).

On the basis of this and subsequent evidence, the material is tentatively assigned structure **7**.

Preparation of 10-Methyl-11-phenyldibenzo[*b,f*][1,4]thiazepin 5,5-Dioxide (8). To 2.07 g (5.86 mmol) of alcohol **7** was added 150 mg of anhydrous zinc chloride. The neat mixture was then heated at 115–120° under a nitrogen atmosphere for 40 min. At this point the mixture had solidified. After cooling, 50 ml of water was added and the mixture was extracted with chloroform. After drying with magnesium sulfate, removal of solvent, and recrystallization from aqueous ethanol, 1.45 g (73%) of a white solid was obtained: mp 211–212°; NMR ($CDCl_3$) δ 2.95 (s, 3 H, NCH_3), 6.02 (broadened s, 1 H, CH), 6.67–7.55 (m, 13 H, aromatic); mass spectrum *m/e* 335 (parent), 306, 270.

Anal. Calcd for $C_{20}H_{16}NO_2S$: C, 71.62; H, 5.11. Found: C, 71.31; H, 5.12.

Registry No.—**1a**, 90-10-8; **1e**, 35088-88-1; **1g**, 53973-86-7; **5**, 53973-87-8; **7**, 53973-88-9; **8**, 53973-89-0; 2,6-dimethylaniline, 87-62-7; benzenesulfonyl chloride, 98-09-9.

References and Notes

(1) (a) Supported in part by the U.S. Public Health Service (Research Grant No. R01-AM11419 from the National Institute of Arthritis and Metabolic Diseases), and by the Alfred P. Sloan Foundation. (b) Presented in part at the 165th National Meeting of the American Chemical Society, Dallas, Texas, April 1973, Abstract ORGN 093. (c) Some similar results have been since reported by D. Hellwinkel and M. Supp, *Angew. Chem.*, **86**, 273 (1974).
(2) (a) D. W. Slocum and P. L. Gierer, *J. Org. Chem.*, **38**, 4189 (1973); (b) H. Watanabe, R. A. Schwarz, C. R. Hauser, J. Lewis, and D. W. Slocum, *Can. J. Chem.*, **47**, 1543 (1969); (c) H. Watanabe, R. L. Gay, and C. R. Hauser, *J. Org. Chem.*, **33**, 900 (1968).
(3) H. Watanabe and C. R. Hauser, *J. Org. Chem.*, **33**, 4278 (1968).
(4) J. Halberkann, *Ber.*, **54**, 1665, 1833 (1921); **55**, 3074 (1922).
(5) B. Lamm, *Acta Chem. Scand.*, **19**, 2316 (1965); B. Lamm and K. Nordfalt, ibid., **20**, 1208, 1221 (1966); **24**, 1597 (1970).
(6) A. R. Gennaro and M. Zanger, *J. Org. Chem.*, **36**, 1321 (1971); O. N. Witt and D. Uermanzi, *Ber.*, **46**, 296 (1913); O. N. Witt and H. Truttwin, ibid., **47**, 2786 (1914).
(7) H. Nozaki, T. Okada, R. Noyori, and M. Kawansi, *Tetrahedron*, **22**, 2177 (1966).
(8) See R. A. Ellison and F. R. Kotsonis, *J. Org. Chem.*, **38**, 4192 (1973), for examples of such effects and leading references.
(9) J. M. Mallan and R. L. Bebb, *Chem. Rev.*, **69**, 693 (1969).
(10) We would like to thank the National Science Foundation for Grant No. GP-28061 for the purchase of the FTS-3 system.
(11) S. Ji, Ph.D. Thesis, State University of New York at Albany, 1970. Satisfactory C and H analysis is reported therein.
(12) F. Ullman and G. Pasdermadjian, *Ber.*, **34**, 1150 (1901).

A Novel and Efficient Route to 5-Arylated γ-Lactones

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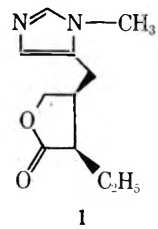
Title compounds (IV) were prepared by oxidation of lactols I with Ag_2CO_3 on Celite in refluxing xylene. Lactols I were obtained from reaction of ketones II with organomagnesium compound III and subsequent hydrolysis of the products V in 10% sulfuric acid. Prepared were the following compounds IV (R_1, R_2 given): H, 3-pyridyl; H, 4-pyridyl; H, 1-benzylimidazol-2-yl; H, 1-methylimidazol-2-yl; H, 1-benzyl-2-methylimidazol-5-yl; H, 1-benzyl-2-isopropylimidazol-5-yl; H, 1,2-dimethylimidazol-5-yl; phenyl, phenyl.

In our current research program we were interested in lactones of type I, bearing an imidazole or pyridine moiety at the 5 position, in order to examine their anticholinergic activities compared to pilocarpine (1). A survey of the literature revealed that there are no convenient methods to synthesize lactones of this particular type, because of the difficult availability of the required starting materials or inconvenient experimental conditions of the documented methods.



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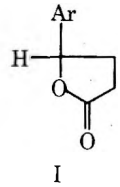


I

However, in a recent report,[2] benzimidazoles could be synthesized by reaction of readily available carboxaldehydes with the Grignard derivative of 2-(2-bromoethyl)-dioxolane-1,3 (**3**)[3] and subsequent cyclization in alcoholic medium. It was established that these reactions proceed *via* lactols as intermediates, which in fact could be isolated. With this consideration in mind, it was obvious that oxidation of the lactols might afford the required lactones.

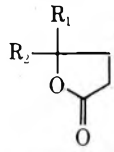
Reaction of the aldehyde **2d** with Grignard derivative **3** in tetrahydrofuran gave **4d**, which upon refluxing in 10% sulfuric acid afforded lactol **5d**. Oxidation of this lactol with convenient reagents such as permanganate, chromous trioxide, manganese dioxide, and silver oxide did not provide the desired lactone **6d**.

At that stage our attention was focussed to the work of Fetizon, *et al.*,[4] who reported that lactones should be generated from 1,5-diols in one simple oxidative conversion by silver carbonate on Celite.

There is much evidence that this reaction proceeds *via* the lactol stage.[5] Indeed, on refluxing lactol **5d** with silver carbonate on Celite, in xylene as solvent, lactone **6d** could be obtained in a 51% yield. Treatment of lactols **5a–c** and **5e,f** under similar conditions gave in moderate to good yields lactones **6a–c** and **6e,f**.

Further elucidation of this reaction showed that this method is not restricted to heterocyclic compounds. So, on

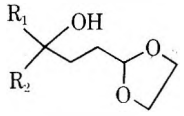
Table I[b]
Lactones



Compd	Yield, %	Mp, °C	Deriv	Mp, °C	Empirical formula
6a	55		Picrate	131–132	$C_9H_9NO_2$
6b	48	56–57	Picrate	152–153	$C_9H_9NO_2$
6c	51	132–132.5			$C_{17}H_{20}N_2O_2$
6d	61	117.5–118.5			$C_{15}H_{16}N_2O_2$
6e	49	88–89			$C_9H_{12}N_2O_2$
6f	25	76–76.5			$C_{14}H_{14}N_2O_2$
6g	22		Picrate	147–149	$C_8H_{10}N_2O_2$
6h[a]	71	86–88			$C_{16}H_{14}O_2$

[a] H. A. Staab, K. Wendel, and A. P. Datta, *Justus Liebigs Ann. Chem.*, **694**, 78 (1966): mp 91–92°. [b] Satisfactory analytical data (±0.3% for C, H, N) were reported for compounds **6a–g**.

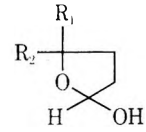
Table II[c]
Open-Chain Precursors



Compd	Yield, %	Mp, °C	Empirical formula
4a	91[a]		$C_{11}H_{15}NO_3$
4b	95	68.5–69.5	$C_{11}H_{15}NO_3$
4c[b]	96	90–91	$C_{19}H_{26}N_2O_3$
4d[b]	84	108–110	$C_{17}H_{22}N_2O_3$
4e	70	106–107	$C_{11}H_{18}N_2O_3$
4f	88	85–86	$C_{16}H_{20}N_2O_3$
4g	80[a]		$C_{10}H_{16}N_2O_3$
4h	90	76.5–77	$C_{18}H_{20}O_3$

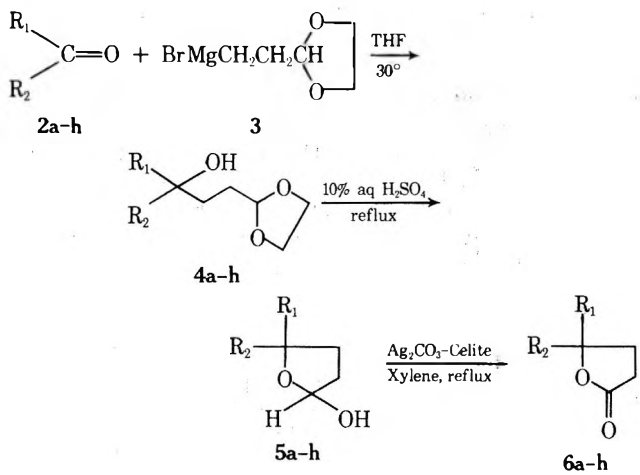
[a] Product was obtained as an oil; the nmr data were consistent with the assigned structure. [b] H. J. J. Loozen and E. F. Godefroi, *J. Org. Chem.*, 38, 3495 (1973). [c] Satisfactory analytical data (±0.3% for C, H, N) were reported for compounds **4b,e,f** (C and H for **4h**).

Table III[c]
Lactols



Compd	Yield, %	Mp, °C	Empirical formula
5a	95[a]		$C_9H_{11}NO_2$
5b	84	117–118	$C_9H_{11}NO_2$
5c[b]	92	138–139	$C_{17}H_{22}N_2O_2$
5d[b]	84	99–100	$C_{15}H_{18}N_2O_2$
5e	94[a]		$C_9H_{14}N_2O_2$
5f	82	117–119	$C_{14}H_{16}N_2O_2$
5g	76	146–148	$C_8H_{12}N_2O_2$
5h	74	122–124	$C_{16}H_{16}O_2$

[a] Yield based on crude oil; nmr was consistent with the assigned structure. [b] H. J. J. Loozen and E. F. Godefroi, *J. Org. Chem.*, 38, 3495 (1973). [c] Satisfactory analytical data (±0.3% for C, H, N) were reported for compounds **5b, 5f,** and **5g** (C and H for **5h**).



2a–h **3** **4a–h** **5a–h** **6a–h**

a, R_1 = 3-pyridyl; R_2 = H
b, R_1 = 4-pyridyl; R_2 = H
c, R_1 = 1-benzyl-2-isopropylimidazol-5-yl; R_2 = H
d, R_1 = 1-benzyl-2-methylimidazol-5-yl; R_2 = H
e, R_1 = 1,2-dimethylimidazol-5-yl; R_2 = H
f, R_1 = R_1 = 1-benzylimidazol-2-yl; R_2 = H
g, R_1 = 1-methylimidazol-2-yl; R_2 = H
h, R_1 = R_2 = phenyl

starting from benzophenone (**2h**) in a three-step sequence 5,5-diphenylbutyrolactone was obtained in 50% overall yield. The results are summarized in Table I–III.

Experimental Section

General. Melting points were determined on a Mettler apparatus and are uncorrected. Nmr data (Varian A-60, TMS as an internal standard) were consistent with the assigned structures. The intermediate oils **5a, 5e, 4a,** and **4f** were characterized by means of nmr and were converted as is into the products offered in Table I and II. Microanalyses were performed in our laboratories by Messrs. H. Eding and P. van den Bosch.

Starting Materials. Benzophenone and the pyridine carboxaldehydes were commercially available. The aldehydes **2c–e** were prepared as reported.[6] Aldehyde **2g** was obtained analogously: (a) from 1-methylimidazole to the 2-hydroxymethyl derivative (aqueous formaldehyde; 72 hr reflux; 51% yield), mp 91–92.5° (ethanol–$(i\text{-Pr})_2O$); (b) from oxidation (MnO_2–benzene)[7] of the corresponding carbinol to **2g** (71%), bp 90–95° (6 mm). Aldehyde **2f** was prepared by oxidation of the corresponding carbinol[8] with MnO_2 in 75% yield, bp 117–125° (0.01 mm).

All lactones, lactols, and their open-chained precursors have been compiled in the corresponding tables. The general preparation of the lactones is illustrated by the synthesis of **6b.**

1-(1,3-Dioxolan-2-yl)-3-hydroxy-3(4-pyridyl)propane (4b). To a solution of **3** in THF, prepared from 5 g (0.026 mol) of the bromide[3] and 0.65 g (0.26 g-atom) of Mg, was added dropwise with stirring a solution of 2.14 g (0.02 mol) of pyridine-4-carboxal-

dehyde in 10 ml of dry ether. After 2 hr the mixture was poured into 100 ml of 10% NH_4Cl solution. Extraction of the reaction product with chloroform and washing, drying, and evaporating of the solvent left 3.9 g (95%) of a solid: mp (benzene–petroleum ether) 68.5–69.5°; nmr ($CDCl_3$) δ 1.64–1.92 (m, 4, $-CH_2CH_2-$), 3.72–4.03 (m, 4, dioxolane protons); ir (KBr) 3300 cm^{-1} broad OH absorption.

4-Hydroxy-4-pyridylbutanal (as Hemiacetal 5b). A solution of 3.6 g (0.017 mol) of **4b** in 50 ml of 10% aqueous sulfuric acid was refluxed for 30 min. The mixture was cooled, made alkaline with 5 *N* NaOH, and extracted with chloroform. After drying and evaporation of the solvent the residual oil was chromatographed over SiO_2 ($CHCl_3$–2% CH_3OH as eluent) and afforded 2.3 g (8) of **5b**: mp ($CHCl_3$–(i-Pr)$_2$O) 117–118°; nmr ($CDCl_3$) δ 1.38–2.70 (m, 4, $-CH_2CH_2-$), 8.04 (ab, 4, pyridine protons); the ir spectrum (KBr) showed no C=O absorption, only broad OH band at 3300 cm^{-1}.

Dihydro-5-(4-pyridyl)-2(3*H*)-furanone (6b). To a solution of 0.33 g (0.002 mol) of **5b** in 20 ml of xylene was added 5.9 g of Ag_2CO_3–Celite (prepared according to the method of Fetizon; five times molar excess). The mixture was refluxed with stirring for 0.5 hr (on monitoring the reaction by tlc). After filtering the reaction mixture and stripping off the solvent, 0.16 g (48%) of **6** was obtained, as a solid: mp 56–57°; ir (KBr) strong C=O lactone absorption at 1760 cm^{-1}; nmr ($CDCl_3$) δ 1.93–3.18 (m, 4, $-CH_2CH_2-$), 5.57 (t, 1, CH), 8.00 (ab, 4, pyridine protons).

Registry No.—**2a**, 500-22-1; **2b**, 872-85-5; **2c**, 39269-79-9; **2d**, 39269-74-4; **2e**, 24134-12-1; **2f**, 10045-65-5; **2f** corresponding carbinol, 5376-10-3; **2g**, 13750-81-7; **2g** corresponding carbinol, 17334-08-6; **2h**, 119-61-9; **4a**, 53798-67-7; **4b**, 53798-68-8; **4c**, 41030-03-9; **4d**, 41030-01-7; **4e**, 53798-69-9; **4f**, 53798-70-2; **4g**, 53798-71-3; **4h**, 53798-72-4; **5a**, 53798-73-5; **5b**, 53798-74-6; **5c**, 41030-06-2; **5d**, 53798-75-7; **5e**, 53821-45-7; **5f**, 53798-76-8; **5g**, 53798-77-9; **5h**, 53798-78-0; **6a**, 20971-79-3; **6a** picrate, 53798-79-1; **6b**, 53798-80-4; **6b** picrate, 53798-81-5; **6c**, 53798-82-6; **6d**, 53798-83-7; **6e**, 53798-84-8; **6f**, 53798-85-9; **6g**, 53798-86-0; **6g** picrate, 53798-87-1; **6h**, 7746-94-3; 2-(1,3-dioxolan-2-yl)ethyl bromide, 18742-02-4; 1-methylimidazole, 616-47-7.

References and Notes

(1) Address correspondence to this author.
(2) H. J. J. Loozen and E. F. Godefroi, *J. Org. Chem.*, **38**, 3495 (1973).
(3) G. Büchi and H. Wüest, *J. Org. Chem.*, **34**, 1122 (1969).
(4) (a) M. Fetizon, M. Golfier, and J. M. Louis, *Chem. Commun.*, 1118 (1969); (b) M. Fetizon and M. Golfier, *C. R. Acad. Sci.*, **267**, 900 (1968).
(5) V. I. Sternberg and P. J. Perkin, *J. Org. Chem.*, **28**, 323 (1963).
(6) H. J. J. Loozen, E. F. Godefroi, and J. Th. J. Luderer-Platje, *Recl. Trav. Chim. Pays-Bas*, **91**, 1383 (1972).
(7) M. Harfenist, A. Bavley, and W. A. Lazier, *J. Org. Chem.*, **19**, 1608 (1954).
(8) R. G. Jones, *J. Amer. Chem. Soc.*, **71**, 383 (1949).

Quinazolines and 1,4-Benzodiazepines. LXX.[1] *v*-Triazolo[1,5-*a*][1,4]benzodiazepines

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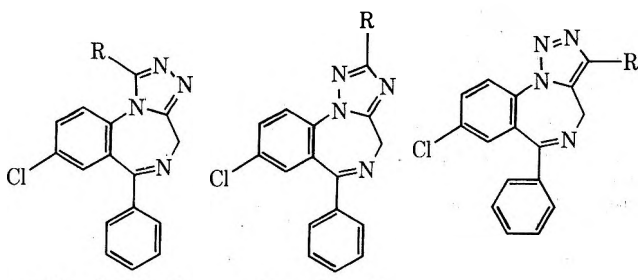
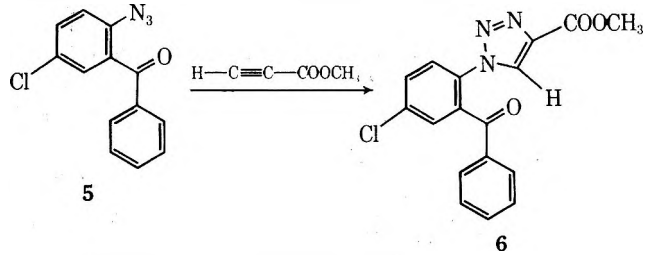
The cycloaddition reaction of 2-azido-5-chlorobenzophenone with dimethyl acetylenedicarboxylate provides 1-(2-benzoyl-4-chlorophenyl)-1*H*-1,2,3-triazole-4,5-dicarboxylic acid dimethyl ester. The oxime of this ketone undergoes reductive cyclization with zinc in acid which, together with subsequent transformations, give the first examples of the new tricyclic ring system named in the title.

1,4-Benzodiazepines embellished with a triazole ring have been the subject of several recent reports in both the journal[2,3] and patent[4–7] literature. Compounds of types 1[2–6] and 2[7] are known compounds and represent the two possible ring systems in which an *s*-triazole ring is fused to the 1,2 positions of a 1,4-benzodiazepine. The third possible ring system of this type in which a *v*-triazole is so incorporated is exemplified in compounds **3** and **4**. A synthesis of such previously unknown compounds is the subject of this paper.



s-triazolo[4,3-*a*] 1 | *s*-triazolo[1,5-*a*] 2 | *v*-triazolo[1,5-*a*] 3, R = H; 4, R = CH_3

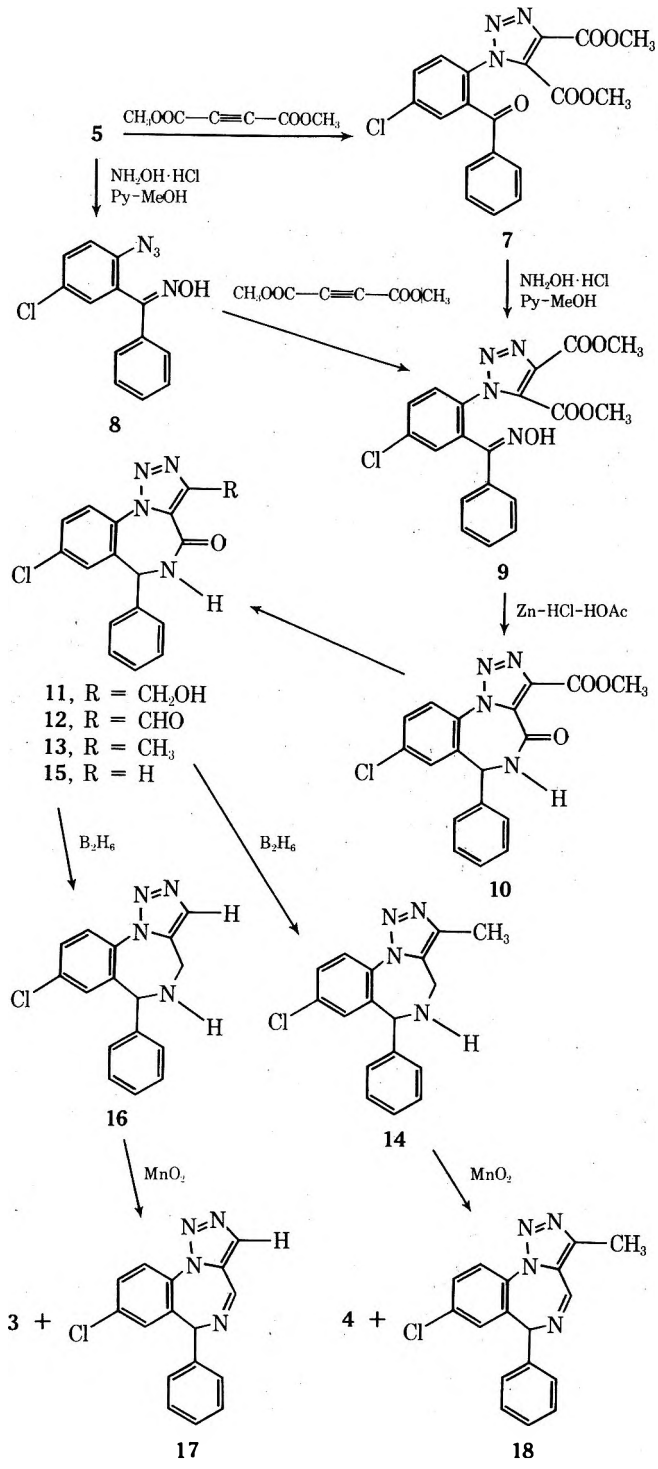
Of the several methods for the synthesis of *v*-triazoles,[8] the cycloaddition of acetylene derivatives to azides[9] appeared to be most applicable in the present instance, particularly since the appropriate azide **5** is readily accessible[10] from (commercially available) 2-amino-5-chlorobenzophenone. We initially anticipated a direct, essentially one-step synthesis of **3** by cycloaddition–condensation of propargyl amine with the azido ketone **5**. After numerous trials it became clear that a more reactive acetylene was necessary. Methyl propiolate reacts with **5** at room temperature to produce a single, crystalline adduct. However, while it was not clear from spectral data which of the two regiochemical modes of cycloaddition prevailed, our sustained inability to produce a tricyclic derivative from the adduct forced us to conclude that it has structure **6**. This result could have been predicted by analogy with the cycloaddition of phenyl azide and methyl propiolate in which the 1,4-disubstituted triazole is the major product (the 1,4 to 1,5 isomer ratio is approximately 7:1).[11]



5 6

This question of regiochemistry in the cycloadduct was simply avoided by using dimethyl acetylenedicarboxylate as the 1,3-dipolarophile. The resulting adduct **7** was converted to its oxime **9** and reductively cyclized to the lactam **10** as shown in Scheme I. Better yields of the cycloaddition

Scheme I



product **9** were obtained by first converting the azido ketone **5** to the azido oxime **8**.

Using compound **10** as the starting material, the series of υ-triazolobenzodiazepines **11**–**18** and the target compounds **3** and **4** were synthesized. Simultaneous reduction of both the amide and ester functions of **10** could be accomplished by prolonged exposure to $LiAlH_4$ in THF at reflux. However, since the chlorine atom was also lost to a large degree under these conditons, a stepwise reduction sequence leading through intermediates **11**–**14** was adopted. Excess sodium borohydride in boiling THF effected a selective reduction of the heterocyclic ester group.[12] Reoxidation to the aldehyde level with MnO_2 or CrO_3 afforded the aldehyde **12** and Wolff–Kishner[13] reduction of this substance to **13** completed a conversion of the "extra" ester function to a methyl group. In an alternative sequence, this "extra" ester function was removed completely by selective hydrolysis and thermal decarboxylation to give the lactam **15**.

Vigorous diborane reduction of the lactams **13** and **15** provided the secondary amines **14** and **16**. Oxidation of these dihydro-υ-triazolobenzodiazepines with MnO_2 produced in each case an isomeric pair of 4H and 6H compounds: **3** and **17** from **16**, and **4** and **18** from **14**. The separation of these isomeric products required recourse to column or preparative layer chromatography, but in all other reactions described, crystalline products were obtained directly following conventional work-up procedures.

Experimental Section[14]

2-Azido-5-chlorobenzophenone (5). A solution of 2-amino-5-chlorobenzophenone (232 g, 1 mol) in a mixture of acetic acid (500 ml), concentrated hydrochloric acid (200 ml), and water (300 ml) was cooled to 5° with an ice bath. A solution of sodium nitrite (75 g, 1.1 mol) in water (300 ml) was also cooled to 5° and then added to the first solution with stirring during the course of 10 min. A solution of sodium azide (71 g, 1.1 mol) in water (300 ml) was slowly added, during which the mixture foamed copiously. Stirring was continued for 30 min at 5° after completion of the addition and then kept for 1 hr without further cooling. The product was collected in two crops to give 227.1 g (88%) of crude azido ketone **5** as a light yellow solid after washing with water and air drying. A sample was recrystallized from petroleum ether to give colorless plates: mp 83–84°; ir (Nujol) 2150, 2120, and 1670 cm^{-1}.

Anal. Calcd for $C_{13}H_8ClN_3O$: C, 60.59; H, 3.13; N, 16.31. Found: C, 60.41; H, 3.13; N, 16.17.

1-(2-Benzoyl-4-chlorophenyl)-1*H*-1,2,3-triazole-4-carboxylic Acid Methyl Ester (6). A solution of **5** (23.5 g) in excess methyl propiolate (50 ml) was kept for several days. Crops of the product were filtered off periodically, washed with ether, and air dried to give a total of 25.5 g (81.5%) of crude adduct in three crops. A sample was recrystallized from ether to give colorless crystals: mp 188–190°; ir (Nujol) 1735, 1680, 1620, 1545, and 1520 cm^{-1}; NMR ($CDCl_3$–DMSO-d_6) δ 3.80 (s, 3 H), 7.2–8.0 (m, 8 H), and 8.94 (s, 1 H); mass spectrum *m/e* 77 (100%), 105, 341 (M^+).

Anal. Calcd for $C_{17}H_{12}ClN_3O_3$: C, 59.75; H, 3.54; N, 12.30; Cl, 10.37. Found: C, 59.85; H, 3.64; N, 12.44; Cl, 10.45.

1-(2-Benzoyl-4-chlorophenyl)-1*H*-1,2,3-triazole-4,5-dicarboxylic Acid Dimethyl Ester (7). A solution of **5** (20 g) in excess dimethyl acetylenedicarboxylate (30 ml) was prepared with warming and kept for 3 days. The crystals which formed were collected, washed with cold ether, and dried in a vacuum oven to give 20.8 g (67%) of crude adduct. A sample was recrystallized from methanol to give colorless crystals: mp 125–126°; ir (Nujol) 1735, 1730, 1670, 1590, and 1575 cm^{-1}; NMR ($CDCl_3$) δ 3.85 (s, 3 H), 3.95 (s, 3 H), and 7.2–7.8 (m, 8 H); mass spectrum *m/e* 105 and 399 (M^+, 100%).

Anal. Calcd for $C_{19}H_{14}ClN_3O_5$: C, 57.08; H, 3.53; N, 10.51; Cl, 8.87. Found: C, 57.00; H, 3.41; N, 10.52; Cl, 8.90.

2-Azido-5-chlorobenzophenone Oxime (8). A mixture of **5** (231 g), excess hydroxylamine hydrochloride (240 g), and pyridine (500 ml) in methanol (2 l.) was stirred and heated under reflux for 3 hr. The condensor was removed periodically to permit loss of water with solvent vapor. The cooled mixture was concentrated under reduced pressure to ca. 750 ml and then partitioned between 2*N* HCl and ether. The ether layer was dried and concentrated to ca. 800 ml. Cyclohexane was added gradually to the boiling ether solution to induce crystallization. The product was collected in three crops, washed with cyclohexane, and vacuum dried at 55° to give 227.3 g (93%) of crude oxime as a pale yellow solid. A sample for analysis was recrystallized from ether–cyclohexane to give nearly colorless needles: mp 140–142° dec; ir (Nujol) 3250, 2140, 2110, and 1585 cm^{-1}; mass spectrum *m/e* 192 (100%), 272 (M^+).

Anal. Calcd for $C_{13}H_9ClN_4O$: C, 57.26; H, 3.33; N, 20.55; Cl, 13.00. Found: C, 57.50; H, 3.22; N, 20.62; Cl, 13.03.

1-[4-Chloro-2-(α-hydroxyimino)benzylphenyl]-1*H*-1,2,3-triazole-4,5-dicarboxylic Acid Dimethyl Ester (9). A. From Ketone 7. A mixture of ketone **7** (75.8 g), hydroxylamine hydrochloride (75.0 g), and pyridine (150 ml) in methanol (500 ml) was stirred and gently boiled for 4 hr. Additional methanol was added periodically to replace that which escaped as solvent vapor. After this time an additional 50 g of hydroxylamine hydrochloride and 20 ml of pyridine were added and the mixture was left at reflux overnight. TLC analysis showed the presence of some starting ma-

terial, wherefore a further addition of hydroxylamine hydrochloride (15 g) and pyridine (15 ml) was made and reflux continued for 4 hr. After cooling the solvent was removed under reduced pressure and the resulting concentrate partitioned between 2 *N* HCl and ether. The ether layer was dried, filtered through Celite, and evaporated to a yellow oil. This material crystallized from hot, aqueous methanol to give 35.2 g (44.8%) of the oxime **9** in two crops. The oxime prepared in this manner is a mixture of syn and anti isomers and shows two spots on TLC. An analytical sample was recrystallized from aqueous methanol to give colorless crystals: mp 129–131°; ir (Nujol) 3200, 1750, 1730, and 1575 cm^{-1}; NMR ($CDCl_3$) δ 3.6–4.0 (4 peaks, 6 H, OCH_3) and 7.2–7.8 (m, 8 H); mass spectrum *m/e* 77 (100%) and 414 (M^+).

Anal. Calcd for $C_{19}H_{15}ClN_4O_5$: C, 55.02; H, 3.65; N, 13.51; Cl, 8.54. Found: C, 54.97; H, 3.41; N, 13.33; Cl, 8.65.

B. From Azido Oxime 8. A solution of the azido oxime **8** (210.5 g) and excess dimethyl acetylenedicarboxylate (235 g) in ether (400 ml) was heated under reflux for 48 hr. Most of the ether was evaporated under reduced pressure and the residue was chilled. The product was collected, washed with 1:1 ether–cyclohexane, and air dried. Recrystallization from aqueous methanol gave 235.5 g (73%) of product in three crops of which the first (190 g) is a single isomer (one spot on TLC) and the second and third crops are syn–anti isomer mixtures. A sample of the first crop was recrystallized to give colorless crystals: mp 167–168°; ir (Nujol) 3200, 1750, 1730, and 1570 cm^{-1}; NMR ($CDCl_3$–DMSO-d_6) δ 3.74 (s, 3 H), 3.92 (s, 3 H), 7.2–7.8 (m, 8 H), and 11.5 (s, OH); mass spectrum *m/e* 77 (100%) and 414 (M^+).

Anal. Found: C, 55.02; H, 3.67; N, 13.43; Cl, 8.59.

8-Chloro-5,6-dihydro-4-oxo-6-phenyl-4*H*-*v*-triazolo[1,5-*a*][1,4]benzodiazepine-3-carboxylic Acid Methyl Ester (10). A mixture of oxime **9** (132 g, 0.318 mol) and zinc dust (100 g, 1.5 g-atoms) in glacial acetic acid (700 ml) was treated with 1 ml of concentrated HCl to initiate the reaction. Thereafter the stirred mixture was cooled to keep the temperature below 50°. After 2 hr, the remaining zinc was filtered out and washed several times with methylene chloride. The combined filtrate and washings were washed repeatedly with sodium carbonate solution until the acetic acid was removed. The organic layer was then dried and concentrated under reduced pressure until precipitation commenced. The concentrated solution was then diluted with twice its volume of ether, kept for 2 min, and then filtered to remove a dimeric by-product. The filtrate was kept overnight at room temperature and the lactam **10** collected, washed with ether, and air dried to give 54.2 g (46%) of colorless product. This isolation procedure was developed to avoid the need for column chromatography in isolating the desired lactam. A sample recrystallized from methylene chloride–methanol had mp 267–269°; ir (Nujol) 3150, 1735, 1685, and 1650 cm^{-1}; NMR (DMSO-d_6) δ 3.79 (s, 3 H), 5.85 (d, J = 7 Hz, 1 H), 6.9–8.1 (m, 8 H), and 9.87 (d, J = 7 Hz, NH); mass spectrum *m/e* 263 (100%) and 368 (M^+).

Anal. Calcd for $C_{18}H_{13}ClN_4O_3$: C, 58.62; H, 3.55; N, 15.19; Cl, 9.61. Found: C, 58.65; H, 3.55; N, 14.96; Cl, 9.59.

8-Chloro-5,6-dihydro-3-hydroxymethyl-4-oxo-6-phenyl-4*H*-*v*-triazolo[1,5-*a*][1,4]benzodiazepine (11). A slurry of the lactam **10** (67.5 g, 0.183 mol) and sodium borohydride (50 g, 1.32 mol) in THF (2.5 l.) was stirred and heated under reflux for 10 hr. The solution was concentrated somewhat by evaporation under reduced pressure. Aqueous 2% HCl was added slowly to destroy excess hydride and the resulting mixture was partitioned between methylene chloride and water. The organic layer was dried and evaporated until the product began to separate. An equal volume of ether was added at this point and the solution chilled. The product was collected, washed with ether, and air dried to give 46.1 g (74%) of alcohol **11** as a colorless solid. A sample was recrystallized from methylene chloride to give colorless crystals: mp 218°; ir (Nujol) 3400, 3200, 3050, 1670, 1610, 1595, and 1575 cm^{-1}; NMR (DMSO-d_6) δ 4.56 (s, 2 H), 4.8 (broad, NH and OH), 5.74 (s, 1 H), and 6.9–8.0 (m, 8 H); mass spectrum *m/e* 217 (100%) and 340 (M^+).

Anal. Calcd for $C_{17}H_{13}ClN_4O_2$: C, 59.92; H, 3.85; N, 16.44; Cl, 10.40. Found: C, 59.90; H, 3.80; N, 16.64; Cl, 10.65.

8-Chloro-5,6-dihydro-3-formyl-4-oxo-6-phenyl-4*H*-*v*-triazolo[1,5-*a*][1,4]benzodiazepine (12). A mixture of alcohol **11** (36.3 g) and activated manganese dioxide (405 g) in acetone (2 l.) was stirred at reflux for 6 hr and then overnight at room temperature. The solid was filtered out and thoroughly extracted several times with hot acetone. The combined filtrate and washings were evaporated to leave 15.4 g (42.5%) of aldehyde **12** as a colorless solid. This oxidation was also carried out on the same scale with chromium trioxide using the Ratcliffe and Rodehorst procedure[15] and gave the same yield.

A sample was recrystallized from ether–methanol to give crystals: mp 244–246°; ir (KBr) 3300 and 1660 cm^{-1}; NMR (DMSO-d_6) δ 5.90 (s, 1 H), 6.8–8.1 (m, 9 H, including NH), and 10.03 (s, 1 H); mass spectrum *m/e* 233 (100%) and 338 (M^+).

Anal. Calcd for $C_{17}H_{11}ClN_4O_2$: C, 60.28; H, 3.27; N, 16.54; Cl, 10.46. Found: C, 60.13; H, 3.43; N, 16.51; Cl, 10.41.

8-Chloro-5,6-dihydro-3-methyl-4-oxo-6-phenyl-4*H*-*v*-triazolo[1,5-*a*][1,4]benzodiazepine (13). A solution of the aldehyde **12** (15.4 g) and 85% hydrazine hydrate (60 ml) in ethanol (300 ml) was heated on a steam bath for 2 hr. The solvent was removed under reduced pressure and the residue taken up in toluene (300 ml). Potassium *tert*-butoxide (15 g) was added and the mixture stirred and heated for 8 hr. The solvent vapors were allowed to escape for the first 15 min and heating thereafter was under reflux. The cooled mixture was washed with water (250 ml) and the aqueous layer was extracted with methylene chloride. The combined organic layers were dried and evaporated. Recrystallization of the residue from methylene chloride–ether gave 13.4 g (91%) of the lactam **13** as colorless crystals: mp 248–250; ir (Nujol) 3170, 3050, 1665, and 1570 cm^{-1}; NMR ($CDCl_3$) δ 2.58 (s, 3 H), 5.55 (d, J = 6 Hz, s after D_2O exchange, 1 H), and 7.1–8.2 (m, 9 H, including NH); mass spectrum *m/e* 219 (100%) and 324 (M^+).

Anal. Calcd for $C_{17}H_{13}ClN_4O$: C, 62.87; H, 4.03; N, 17.25; Cl, 10.92. Found: C, 63.09; H, 4.17; N, 17.13; Cl, 10.90.

8-Chloro-5,6-dihydro-4-oxo-6-phenyl-4*H*-*v*-triazolo[1,5-*a*][1,4]benzodiazepine (15). The lactam **10** (10.0 g) was taken up in excess 10% methanolic KOH and the solution kept at room temperature for 15 min, during which the potassium salt of the acid precipitated. The entire mixture was acidified with dilute HCl and the product collected and dried. The crude acid (8.6 g) was slurried in ethylene glycol (60 ml) and the mixture boiled for 5 min. After partitioning between water and methylene chloride, the organic layer was dried and evaporated to give 6.6 g (78%) of lactam **15.** An analytical sample prepared by vacuum sublimation at 195° had mp 248–249°; ir (Nujol) 3150, 3080, 1675, 1610, 1590, and 1550 cm^{-1}; NMR ($CDCl_3$–DMSO-d_6) δ 5.70 (d, J = 6 Hz, 1 H), 7.0–8.2 with singlet at 8.02 (9 H), and 9.51 (d, J = 6 Hz, NH); mass spectrum *m/e* 205 (100%) and 310 (M^+).

Anal. Calcd for $C_{16}H_{11}ClN_4O$: C, 61.84; H, 3.57; N, 18.03; Cl, 11.90. Found: C, 61.87; H, 3.53; N, 18.27; Cl, 11.53.

8-Chloro-5,6-dihydro-3-methyl-6-phenyl-4*H*-*v*-triazolo[1,5-*a*][1,4]benzodiazepine (14). A solution of the lactam **13** (8.0 g) in THF (125 ml) was treated with 1 *M* diborane in THF (50 ml) and heated to reflux for 15 hr. Excess diborane was destroyed by addition of saturated aqueous Na_2SO_4 and the mixture partitioned between water and methylene chloride. The organic layer was dried and evaporated. The residue was triturated wth ether, filtered, and dried to give 6.1 g (80%) of the amine **14** as colorless solid. Recrystallization from methylene chloride–ether provided material with mp 161–163°. It was suitable for use as in the MnO_2 oxidation step but analyzed poorly and contained, in its infrared spectrum, an anomalous band at 2400 cm^{-1}. It may be an amine–borane complex. An analytically pure sample was prepared by boiling a solution of the product in methanol containing concentrated HCl for 10 min followed by work-up with aqueous NaOH and methylene chloride. The base from the organic layer was crystallized from ether–hexane, giving colorless crystals: mp 140–142°; ir (Nujol) 3300 and 1605 cm^{-1}; NMR ($CDCl_3$) δ 2.2 (broad, 1 H, NH), 2.50 (s, 3 H), 4.03 (AB q, J = 15 Hz, 2 H), 5.03 (s, 1 H), and 6.8–8.0 (m, 8 H); mass spectrum *m/e* 205 (100%) and 310 (M^+).

Anal. Calcd for $C_{17}H_{15}ClN_4$: C, 65.70; H, 4.86; N, 18.03; Cl, 11.41. Found: C, 65.79; H, 4.74; N, 18.13; Cl, 11.19.

8-Chloro-5,6-dihydro-6-phenyl-4*H*-*v*-triazolo[1,5-*a*][1,4]-benzodiazepine (16). The reduction of lactam **15** (5.4 g) with diborane was carried out as described for lactam **13** to give 3.6 g (70%) of the amine **16.** A sample recrystallized from methylene chloride–ether had mp 138–140°; ir (Nujol) 3200 and 1600 cm^{-1}; NMR ($CDCl_3$) δ 2.18 (s, 1 H, NH), 4.12 (AB q, J = 15 Hz, 2 H), 5.00 (s, 1 H), and 6.8–8.0 (m, 8 H); mass spectrum *m/e* 191 (100%) and 296 (M^+).

A sample for analysis was vacuum sublimed.

Anal. Calcd for $C_{16}H_{13}ClN_4$: C, 64.76; H, 4.42; N, 18.88; Cl, 11.96. Found: C, 64.78; H, 4.36; N, 19.04; Cl, 11.89.

8-Chloro-6-phenyl-4*H*-*v*-triazolo[1,5-*a*][1,4]benzodiazepine (3) and 8-Chloro-6-phenyl-6*H*-*v*-triazolo[1,5-*a*][1,4]benzodiazepine (17). A solution of the amine **16** (4.3 g) in methylene chloride (100 ml) was treated with activated manganese dioxide (25 g) and stirred under reflux for 2 hr. The solid was filtered out and

thoroughly washed with methylene chloride. The filtrate and washing were combined and evaporated to leave a colorless, crystalline mixture of two products (TLC). These were separated by column chromatography on 100 g of silica gel using methylene chloride as eluent. The 6H isomer **17**, 1.3 g (30%), was eluted first and then the more polar 4H isomer **3**, 1.2 g (28%), was obtained. A sample of compound **3** was vacuum sublimed at 140°, giving colorless crystals: mp 168–169°; ir (Nujol) 1620 and 1575 cm^{-1}; NMR ($CDCl_3$) δ 4.75 (s, 2 H) and 7.3–8.2 (m, 9 H); mass spectrum *m/e* 231, 265 (100%), and 294 (M^+).

Anal. Calcd for $C_{16}H_{11}ClN_4$: C, 65.20; H, 3.76; N, 19.00; Cl, 12.03. Found: C, 65.24; H, 3.82; N, 19.14; Cl, 12.09.

A sample of compound **17** was recrystallized from methylene chloride–ether to give colorless crystals: mp 123–125°; ir (Nujol) 1640 cm^{-1}; NMR ($CDCl_3$) δ 5.33 (broad s, 1 H), 6.83 (d, 1 H), 7.3–7.7 (m, 6 H), 7.90 (d, 1 H), 8.10 (s, 1 H), and 8.67 (broad s, 1 H); mass spectrum *m/e* 204, 238, 266, and 294 (100%, M^+).

Anal. Found: C, 65.49; H, 3.67; N, 19.22; Cl, 11.93.

8-Chloro-3-methyl-6-phenyl-4*H*-*v*-triazolo[1,5-a][1,4]benzodiazepine (4) and 8-Chloro-3-methyl-6-phenyl-6*H*-*v*-triazolo[1,5-a][1,4]benzodiazepine (18). The MnO_2 oxidation of amine **14** (3.6 g) under the conditions described above for amine **16** required 48 hr at reflux. The crude mixture of two products (3.0 g) was separated by chromatography on 15 preparative layer plates (silica gel with 5% CH_3OH in $CHCl_3$) giving 1.50 g (42%) of compound **4**, the more polar component, and 0.80 g (22%) of **18**.

A sample of compound **4** was recrystallized from methylene chloride–ether to give colorless crystals: mp 196–196.5°; ir (Nujol) 1620 cm^{-1}; NMR ($CDCl_3$) δ 2.42 (s, 3 H), 4.66 (s, 2 H), and 7.2–8.2 (m, 8 H); mass spectrum *m/e* 245, 279 (100%), and 308 (M^+).

Anal. Calcd for $C_{17}H_{13}ClN_4$: C, 66.13; H, 4.24; N, 18.15; Cl, 11.48. Found: C, 66.29; H, 4.46; N, 18.16; Cl, 11.36.

A sample of compound **18** recrystallized from ether had mp 133–135°; ir (Nujol) 1635 and 1555 cm^{-1}; NMR ($CDCl_3$) δ 2.53 (s, 3 H), 5.30 (d, J = 2 Hz, 1 H), 6.8–8.0 (m, 8 H), and 8.48 (d, J = 2 Hz, 1 H); mass spectrum *m/e* 203, 218, 252, 280 (100%), and 308 (M^+).

Anal. Found: C, 66.24; H, 4.22; N, 18.44; Cl, 11.81.

Registry No.—**3**, 53878-78-7; **4**, 53993-42-3; **5**, 53878-93-6; **6**, 53993-43-4; **7**, 53993-44-5; **8**, 53878-98-1; *syn*-**9**, 53993-45-6; *anti*-**9**, 53993-46-7; **10**, 53879-01-9; **11**, 53993-47-8; **12**, 53993-48-9; **13**, 53993-49-0; **14**, 53993-50-3; **15**, 53879-03-1; **16**, 53879-04-2; **17**, 53879-05-3; **18**, 53993-51-4; 2-amino-5-chlorobenzophenone, 719-59-5; methyl propiolate, 922-67-8; dimethyl acetylenedicarboxylate, 762-42-5; hydroxylamine hydrochloride, 5470-11-1.

References and Notes

(1) Part LXIX: R. I. Fryer and A. Walser, *J. Med. Chem.*, **17**, 1228 (1974).
(2) K. Meguro and Y. Kuwada, *Tetrahedron Lett.*, 4039 (1970); K. Meguro, H. Tawada, and Y. Kuwada, *Chem. Pharm. Bull.*, **21**, 1619 (1973); K. Meguro and Y. Kuwada, ibid., **21**, 2375 (1973); K. Meguro, H. Miyano, Y. Sato, and Y. Kuwada, ibid., **21**, 2382 (1973); K. Meguro and Y. Kuwada. *Heterocycles*, **2**, 335 (1974).
(3) J. B. Hester, D. J. Duchamp, and C. G. Chidester, *Tetrahedron Lett.*, 1609 (1971); J. B. Hester, A. D. Rudzik, and B. V. Kamdar, *J. Med. Chem.*, **14**, 1078 (1971).
(4) The Upjohn Co., U.S. Patents 3,701,782 (1972), 3,709,898 (1973), 3,734,922 (1973), 3,743,652 (1973), 3,767,660 (1973), 3,772,318 (1973), 3,708,592 (1973), 3,709,899 (1973), 3,741,957 (1973), 3,759,943 (1973), and 3,767,661 (1973).
(5) Takeda Chemical Industries, German Patents 2,056,174 (1971) and 2,153,519 (1972); Japanese Patent 7,343,754 (1973).
(6) Ciba-Geigy, German Patents 2,215,939 (1972) and 2,308,280 (1973).
(7) Ciba-Geigy, German Patents 2,234,620 (1973), 2,234,652 (1973), and 2,304,307 (1973); Netherlands Patent 7,301,601 (1973); U.S. Patent 3,784,556 (1974).
(8) F. R. Benson and W. L. Savell, *Chem. Rev.*, **46**, 1 (1950).
(9) R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, **2**, 565 (1963).
(10) The conversion of various o-aminobenzophenones to azides has been described: P. A. Smith, B. B. Brown, R. K. Putney, and R. F. Reinisch, *J. Am. Chem. Soc.*, **75**, 6335 (1953); J. H. Hall, F. E. Behr, and R. L. Reed, ibid, **94**, 4952 (1972); R. Y. Ning, W. Y. Chen, and L. H. Sternbach, *J. Heterocycl. Chem.*, **11**, 125 (1974).
(11) R. Huisgen, R. Knorr, L. Mobius, and G. Szeimies, *Chem. Ber.*, **98**, 4014 (1965).
(12) M. S. Brown and H. Rapoport, *J. Org. Chem.*, **28**, 3261 (1963).
(13) The Grundon–Henbest–Scott modification was used to minimize lactam hydrolysis: M. F. Grundon, H. B. Henbest, and M. D. Scott, *J. Chem. Soc.*, 1855 (1963).
(14) Melting points are uncorrected. NMR spectra were recorded on Varian T-60 and HA-100 instruments and are reported in parts per million from internal tetramethylsilane. Infrared and mass spectra were recorded on Perkin-Elmer 137 and CEC-110B instruments, respectively. Elemental analyses were conducted under the supervision of Dr. F. Scheidl of our microanalytical laboratory.
(15) R. Ratcliffe and R. Rodehorst, *J. Org. Chem.*, **35**, 4000 (1970).

Nuclear Magnetic Resonance Studies on Conformations about the Nitrogen–Carbon Bond in Some *N*-Malonylimides and Some Comments on the Origin of Nitrogen–Nitrogen Bond Torsional Barriers

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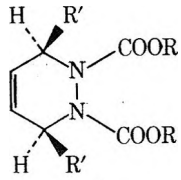
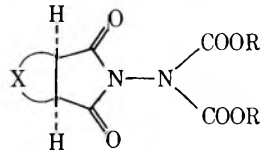
The preparation and NMR studies of a series of *N*-malonyl derivatives of Diels–Alder adducts of anthracene–maleimide and anthracene–citraconimide have been described. In contrast to the tetraacylhydrazine systems, these compounds show no spectral multiplicities in their NMR signals at 44.5° owing to slow rate processes indicating that rotation about the N–C bond in these compounds is free on the NMR time scale. It has been further demonstrated that the nonbonding repulsion between the substituents is not the main contribution to the N–N bond torsional barriers in tetraacylhydrazine systems but that the lone-pair electronic interactions at the two nitrogen atoms are sufficiently effective. This is supported by preparing the sodium salts of the title compounds possessing a >N–$^-$C< system, isoeletronic with the N–N bond in tetraacylhydrazines which show multiplicity in their NMR spectra indicating hindered rotation about the N–C bond.

Studies on conformations by NMR spectroscopy have been receiving considerable attention during recent years.[1] Barriers to nitrogen inversion in cyclic hydrazines[2] and acyclic hydrazines[3] have been studied by dynamic NMR spectroscopy. Hindered inversion at the pyramidal nitrogen in aziridines has been rationalized[4] in terms of ring strain during inversion, while restricted rotation about the N–CO bonds has been assigned[5] to the partial double bond character of the amide bonds. High energy barriers to the inversion of *N,N'*-diacyltetrahydropyridazine of the type I (18–19 kcal/mol)[6] and the restricted rotation about the N–N bonds in tetraacylhydrazine systems of the type II and III[7] have been demonstrated by NMR spectroscopy and attributed largely to the nonbonding repulsions between the acyl substituents in the planar transition state. Existence of nonplanar conformations and high energy barriers to the N–N bond torsion in the *N,N'*-diacyl-*N,N'*-dialkylhydrazine system[8] (21–22 kcal/mol, the values fairly



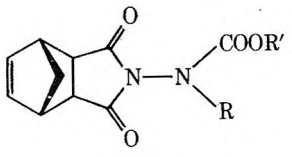
I



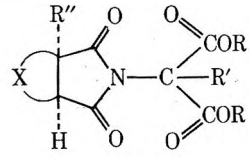
II, X = $-CH_2CH{=}CHCH_2-$

III, X = 9,10-dihydroanthracene

comparable to those of the tetraacylhydrazine system) prompt us to suspect that the nonbonding repulsive interactions between the acyl substituents may not be solely responsible for the high torsional barriers in all these cases. Conformational studies on N′ derivatives of *N*-aminoimides of the type IV,[9] which showed a similar order of barriers (21 kcal/mol) to the N–N bond torsion for the different substituents, R = CH_3, C_6H_5, COR′, SO_2R', etc., also support the above suggestion. It is on this point that we wish to address this communication along with the NMR studies on the N–C bond system, V, which throw light on the origin of N–N bond torsional barriers.



IV



V

X represents a chain of four or more carbon atoms forming a planar or nonplanar bicyclic cage type structure

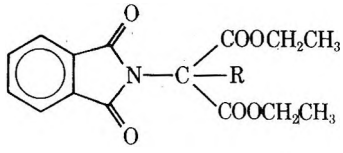
R = CH_3, CH_2CH_3

R′ = H, $CH_2C_6H_5$, CH_2CH_3

R″ = H, CH_3

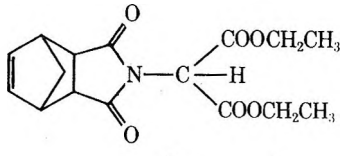
Results and Discussion

A series of compounds of type V (1–13) has been synthesized and their NMR spectra studied.



1, R = H

2, R = $CH_2C_6H_5$



3

The NMR spectra of compounds 1 and 3 are quite normal. The ester methylene (4 H) and methyl protons (6 H) appear as a sharp quartet (δ 4.3) and a sharp triplet (δ 1.31), respectively, in $CDCl_3$ at 44.5°.

Analogous to the tetraacylhydrazine systems,[10] these compounds may be expected to exhibit slow rotation about the N–C bond and ground-state conformations in which the ester groups would lie one on either side of the imide ring plane. However, neither of these two compounds indicate, from their NMR spectra, any such conformation, stable on the NMR time scale. Even if the N–C bond rotation is slow on the NMR time scale, compound 1, as its imidyl moiety is planar, cannot show any spectral multiplicity, while it may be presumed that the cage moiety of compound 3 is not sufficiently effective to resolve the signals of the two ester groups.

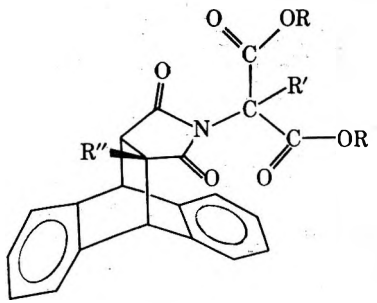
The NMR spectrum of compound 4 in $CDCl_3$ shows (Table I) a singlet for the two ester methyl groups, while that of compound 5 shows (Table I) a normal quartet and a triplet (J = 7.5 Hz) for the two ester ethyl groups. The N compound III (R = CH_3) exhibited,[11] in its NMR spectrum, two signals for the two ester methyl groups with an internal chemical shift of 30 Hz, where restricted rotation and nonplanar ground-state conformation about the N–N bond have been inferred. Similarly, if there is any hindrance to the rotation about the N–C bond in compound 4, two different signals for the two ester groups, with an appreciable internal chemical shift, might have been observed. Therefore, it may be presumed that the rotation about the N–C bonds in these compounds is free on the NMR time scale. This has been further verified by the absence of exchange broadening in the signals of compound 4 in $CDCl_3$ at −48°. The NMR spectrum of compound 5 is also consistent with a free rotation about the N–C bond. The ester methylene and methyl group protons in compound 5 resonate at relatively higher fields (δ 4.2 and 1.22, respectively) as compared to the corresponding resonance positions of compounds 1 and 3. This observation indicates that both the ester groups in compound 5 experience a time-averaged shielding effect from the cage moiety, which is an added evidence for the free rotation about the N–C bond.

The spectrum of compound 6 exhibits (Table I) two singlets for the two ester methyl groups, with an internal chemical shift ($\Delta\nu$) of 2 Hz, while that of compound 7 shows (Table I) two quartets ($\Delta\nu$ = 2 Hz) for the ester methylene protons and a broad triplet for the ester methyl protons. The observed multiplicity in signals of the geminal protons of ester groups at the exocyclic carbon atom with a small internal chemical shift may be attributed to the long-range induced asymmetry[12] of the cage moiety due to the C_{11} methyl group.

The NMR spectrum of compound 8 is quite normal (Table I), whereas compound 9 shows a complex multiplet for the four ester methylene protons, a triplet (J = 7.5 Hz) for the six ester methyl protons, and a singlet for the two benzylic protons. The carbon carrying the ester groups in all these compounds is asymmetric when viewed from either of the ester groups.[13] In compound 9, the intrinsic nonequivalence of the two geminal methylene protons of the ester groups caused by so-called asymmetry gives rise to a complex multiplet, while the other signals remain normal. Compound 2 in $CDCl_3$ (as well as in nitrobenzene) also shows a more or less similar pattern, with less resolution, for the ester methylene protons at δ 4.4 (4 H), while it shows normal signals for the rest of the protons: δ 1.29 t (6 methyl protons), 3.88 s (2 benzylic protons) and 7.58 (9 aromatic protons). In compounds 1, 3, 5, and 7, which do not possess a benzyl group at the exocyclic carbon atom, the intrinsic nonequivalence offered by the system is not sufficiently effective to cause a resolution in their ester methylene proton signals resulting in simplified spectral patterns.

Compound 10 in $CDCl_3$ shows (Table I) an AB pattern for the benzylic protons which experience the long-range asymmetry of the cage moiety and shielding of the cage methyl protons by the benzylic phenyl group. The spectrum of this compound in nitrobenzene shows two singlets for the ester methyl groups, indicating that these groups also experience the cage asymmetry. The spectrum of compound 11 is quite similar to that of compound 10. The spectra of compounds 12 and 13 show an abnormal shielding of

Table I
NMR[a] Data for Compounds 4–13



4, R = CH_3; R′ = R″ = H
5, R = CH_2CH_3; R′ = R″ = H
6, R = CH_3; R′ = H; R″ = CH_3
7, R = CH_2CH_3; R′ = H; R″ = CH_3
8, R = CH_3; R′ = $CH_2C_6H_5$; R″ = H
9, R = CH_2CH_3; R′ = $CH_2C_6H_5$; R″ = H
10, R = CH_3; R′ = $CH_2C_6H_5$; R″ = CH_3
11, R = CH_2CH_3; R′ = $CH_2C_6H_5$; R″ = CH_3
12, R = CH_2CH_3; R′ = CH_2CH_3; R″ = H
13, R = CH_3; R′ = CH_2CH_3; R″ = CH_3

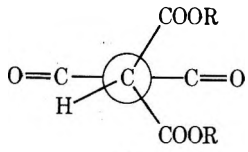
Compd	Solvent	R	R′	R″	H_{12}[b]	H_{10}	H_9[b]	Aromatic protons
4	$CDCl_3$	3.65 (6 H, s)	5.03 (1 H, s)	3.35 (1 H, m)	3.35 (1 H, m)	4.88 (1 H, m)	4.88 (1 H, m)	7.4 (8 H, m)
	$C_6H_5NO_2$	3.70 (6 H, s)	5.28 (1 H, s)	3.62 (1 H, m)	3.62 (1 H, m)	5.11 (1 H, m)	5.11 (1 H, m)	
5	$CDCl_3$	4.21 (4 H, q)[c] 1.22 (6 H, t)	4.93 (1 H, s)	3.35 (1 H, m)	3.35 (1 H, m)	4.88 (1 H, m)	4.88 (1 H, m)	7.4 (8 H, m)
	$C_6H_5NO_2$	4.28 (4 H, q)[c] 1.22 (6 H, t)	5.22 (1 H, s)	3.58 (1 H, m)	3.58 (1 H, m)	5.12 (1 H, m)	5.12 (1 H, m)	
6	$CDCl_3$	3.7 (6 H, ds) 1:1; 2 Hz	5.0 (1 H, s)	1.23 (3 H, s)	2.81 (1 H, d)	4.48 (1 H, s)	4.83 (1 H, d)	7.4 (8 H, m)
	$C_6H_5NO_2$	3.77 (6 H, ds) 1:1; 2 Hz	5.24 (1 H, s)	1.33 (3 H, s)	3.01 (1 H, d)	4.68 (1 H, s)	5.04 (1 H, d)	
7	$CDCl_3$	4.21 (4 H, dq)[d] 1:1; 2 Hz 1.22 (6 H, t)	4.98 (1 H, s)	1.22 (3 H, s)	2.81 (1 H, d)	4.48 (1 H, s)	4.83 (1 H, d)	7.4 (8 H, m)
	$C_6H_5NO_2$	4.29 (4 H, dq)[d] 1.23 (6 H, t)	5.17 (1 H, s)	1.30 (3 H, s)	2.98 (1 H, d)	4.65 (1 H, s)	5.0 (1 H, d)	
8	$CDCl_3$	3.65 (6 H, s)	3.56 (2 H, s)	2.90 (1 H, m)	2.90 (1 H, m)	4.70 (1 H, m)	4.70 (1 H, m)	7.4 (13 H, m)
	$C_6H_5NO_2$	3.79 (6 H, s)	3.79 (2 H, s)	3.15 (1 H, m)	3.15 (1 H, m)	4.97 (1 H, m)	4.97 (1 H, m)	
9	$CDCl_3$	4.17 (4 H, mq)[c] 1.15 (6 H, t)	3.55 (2 H, s)	2.87 (1 H, m)	2.87 (1 H, m)	4.77 (1 H, m)	4.77 (1 H, m)	7.37 (13 H, m)
	$C_6H_5NO_2$	4.34 (4 H, mq)[c] 1.26 (6 H, t)	3.79 (2 H, s)	3.10 (1 H, m)	3.10 (1 H, m)	4.97 (1 H, m)	4.97 (1 H, m)	
10	$CDCl_3$	3.67 (6 H, s)	3.60 (2 H, q)[e]	0.69 (3 H, s)	2.37 (1 H, d)	4.29 (1 H, s)	4.72 (1 H, d)	7.37 (13 H, m)
	$C_6H_5NO_2$	3.85 (6 H, ds) 1:1; 0.7 Hz	3.80 (2 H, q)[e]	0.78 (3 H, s)	2.49 (1 H, d)	4.45 (1 H, s)	4.89 (1 H, d)	
11	$CDCl_3$	4.19 (4 H, mq)[d] 1.18 (6 H, t)	3.57 (2 H, q)[e]	0.66 (3 H, s)	2.38 (1 H, d)	4.30 (1 H, s)	4.73 (1 H, d)	7.35 (13 H, m)
	$C_6H_5NO_2$	4.36 (4 H, mq)[d] 1.25 (6 H, dt) J = 1 Hz	3.79 (2 H, q)[e]	0.73 (3 H, s)	2.47 (1 H, d)	4.45 (1 H, s)	4.91 (1 H, d)	
12	$CDCl_3$	4.28 (4 H, q)[d] 1.21 (6 H, t)	2.04 (2 H, q)[c] 0.09 (3 H, t)	3.37 (1 H, m)	3.37 (1 H, m)	4.90 (1 H, m)	4.90 (1 H, m)	7.46 (8 H, m)
	$C_6H_5NO_2$	4.40 (4 H, q)[d] 1.28 (6 H, t)	2.27 (2 H, q)[c] 0.37 (3 H, t)	3.50 (1 H, m)	3.50 (1 H, m)	5.09 (1 H, m)	5.09 (1 H, m)	
13	$CDCl_3$	3.35 (6 H, s)	2.10 (2 H, q)[c] 0.27 (3 H, t)	1.23 (3 H, s)	2.83 (1 H, d)	4.50 (1 H, s)	4.85 (1 H, d)	7.45 (8 H, m)
	$C_6H_5NO_2$	3.87 (6 H, s)	2.31 (2 H, q)[c] 0.48 (3 H, t)	1.31 (3 H, s)	2.93 (1 H, d)	4.68 (1 H, s)	5.04 (1 H, d)	

[a] Chemical shifts (δ) are recorded in $CDCl_3$ and nitrobenzene ($C_6H_5NO_2$) at 44.5° using Me_4Si as internal reference standard. In case of multiplicities, algebraic mean positions of the signals are given. Parentheses include proton count and the multiplicities abbreviated as s = singlet, d = doublet, t = triplet, q = quartet, ds = double singlet, dt = doublet triplet, and m = multiplet. [b] J between H_9 and H_{12} protons was 3.5 Hz. [c] J = 7.5 Hz between ester ethyl protons. [d] J = 7 Hz between ester ethyl protons. [e] J_{AB} = 14 Hz.

the C-methyl (R′) protons and absence of nonequivalence for the ester methylene protons (Table I).

All the spectra discussed above are consistent with the suggestion that the N–C bond rotation in these compounds is free on the NMR time scale.

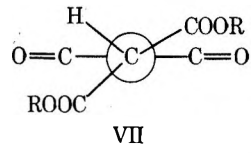
There are certain points which need consideration for comparison between the tetraacylhydrazines and the present system. The N–N′–CO bond angles (~120°) in the tetraacylhydrazine system are fairly larger than the N–C–CO bond angles (~109°) in the present system. Therefore, the nonbonding repulsive forces between any two carbonyl groups, one on either side of the N–C bond, in the transition state would be more than those for the N–N bond system. Then, if it is assumed that the exocyclic malonyl proton pushed toward a carbonyl group of the imide ring (VI)



VI

in compounds 3–7 would not raise considerably the ground-state energy of the molecule, larger barriers could be expected for the N–C bond rotation. Of course, this is not true in the case of compounds 8–11, where the bulky benzyl group at the exocyclic carbon atom would raise considerably the ground-state energy of the molecule.

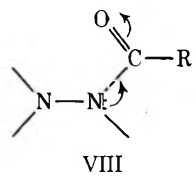
The two *N′*-carbonyls of the tetraacylhydrazine system cross the two imide ring carbonyls simultaneously in the transition state for the rotation, whereby the repulsive forces of the each pair of the crossing carbonyls reinforce those of the other pair. In the present system, two carbonyls at the exocyclic carbon atom cross the two imide ring carbonyls, respectively, one after the other with a difference of about 30° rotation (VII), thereby reducing the bar-



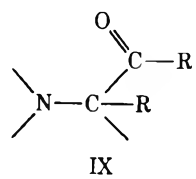
VII

rier height of the N–C bond rotation. Spectral studies of compounds of type IV (R = CH_3), which possess only one *N′*-carbonyl group to cross any one of the imide ring carbonyls in the transition state and still show large barriers to rotation (19–21 kcal/mol), indicate that this type of interaction may not be exclusively effective in making the N–C bond rotation free.

A carbonyl group on the hydrazine system lies preferably in the same plane as the N–N bond (VIII) because of delo-

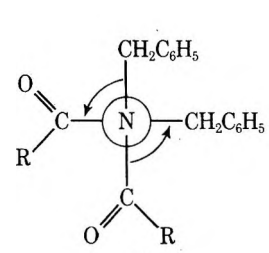


VIII

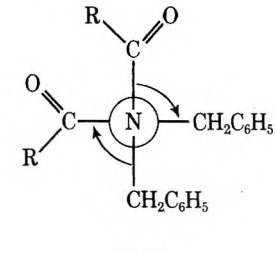


IX

calization of the nitrogen lone pair electrons, and thus the repulsive interactions in the transition state may be greater in this case. This is not the case with the present system, where the exocyclic C-carbonyls may assume any conformation (IX) about the C–CO bonds depending upon the stereoelectronic factors in the system. It would be helpful to consider here an acyclic *N,N′*-diacyl-*N,N′*-dialkylhydrazine system. For the interconversion of the two conformational diastereomers X and XI, a carbonyl group on one nitrogen atom may cross the alkyl group on the other nitro-



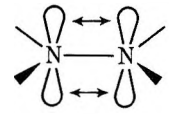
X



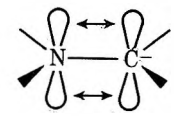
XI

gen atom and crossing of a carbonyl group with the other carbonyl group in the transition state is not a necessary condition. In the present system the two carbonyls of the imide ring lie in the plane of the N–C bond, and therefore, whatever the conformation of the *C*-carbonyls may be, the nonbonding interactions would not be less than those in the *N,N′*-diacyl-*N,N′*-dialkylhydrazine system.

The foregoing data strongly suggest that nonbonding repulsions between the substituents are not the main contribution to the N–N bond torsional barriers. Besides other factors, it may now be considered that the acylhydrazine system of the type discussed above possesses two lone pairs containing p orbitals on the two nitrogen atoms, whereas the present system possesses only one such orbital. Therefore, the main cause of hindrance to the N–N bond rotation seems to be the electrostatic repulsions between the two parallel p orbitals in the transition state (XII). This could be tested by preparing sodium salts of compounds 4 and **6**, which form a >N–⁻C< system (XIII), isoelectronic with



XII



XIII

the N–N bond system. The NMR spectra of both these salts in pyridine show two singlets each of 3 H intensity for their two ester methyl groups, with an internal chemical shift of 16 Hz. This multiplicity of ester methyl signals can be attributed to restricted rotation about the N–C bond, and supports the above conclusions. The barrier to rotation about the N–C bond of the sodium salt of compound 4 has been evaluated to be 20 kcal/mol by VTNMR measurements (solvent quinoline, $\Delta\nu$ at 44.5° = 17 Hz, coalescence temperature 120°) using Eyring's rate equation.[1] It may be mentioned that compound 4 could be regenerated from the sodium salt on acidification, which does not show any multiplicity in pyridine or in nitrobenzene (Table I) for the two ester methyl protons.

Experimental Section

NMR spectra were recorded on a Varian A-60D spectrometer equipped with a variable-temperature controller (Model V-6040). Ir spectra were recorded in Nujol on a Perkin-Elmer 257 spectrophotometer. Chemical analyses, ir spectra and melting points of all compounds are given in Table II.

A. 9,10-Dihydroanthracene-9,10-*endo*-α,β-succinimide (**14**) was prepared by heating anthracene-maleic anhydride adduct (1 mol) and urea (a little more than 0.5 mol) in a long-necked round-bottom flask at 140–150° for 1.5 hr. At the end of the reaction, the evolution of ammonia ceased and the boiling reaction mixture turned into a solid. After cooling, the solid mass was disintegrated by addition of water, filtered, and dried. It was recrystallized from hot xylene: mp 322–325° (327°);[14] ir ν_{max} 1735 s, 1795 m, 3370 s cm^{-1}.

9,10-Dihydroanthracene-9,10-*endo*-α-methyl-α,β-succinimide (**15**) was obtained by a similar method using anthracene–citraconic anhydride adduct and urea and was recrystallized from hot ethanol: mp 227–230°; ir ν_{max} 1720 s, 1777 s, 3086 m, 3160 m cm^{-1}.

Bicyclo[2.2.1]-5-heptene-2,3-*endo*-dicarboximide (**16**) was prepared by the method of Morgan et al.:[15] mp 182–184°; ir ν_{max} 1710 s, 1760 s, 3084 s, 3180 s cm^{-1}.

Table II
Melting Points, Elemental Analysis, and Characteristic Infrared[a] Peaks of Compounds 1–13

Compd	Mp, °C	Found, % C	Found, % H	Calcd, % C	Calcd, % H	Ir, ν_{max}, cm^{-1}
1	75–76	58.88	4.78	59.02	4.92	1734 s, 1758 s, 1787 w
2	109	66.48	5.27	66.83	5.32	1730 s, 1762 s, 1789 m
3	85	59.64	5.80	59.81	5.92	1710 s, 1745 s, 1760 s, 1733 s, 1756 s, 1790 m
4	176–177	68.25	4.68	68.14	4.69	1710 s, 1747 s, 1760 s, 1785 m
5	157–159	69.52	5.45	69.28	5.31	1717 s, 1744 s, 1782 m
6	166–167	68.81	4.90	68.73	5.0	1718 s, 1750 s, 1780 w
7	121–122	69.88	5.60	69.70	5.59	1710 s, 1748 s, 1782 m
8	198–200	72.58	5.24	72.72	5.05	1708 s, 1722 m, 1748 m, 1760 s, 1780 s
9	165–167	73.03	5.51	73.42	5.54	1712 s, 1753 s, 1778 m
10	180–181	72.88	5.50	73.08	5.30	1715 s, 1744 s, 1764 s
11	154–155	73.44	5.66	73.74	5.77	1713 s, 1752 s, 1778 m
12	123–125	69.89	5.83	70.28	5.86	1720 s, 1754 s, 1773 m, 1790 w
13	182–183	69.66	5.48	69.80	5.59	1722 s, 1748 s, 1766 s, 1788 m

[a] Ir taken in Nujol medium. Abbreviations: s = strong, m = medium, w = weak.

B. Compounds **3–7** were derived from the dicarboximides **14–16**. The imides were converted into their potassium salts by reaction with equimolar proportions of alcoholic potassium hydroxide and were recovered as solids on evaporation. The potassium salts of these imides were mixed with appropriate bromomalonic ester in equimolar amounts and heated at 120° for 1 hr in an oil bath. The reaction mixtures were then cooled to obtain solids which were washed with water to remove the potassium bromide formed in the reaction. The products were recovered by dissolving these solids in cold benzene and discarding the remaining residues (which were supposed to be unreacted starting materials). All the compounds were recrystallized from ethanol. The melting points and characteristic ir bands are given in Table II.

C. Compounds 8–11. Compound **8** was obtained by adding an equimolar amount of benzyl chloride to the mixture of compound **4** and anhydrous potassium carbonate in dimethylformamide. The reaction mixture was stirred at room temperature for about 1 hr and thereafter heated at 140° for another 1 hr. The solvent (DMF) was then removed under reduced pressure and the solid mass was triturated with crushed ice. The product was filtered, dried, and recrystallized from ethanol. The other benzyl derivatives **9–11** were obtained by benzylation of appropriate *N*-malonyl compounds **5–7**, under similar conditions. Compounds **12** and **13** were also obtained under similar conditions by reaction of ethyl bromide with compounds **5** and **6**, respectively.

D. Sodium Salts of Compounds 4 and 6. Compound **4** dissolved in dry benzene was treated with 1 mol of sodium hydride in dry benzene. The reaction mixture was refluxed for about 1 hr to complete the reaction. White, powdered solid was recovered by removing the solvent under reduced pressure and dried under vacuum.

Acknowledgment. We thank Professor G. B. Singh and Dr. C. Koteswara Rao for their interest and the C.S.I.R., India, for the award of a Research Fellowship (to R. M. Singh).

Registry No.—**1**, 5680-61-5; **2**, 17102-94-2; **3**, 53965-75-6; **4**, 53965-76-7; **5**, 53965-77-8; **6**, 53965-78-9; **7**, 53965-79-0; **8**, 53965-80-3; **9**, 53965-81-4; **10**, 53965-82-5; **11**, 53965-83-6; **12**, 53965-84-7; **13**, 53965-85-8; **14**, 5721-34-6; **15**, 53965-86-9; **16**, 6319-06-8.

References and Notes

(1) W. A. Thomas, *Annu. Rev. NMR Spectrosc.*, **1**, 43 (1968); G. Binsch, *Top. Stereochem.* **3**, 97 (1968); J. E. Anderson, *Q. Rev., Chem. Soc.*, **19**, 426 (1965).
(2) J. E. Anderson, *J. Am. Chem. Soc.*, **91**, 6374 (1969).
(3) M. J. S. Dewar and W. B. Jennings, *J. Am. Chem. Soc.*, **95**, 1562 (1973); *Tetrahedron Lett.*, 339 (1970).
(4) T. J. Bardos, C. Szantay, and C. K. Navada, *J. Am. Chem. Soc.*, **87**, 5796 (1965); F. A. L. Anet and J. M. Osyany, ibid., **89**, 352 (1967); J. D. Andose, J. M. Lehn, K. Mislow, and J. Wagner, ibid., **92**, 4050 (1970); S. J. Brois, *Tetrahedron Lett.*, 5997 (1968); R. G. Kostyanovskii, A. A. Fomichev, and Z. E. Somoilava, ibid., 3459 (1970); D. J. Anderson, D. C. Horwell, and R. S. Atkinson, *J. Chem. Soc. C*, 624 (1971).
(5) W. E. Stewart and T. H. Siddall, III, *Chem. Rev.*, **70**, 517 (1970).
(6) J. E. Anderson and J. M. Lehn, *Tetrahedron*, **24**, 123, 137 (1968); E. L. Allred, C. L. Anderson, R. L. Miller, and A. L. Johnson, *Tetrahedron Lett.*, 525 (1967); J. P. Kintzinger, J. M. Lehn, and J. Wagner, *Chem. Commun.*, 206 (1967).
(7) B. H. Korsch and N. V. Riggs, *Tetrahedron Lett.*, 5897 (1966).
(8) G. J. Bishop, B. J. Price, and I. O. Sutherland, *Chem. Commun.*, 672 (1967); J. R. Fletcher and I. O. Sutherland, *J. Chem. Soc. D*, 687 (1970).
(9) S. M. Verma and C. Koteswara Rao, *Tetrahedron*, **28**, 5029 (1972).
(10) S. M. Verma and R. Prasad, *J. Org. Chem.*, **38**, 1004, 3745 (1973); S. M. Verma and O. S. Rao, *Aust. J. Chem.*, **26**, 1963 (1973); S. M. Verma and K. O. P. Sinha, *Indian J. Chem.*, **11**, 1138 (1973).
(11) B. H. Korsch, Ph.D. Thesis (unpublished) submitted to the University of New England, Australia, 1967.
(12) R. E. Lyle and J. J. Thomas, *Tetrahedron Lett.*, 897 (1969), and references cited therein.
(13) In molecules of type U–CH–H –CXY–CH–H –U which do not possess an asymmetric center, the methylene protons will, in general, be nonequivalent because "from the point of view" of either of the pairs of methylene protons, the central carbon atom bears three different substituents, thus making this case virtually equivalent to U–CH–H –CXYZ.
(14) F. E. Ray, E. Sawicki, and O. H. Borum, *J. Am. Chem. Soc.*, **74**, 1247 (1952).
(15) M. S. Morgan, R. S. Tipson, A. Lowy, and W. E. Baldwin, *J. Am. Chem. Soc.*, **66**, 404 (1944).

Nitrogen Analogs of 1,6-Methano[12]annulene. Effect on Valence Tautomerism of the Locus of Aza Substitution[1]

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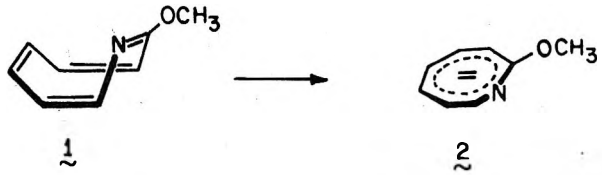
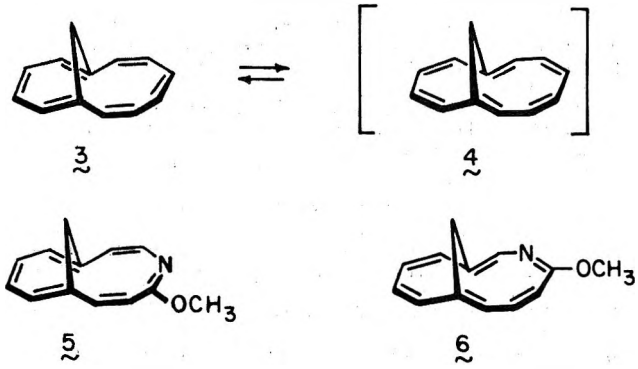
Beckmann rearrangement of 4,9-methano[11]annulenone oxime with tosyl chloride in pyridine and subsequent direct methanolysis leads to azaannulene **5** in 90% yield. The oxime of 3,8-methano[11]annulenone rearranges only with difficulty to give β-lactam **13**. The valence isomeric lactam **14** cannot be detected at temperatures up to 110°. The contrasting behavior of **8** and **13** and the question of heavy thermodynamic weighting in the direction of the bridged cycloheptatriene form are discussed. It is concluded that planar bridged cycloheptatriene derivatives are more stable because of lessened strain and electronic delocalization of the neutral homoaromatic type. The electrochemical reduction of **5** reveals that multielectron (2ϵ) discharge occurs, but that the resulting dianion is highly reactive or unstable (cyclic voltammetry data). Alkali metal reductions performed in liquid ammonia support the surprising instability of dianion **18**. Dihydro products **19** and **20** were formed upon quenching.

To date, studies of the consequences of ring nitrogen substitution for trigonal carbon on the chemical properties of $4n$-π monocyclic polyolefins have been limited to the azocine group.[2,3] Although such π-equivalent heterocycles as **1** are true polyolefins, alkali metal reduction affords the very stable planar 10-π-electron dianions **2** which are endowed with substantial aromatic character.[4] Electrochemical measurements have shown that reductions under these conditions occur by direct two-electron transfer and that azocinyl dianions are not reoxidized until the potential is scanned 1 V anodic of the initial reduction wave.[5] The properties of multielectron addition and resistance to oxidation are not shared by cyclooctatetraene and its derivatives. The azocines are endowed with a sufficient number of unique chemical features that systematic investigation of higher homologs of this ring system appeared desirable.



1 **2**

This paper, therefore, describes a study of the aza analogs **5** and **6** of 1,6-methano[12]annulene (**3**). The compan-

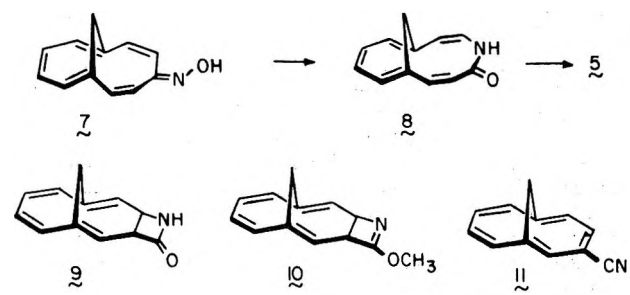


3 **4**

5 **6**

ion study by Vogel of the parent hydrocarbon[6] has shown the bridged annulene to be highly puckered, to exist essentially exclusively as valence tautomer **3** having the cycloheptatriene part structure, and to possess a paramagnetic ring current. Positioning of the imidate group as in **5** should permit the π-electron array which is energetically favored in **3**. In **6**,[7] however, maintenance of the imidate function should lead to bond fixation in the less stable electronic arrangement. Consequently, these isomeric heterocycles were expected to focus attention upon those electronic features peculiar to the [12]annulene model. Efforts to prepare **6** have failed in the final step, but the study has provided experimental information concerning the interrelationship of the locus of the nitrogen atom (as amide and imidate groups) and the preferred direction of valency tautomerism.

Synthetic Considerations. The approach to **5** involved ring expansion of 4,9-methano[11]annulenone.[8] This ketone was converted to its oxime **7** by refluxing with hydroxylamine hydrochloride and pyridine in ethanol solution. Beckmann rearrangement of **7** proved to be exceptionally facile, stirring with a twofold excess of tosyl chloride in pyridine at room temperature for 3 hr being adequate to provide good yields of **8** after hydrolysis. The ir spectrum



7 **8** **5**

9 **10** **11**

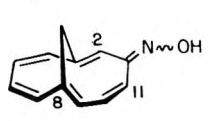
of this lactam shows intense absorptions at 3300, 2920, and 1675 cm^{-1}. Its ^1H NMR features a multiplet at δ 5.8–7.0 of area 9 due to the perimeter hydrogens and the >NH group and broadened doublets (J = 14 Hz) at 3.1 and 2.1 for the pair of bridge protons. The spectrum revealed no evidence for the presence of β-lactam isomer **9**, in marked contrast to the recognized predominance of 7-azabicyclo[4.2.0]octatrien-8-ones in equilibrium with their ring-opened monocyclic counterparts.[3e]

In the presence of trimethyloxonium fluoroborate, **8** was converted to **5** (60%) with concomitant formation of considerable polymer. Subsequently, it was recognized that attempted formation of the fluoroborate and perchlorate salts of **5** also led to decomposition. Since attempted ring expansion of oxime **7** with phosphorus pentachloride or polyphosphoric acid afforded only polymer, the lability of these polyenes to acidic media was made clearly evident. These difficulties could be totally bypassed by allowing oxime **7** to react with tosyl chloride in pyridine followed by direct methanolysis to give **5** in 90% yield.

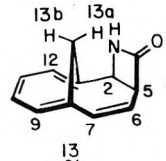
Azaannulene **5** is an air-stable, bright orange solid showing intense imidate absorption in the infrared at 1670 cm^{-1} and an ultraviolet maximum at 257 nm (ϵ 40,000). Its ^1H NMR spectrum consists of the expected olefinic pattern showing seven of the eight olefinic protons as a series of

multiplets at δ 5.85–6.60, H_2 appearing at higher field (5.08, broadened d, J = 10 Hz) owing to its unique position β to the nitrogen atom.[3] The bridgehead methylene protons are seen as widely separated doublets (J = 12 Hz) at δ 5.34 and 1.64, their mutual spin interaction having been unequivocally established by double-resonance experiments. As in the case of **8**, no spectroscopic evidence was obtained to suggest that **5** is in tautomeric equilibrium with **10** or its norcaradiene valence tautomer. Given that low levels of **10** could be present in <2% concentration and thereby escape spectral detection, then exposure to a strong base would be expected to produce nitrile **11**, much in the same way that **1** is converted to benzonitrile.[3d] However, **5** proved to be totally inert to the action of potassium *tert*-butoxide in refluxing tetrahydrofuran (8 hr) or dimethylformamide at 25° (16 hr). It would appear, therefore, that **10** is not present. Furthermore, the inability of **5** to undergo cycloaddition with *N*-phenylmaleimide (threefold excess, refluxing xylene, 30 hr) or dimethyl acetylenedicarboxylate (40-fold excess, refluxing toluene, 24 hr) attests to the unimportance of the norcaradiene isomer.

The oxime of 3,8-methano[11]annulenone (**12**) was synthesized from the corresponding ketone, which was obtained from reduction of 11-chloro-3,8-methano[11]annulenone.[9] In this instance the yields of oxime were not high, a maximum of 30% being realized in pyridine solution at room temperature for 48 hr. Unlike its symmetrical counterpart, the tosylate of **12** did not readily undergo the Beckmann rearrangement. For example, decomposition was encountered when this oxime tosylate was stirred at 0–25° in methanol–pyridine or water–acetone–pyridine solvent systems. However, prior removal of the pyridine in vacuo and subsequent solvolysis in an aqueous dioxane medium containing sodium acetate did give lactam product in 35% yield. When the less nucleophilic base 2,6-lutidine replaced sodium acetate under these conditions, the optimal yield for conversion to **13** (55%) was realized.



12



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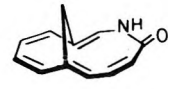


14

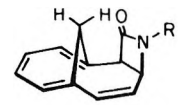
Noteworthy spectral features of **13** are the intense ir signals at 3418 and 1764 cm^{-1} and a parent molecular ion at m/e 185.0843 indicative of a β-lactam structure of molecular formula $C_{12}H_{11}NO$. In striking contrast to the behavior of **8**, where the base peak is the molecular ion, **13** exhibits a weak molecular ion and a base peak at m/e 142 (M − 43, loss of [CONH] ·). This type of fragmentation conforms to the usual behavior of β-lactams.[10]

Spin decoupling studies elucidated the gross structural features of **13** and the magnitude of the coupling constants $J_{2,5}$ = 5.0, $J_{5,6}$ = 7.0, $J_{6,7}$ = 12.0, and $J_{13a,13b}$ = 11.5 Hz. The syn stereochemical assignment was derived by pseudocontact shifting of the ^1H NMR spectrum with $Eu(fod)_3$.[11] The relevant ΔEu values[12] are H_2, −6.80; H_3, −11.66; H_5, −18.09; H_6, −11.68; H_7, −5.03; H_9, H_{12}, −2.72; H_{10}, H_{11}, −1.41; H_{13a}, −8.83; H_{13b}, −3.17. Since the lanthanide shift reagent complexes principally to the oxygen atom, the enhanced downfield shifting of both H_5 and H_{13a} requires that H_5 be α to the amide carbonyl and the methano bridge be syn to the β-lactam ring. That H_2 appears as a doublet coupled only to H_5 necessitates that the β-lactam ring be oriented as shown rather than in the reverse sense. This finding implicates C_2 as the vinyl carbon in **12** (in the form of the tosylate derivative) with the greater capability for migration to nitrogen, perhaps because of the stereochemistry prevailing in the crystalline oxime isomer employed.

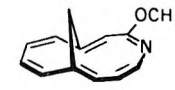
Despite the fact that **13** probably arises by ring closure of initially formed lactam **14**, no evidence for the reversal of this process could be gained by ^1H NMR studies at temperatures up to 110°. Nor was there any indication that the anti isomer of **13** was present during any of these experiments.

All attempts to effect the O-methylation of **13** resulted in decomposition with formation of noncharacterizable oils. Surprisingly, even the action of trimethyloxonium fluoroborate[10,13] and methyl fluorosulfonate,[14] two of the most powerful sources of methyl cation, were not successful in providing the desired imino ether. Efforts to generate the ring-expanded imino chloride and tosylate likewise failed.

Speculation then centered about the isomeric structure **15a** as a possible precursor to the π electronically related azaannulene **16**. The earlier observation that methano-



15a, R = H
b, R = SO_2Cl



16

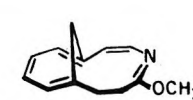
17a, R = H
b, R = Br
c, R = $CONH_2$
d, R = CN
e, R = COOH

[10]annulene reacts with bromine at −78° with formation of an addition product capable of dehydrobromination to give **17b**[15] seemingly points to preferential electrophilic attack at C_2 in this system. This suggested that [2 + 2] cycloaddition of chlorosulfonyl isocyanate (CSI) to **17a** might proceed so as to produce **15b**. Treatment of **17a** with CSI at −78° gave only very small quantities of a product possessing absorption at 1805 cm^{-1} as revealed by direct infrared analysis of the reaction mixture. Warming of the solution to −15° caused disappearance of this band with simultaneous appearance of an intense new carbonyl peak at 1700 cm^{-1}. Hydrolysis with alkaline sodium sulfite[16] and chromatography on Florisil furnished only amide **17c** and nitrile **17d**, which were prepared independently from the known carboxylic acid **17e**.[15] Evidently, the driving force of electronic delocalization in the cyclodecapentaene ring facilitates proton transfer from C_2 to nitrogen in the initial zwitterion. If **15b** is involved as an intermediate of kinetic consequence, its heterolytic ring opening at the C–N bond would generate the same dipolar species.

Electrochemical Reduction of 5. The $4n$-π-electronic nature of **5** is perhaps most clearly revealed by its ^1H NMR spectrum, which provides evidence for the presence of localized π bonds and adoption of a conformation which deviates significantly from planarity. In contrast, the dianion of **5** comprises a $(4n + 2)$-π-electron system and might consequently exhibit extended delocalization and "aromatic" character as denoted by **18**. Introduction of a pair of elec-

18

19



20

trons into the π network of **5** is expected to carry with it the requirement for attainment of a more nearly planar conformation as well. Because of the intrinsic capability of electrochemical techniques for providing diagnostic information on such questions, the polarographic reduction of **5** was examined initially. Polarographic reduction of **5** (10^{-4} M) was conducted at a dropping mercury electrode in dry,

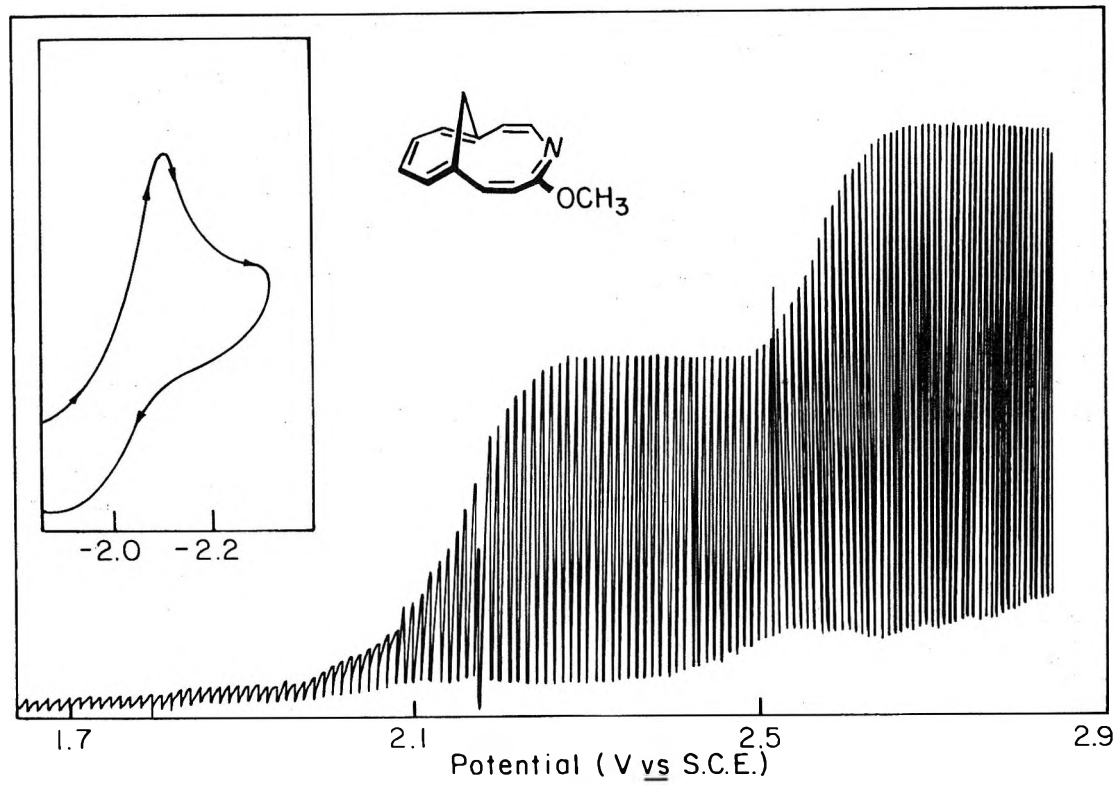


Figure 1. Polarography of 1.15×10^{-4} *M* **5** in anhydrous THF, 0.2 *M* TBAP. Inset shows cyclic voltammetry of this sample at a scan rate of 200 mV/sec.

oxygen-free tetrahydrofuran solution containing 0.2 *M* tetra-*n*-butylammonium perchlorate as background electrolyte. Two non-Nernstian waves were seen with half-wave potentials of −2.18 and −2.58 V vs. SCE (Figure 1). The respective diffusion current constants, $I = i_d/(C^\circ m^{2/3} t^{1/6})$, were measured to be 5.3 and 4.2×10^2 $\mu A m M^{-1} g^{-2/3} t^{1/2}$, indicative of greater than one-electron transfer at each step. Comparison with the *I* values measured for cyclooctatetraene and 2-methoxyazocine showed the first wave to be an overall two-electron process. The second wave is a fractional one (1–2 electrons), the source of which is believed to be one or more dihydro products which may arise by in situ Hofmann elimination involving the background electrolyte.[17]

In an effort to test this assumption, the 11,12-dihydro derivative **19** was also electrolytically reduced under identical conditions. A one-electron wave was observed at −2.50 V, the features of which compared very favorably to those seen with **5**. A postwave was also in evidence, appearing at very negative potential (−2.84 V) just prior to discharge of solvent. Addition of small quantities of **5** to the cell containing **19** did, however, not produce an additive effect on the wave attributable to initial reduction of **19**.

Introduction of water into the tetrahydrofuran solution of **5** increased the height of the two-electron wave by 10%. Significantly, the two waves did not coalesce and the half-wave potentials remained essentially invariant, indicating that radical anion $\mathbf{5}\cdot^-$ is short lived and that further reduction to **18** occurs in a fast step prior to significant protonation.[5] The net observable polarographic result is multielectron discharge, now recognized as a rather general feature of π-equivalent nitrogen-containing polyolefins.

In anhydrous acetonitrile (AN) as solvent, the reducibility of **5** was made more facile ($E_{1/2} = -1.82$ V, Table I). The overall irreversibility of the two-electron reductions in the two solvent systems was verified by cyclic voltammetry. At scan speeds up to 500 mV/sec, no anodic current appears (see, for example, inset of Figure 1) in agreement with the earlier assumption that the reactive intermediate so produced is rapidly consumed under these conditions. This behavior contrasts with the previously reported electrochemical properties of various simple 2-methoxyazocines and 6-methoxydibenz[*b,f*]azocine.[5] Should the species generated under these conditions be dianion **18**, the data require that it possess a high level of reactivity. Chemical verification of this conclusion is given below.

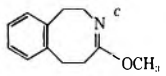
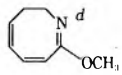
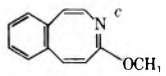
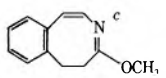
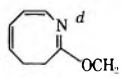
Table I
Electrochemical Data

Polyene	Solvent	$E_{1/2}$, V vs. SCE	*n* overall
Cyclooctatetraene[b]	THF	−1.96	1
		−2.16	1
	AN	−1.87	1
2-Methoxyazocine[c]	THF	−1.94	2
3,8-Dimethyl-2-methoxyazocine[c]	THF	−2.28	2
3[d]	DMF	−1.51	1
		−1.72	1
5	THF	−2.18	2
	AN	−1.82	2
19	THF	−2.50	1

[a] Derived from the relationship $n_{app} = I_{unk}(n_{COT}/I_{COT})$, except for **3**. [b] Data taken from ref 17a. [c] Data taken from ref 5b. [d] Data taken from ref 18.

Comparison of $E_{1/2}$ values indicates that **5** is reduced 0.1 V more readily than 3,8-dimethyl-2-methoxyazocine but with greater difficulty (by 0.24 V) than the parent system. The behavior of **5** contrasts expectedly with that reported recently for hydrocarbon **3**[18] which, much like cyclooctatetraene, undergoes stepwise reversible one-electron reduction, presumably via the intermediate radical anion. Unfortunately, the solvent system employed for **3** differs from those utilized in this study; a more precise comparison is thereby precluded.

Table II
Summary of ^{1}H NMR Chemical Shift Data for Certain Protons of Various Imino Ethers ($CDCl_3$ Solution, 60 MHz, δ Values)

Compd	$H_{\alpha N}$[a]	$H_{\beta N}$[a]	$H_{\alpha OCH_3}$[b]	$H_{\beta OCH_3}$[b]	Uv data
	3.60–4.00		2.53–3.30		
	3.78–4.10	2.38–2.80	5.40	6.30	λ_{max} (isooctane) 246 nm (ϵ 3860)
19	3.70–4.10	2.60–3.05	5.50	6.35	λ_{max} (C_2H_5OH) 236 nm (ϵ 20,000) and 312 (7900)
	6.67	5.87	6.02	6.82	
	6.68	5.73	2.60–3.25		
	6.36	5.10	2.56		λ_{max} (isooctane) 263 nm (ϵ 4900)
20	6.25	5.52	1.6–2.95		λ_{max} (C_2H_5OH) 237 nm (ϵ 18,000) and 325 (8640)

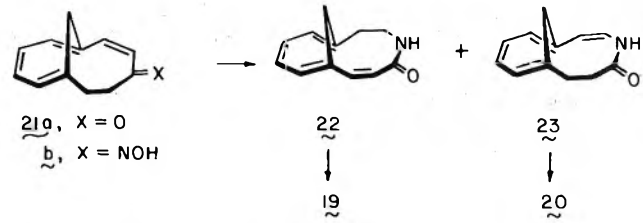
[a] The symbols αN and βN refer to those protons positioned α and β, respectively, relative to nitrogen. [b] Symbolism is used to designate those protons situated α and β to the methoxyl group. [c] Data taken from ref 3f. [d] Data taken from ref 4b.

Alkali Metal Reduction of 5. All of the chemical reductions were conducted in rigorously purified dry solvents on freshly sublimed samples of **5**. Rather unexpectedly, treatment of **5** with 2.15 g-atoms of potassium metal in ammonia–tetrahydrofuran (9:1) for 50 min at −78° returned 80% of unreacted imino ether. Extension of the reaction period to 8 hr and enhancement of the level of potassium to 8.3 g-atoms resulted in 2% recovery of **5**. In addition, a mixture of **19** (24%) and **20** (18%) was now obtained. The actual amounts of **19** and **20** varied due to the incidence of polymerization. To illustrate, when the identical reduction was performed at the reflux temperature of ammonia (−33°) for 30 min (2.7–3.2 g-atomic equiv of potassium), there could be isolated only 8–10% of **20**. Under these conditions, a rapid color change from red-orange to dull brown was evident and deposition of polymer began to occur after 20 min. Quenching of these solutions with a proton source produced no color change.

In the most favorable circumstances, a rather large excess of potassium (ca. 9 equiv) and rather long reaction times (9–10 hr) at −78° were required. To minimize possible decomposition during work-up, ice water and ether were simultaneously introduced, and organic layer was separated, and the product was subjected directly to silica gel chromatography.

Structures **19** and **20** were deduced from their respective uv and ^{1}H NMR features as gauged by comparison with spectra of known compounds (Table II). Both dihydro derivatives show a characteristic pair of doublets in the vinyl region; for **19**, the mutual splitting of these signals (due to H_3 and H_4) is 13 Hz, while that for **20** (attributable to H_{11}, H_{12}) is of diminished magnitude (10 Hz). The latter value seemingly is typical for the –CH=CHN=C(OCH$_3$)– unit.[3,4]

As further proof, **19** and **20** were independently synthesized from bicyclo[5.4.1]dodeca-2,7,9,11-tetraen-4-one (**21a**) by Beckmann rearrangement of its oxime (**21b**) through use of tosyl chloride in pyridine. Under these conditions, the dihydro lactams **22** and **23** were produced in a



5:1 ratio, a result anticipated from the recognized greater migratory aptitude of the trigonal carbon in related α,β-unsaturated oximes.[19] Subsequent to their chromatographic separation, these lactams were individually treated with trimethyloxonium fluoroborate to give **19** and **20**, respectively. The identity of these imino ethers with those isolated previously served specifically to remove from consideration other possible isomers in which the integrity of the bridged cycloheptatriene ring had been destroyed by protonation.

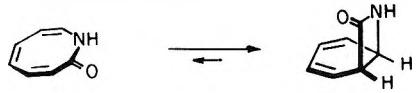
All attempts to generate dianion **18** for the purpose of spectroscopic detection met with serious difficulties because of rapid decomposition or polymerization. Thus, exposure of **5** to 2 equiv of potassium in ND_3 at −78° in an NMR tube on a vacuum line[20] resulted in formation of a deep red color just prior to becoming black. Only broad ^{1}H NMR signals were seen during and after this color change. When a solution of **5** (1.5–50 mg) in THF-d_8 contained in an NMR tube under nitrogen was brought into contact with a potassium mirror at −78°, gradual decomposition set in. No meaningful new peaks were seen to develop. Experiments with low concentrations of **5** were made with pulse Fourier transform techniques, but no spectral evidence for **18** could be secured.

The factors preventing observation of **18** are not yet known.[21] If this result is due to the inherent instability of **18**, the lack of aromatic character would contrast noticeably with the properties of azocinyl dianions[3,22] and the dianions of **3** and 1,7-methano[12]annulene,[18] which show diamagnetic ring currents.

Discussion

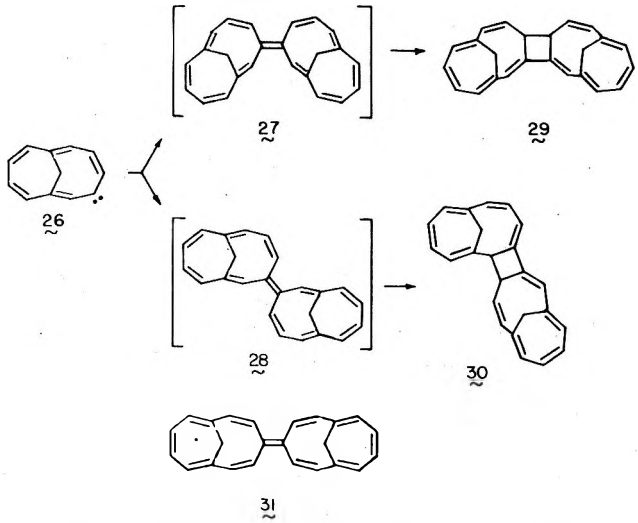
The identification of hydrocarbon **3** and its π-equivalent heterocyclic congener **5** as bridged [12]annulenes devoid of an observable capability for π bond shift isomerization points up the greater thermodynamic stability of those valence isomers which contain a bridged cycloheptatriene unit. Although it has been justifiably argued that the absence of the 1,6-dimethylenecyclohepta-2,4-diene form **4** is due to its greater strain,[6] we are currently of the opinion that this energetic discrepancy arises in part from electronic considerations as well.

The thermodynamic relationship between the dihydroazocinone **24** and its β-lactam valence isomer **25** is recognized to be weighted heavily (97.6%) in favor of **25** at 60°.[3e]



24 25

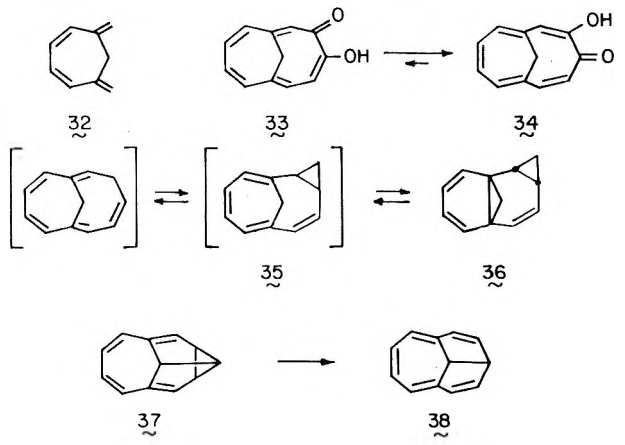
The amide function clearly plays a very different role than an imino ether moiety, since in the latter event the medium ring structure (e.g., **1**) is overwhelmingly adopted. Speculation has centered upon the improved electrostatic and π conjugative situation in **25** as the source of its lower free energy.[3e] On this basis, the rapid disrotatory closure of **14** to **13** is fully expected, although the apparent irreversibility of this change is somewhat surprising at first glance. In these terms, the reluctance of **8** to undergo intramolecular cyclization with formation of β-lactam **9** is still more anomalous, at least until an added structural feature is recognized. Should the instability of the yet elusive lactams **9** and **14** be further increased because of the necessity to incorporate a 1,6-dimethylenecyclohepa-2,4-diene unit, then the added disparity in ground-state energy would demonstrate itself in the manner observed experimentally. Valence isomerization *away from* such bridged annulenes seems to be an entirely general phenomenon. For example, the dimeric [11]annulenes **27** and **28** believed to arise from dimerization of carbene **26** undergo irreversible electrocyclic ring closure to give divinylcyclobutanes **29** and **30.**



26 27 28 29 30 31

Jones has attributed this propensity for cyclization to "a gain in homoaromaticity".[23] In contrast, fulvalene **31** resulting from the dimerization of 4,9-methano[11]annulenylidene is entirely stable,[24] no bond shift isomerization being required to avoid 1,6-dimethylenecycloheptadiene part structures in this instance.

Despite the independent existence of parent hydrocarbon **32**,[25] the instability which this tetraene unit brings to bridged annulenes is reflected further in the dominance of **34** over **33** (spectroscopically nondetectable),[26] a simple prototropic shift otherwise separating these 10-π-electron tropolone analogs, and the preference of **35** to exist in tetracyclic form **36** which contains, inter alia, two cyclopropane rings.[9,27] This latter phenomenon may be compared



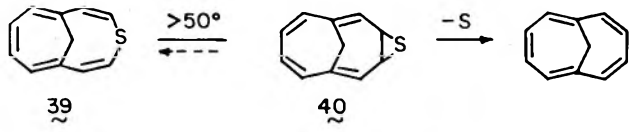
32 33 34

35 36

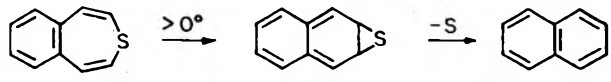
37 38

with recent work showing that pentaene **38** far outweighs tautomer **37** in thermodynamic stability.[28,29]

A like assessment of the π-electronic structure of bridged heteroannulenes such as **39** has shown tricyclic valence tautomer **40** to be destabilized to an extent which renders negligible the equilibrium concentration of the latter.[30] That a small equilibrium concentration of **40** is attainable is suggested by the demonstrated propensity of the system to extrude sulfur above 50°. It is noteworthy, however, that 4,5-benzothiepin (**41**) loses sulfur at approximately 0°.[26a] Thus, even though the latter compound must become o-quinonoid with loss of benzenoid character (cf. **42**), its reactivity exceeds that of **39**, which likely undergoes such cheletropic transformation via **40.**



39 40



41 42

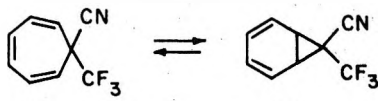
As an extension of this analysis, we would predict that the unknown heteroannulene class **43** will exhibit equilibrium tendencies heavily in favor of tricyclic structure **44.** The

43 44

close relationship of **44** to β-lactam **13** requires no further comment.

In our assessment, the remarkable thermodynamic stability of bridged cycloheptatriene structures relative to their 1,6-dimethylenecycloheptadiene counterparts is ascribable to some degree to strain effects and in part to electronic influences. The implication which the latter consid-

eration carries is that the cycloheptatriene ring is capable to some degree of homoaromatic interaction (the more planar the more so). Since neutral homoaromaticity[28] is involved, the effect cannot realistically be as pronounced as it is in an ionic species,[31] e.g., the homotropylium ion, where minimization of charge concentration further enhances (markedly) electronic delocalization. Admittedly, the effect must be a more delicate one. Although a detailed discussion of this point is deferred to a later paper, the **45** ⇄ **46** equilibrium serves to illustrate the relevant issue. Discov-



45 **46**

ery of the existence of **45** and **46** as separate structural entities was construed to mean that there could be no energy minimum between these valence tautomers.[32] The homobenzene possibility was thereby considered eliminated. However, it does not seem to have been considered that either (or both) structure could be stabilized by homoaromatic interaction in its own right.

Experimental Section

Melting points are corrected and boiling points are uncorrected. Proton magnetic resonance spectra were obtained on Varian A-60A, Varian HA-100, and Jeolco MH-100 spectrometers; apparent splittings are given in all cases. Infrared spectra were determined on a Perkin-Elmer Model 137 instrument. Mass spectra were recorded on an AEI-MS9 spectrometer at an ionization potential of 70 eV. Elemental analyses were performed by the Scandinavian Microanalytical Laboratory, Herlev, Denmark. Preparative VPC work was done on a Varian Aerograph A90-P3 instrument equipped with a thermal conductivity detector.

4,9-Methano[11]annulenone Oxime (7). A solution of 510 mg (3.0 mmol) of 4,9-methano[11]annulenone[8] and 315 mg (4.5 mmol) of hydroxylamine hydrochloride in a 1:1 mixture of pyridine and ethanol (6 ml) was refluxed for 3 hr under nitrogen. The cooled reaction mixture was partitioned between water (100 ml) and methylene chloride (100 ml) and the organic phase was separated, dried, and concentrated. The residue was recrystallized from ethanol (8 ml) to give 420 mg (77%) of **7**, mp 190–193° (lit.[8] mp 197–198°). This material was used without further purification.

1-Aza-1,2-dihydro-5,10-methano[12]annulen-2-one (8). A solution of **7** (0.50 g, 2.7 mmol) and tosyl chloride (1.0 g, 5.3 mmol) in 20 ml of pyridine was stirred at 0° for 30 min and at room temperature for 3 hr. The deep orange solution soon became black in color. The dark reaction mixture was diluted with methylene chloride and water and the organic phase was washed with saturated sodium bicarbonate solution and water. This solution was dried and evaporated to afford a black solid, chromatography of which on silica gel (elution with 10% ether–benzene) furnished a yellow solid. Recrystallization from methylene chloride–hexane gave 350 mg (70%) of **8**: mp 148–149°; ν_{max} ($CHCl_3$) 3300, 2920, and 1675 cm^{-1}; λ_{max} (C_2H_5OH) 257 nm (ϵ 40,000); δ_{TMS} ($CDCl_3$) 5.8–7.0 (m, 9, olefinic and >NH), 3.1 (br d, J = 14 Hz, bridgehead proton), and 2.1 (br d, J = 14 Hz, bridgehead proton).

Anal. Calcd for $C_{12}H_{11}NO$: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.73; H, 5.97; N, 7.49.

1-Aza-2-methoxy-5,10-methano[12]annulene (5). Procedure A. A solution of lactam **8** (370 mg, 2.0 mmol) and trimethyloxonium fluoroborate (326 mg, 2.2 mmol) in 10 ml of methylene chloride was stirred under nitrogen for 5.5 hr. The solution was neutralized with sodium bicarbonate (400 mg) in 10 ml of water. The mixture was partitioned between methylene chloride and water and the organic phase was dried and evaporated to produce a red-orange solid. Purification by silica gel chromatography (elution with 50% hexane–benzene) gave 270 mg (68%) of pure orange crystals: mp 68–70°; ν_{max} ($CHCl_3$) 3003, 1675, 1600, 1432, 1400, and 1210 cm^{-1}; δ_{TMS} ($CDCl_3$) 5.85–6.55 (m, 7, olefinic), 5.34 (d, J = 12 Hz, bridgehead proton), 5.08 (d, J = 10 Hz, H_{11}), 3.76 (s, methoxyl), and 1.64 (d, J = 12 Hz, bridgehead proton). Double irradiation at δ 1.64 caused the signal at δ 5.34 to collapse to a singlet.

Anal. Calcd for $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.34; H, 6.64; N, 6.84.

Procedure B. A solution of oxime **7** (100 mg, 0.54 mmol) and tosyl chloride (200 mg, 1.05 mmol) in 3 ml of pyridine was stirred under nitrogen for 15 min at 0° and then for 3.5 hr at 25°. Methanol (4 ml) was added and the resulting black solution was kept at room temperature for 30 min. Water (100 ml) and methylene chloride (100 ml) were added and the organic phase was worked up as before to give 98 mg (90%) of **5** after sublimation.

3,8-Methano[11]annulenone Oxime (12). A solution of 3,8-methano[11]annulenone[9] (380 mg, 2.2 mmol) and hydroxylamine hydrochloride (184 mg, 2.6 mmol) in 1:1 pyridine–ethanol (4 ml) was stirred at room temperature for 48 hr under nitrogen. Work-up in the predescribed manner left a red oil. Chromatography on silica gel (elution with 10% ethyl acetate in methylene chloride) and recrystallization from pentane afforded 150 mg (30%) of **12** as a red solid: mp 148–149°; ν_{max} (neat) (on oily mixture of isomers) 3200, 1620, and 1595 cm^{-1}; δ_{TMS} ($CDCl_3$) 7.0 (br s, –OH), 5.76–6.68 (m, 8, olefinic), 3.97 (d, J = 12 Hz, bridgehead proton), and 2.86 (d, J = 12 Hz, bridgehead proton); calcd m/e 185.0840, found 185.0843.

Anal. Calcd for $C_{12}H_{11}NO$: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.72; H, 6.17; N, 7.27.

Ring Expansion of 12. A solution of oxime **12** (84 mg, 0.45 mmol) in 2 ml of pyridine cooled to 0° was treated with tosyl chloride (95 mg, 0.50 mmol) and stirred for 55 min under nitrogen. The reaction mixture was poured into methylene chloride and water and the aqueous layer was extracted twice with additional CH_2Cl_2. The combined organic phases were dried, evaporated, and removed of residual pyridine at 0.05 mm. When free of pyridine, the oxime tosylate is stable for several days in a freezer.

The unpurified tosylate (170 mg) was dissolved in a mixture of dioxane (3 ml), water (3 ml), and 2,6-lutidine (100 mg) and stirred under nitrogen at room temperature for 3 hr. Work-up as predescribed gave crude product which was purified by silica gel chromatography (elution with 50% ether–pentane). There was obtained 60 mg of β-lactam **13** which after recrystallization from ether–pentane had mp 124–126° (47 mg, 55%); ν_{max} ($CHCl_3$) 3418 and 1764 cm^{-1}; λ_{max} (C_2H_5OH) 226 nm (ϵ 31,000) and 284 (4480); for ^1H NMR data see text.

Anal. Calcd for $C_{12}H_{11}NO$: C, 77.81; H, 5.99. Found: C, 77.36; H, 6.10.

Chlorosulfonyl Isocyanate Addition to 1,6-Methano[10]annulene. A stirred solution of the annulene (1.03 g, 7.3 mmol) in 15 ml of dry methylene chloride cooled to −78° was treated under nitrogen with freshly distilled chlorosulfonyl isocyanate (1.00 g, 7.1 mmol). After 3 hr, infrared analysis indicated the presence of a weak carbonyl bond at 1850 cm^{-1}. The temperature was increased to 0° and after 7 hr an intense new carbonyl band appeared at 1700 cm^{-1} with disappearance of the peak at 1805 cm^{-1}. After an additional 12 hr at room temperature, the CSI was completely reacted. Solvent was removed in vacuo and the residue was dissolved in ether and added dropwise with stirring to a mixture of 25% sodium sulfite solution (10 ml) and ether (5 ml) cooled to 0°. Potassium hydroxide solution (10%) was added intermittently to maintain a pH of 7–8. After 15 min at room temperature the layers were separated and the aqueous layer reextracted with CH_2Cl_2 (3 × 20 ml). The dried and concentrated organic extracts were chromatographed on Florisil (pentane elution) to give a small amount of unreacted annulene. A solvent polarity increase to 10% ether in pentane afforded 130 mg (11%) of nitrile **17d** while elution with ethyl acetate led to isolation of amide **17c** (40 mg, 3%).

The nitrile was further purified by preparative vpc on a 5% SF-96 column at 165°: ν_{max} (neat) 3050, 2960, 2203, 1450, 1350, 1250, 1100, and 770 cm^{-1}; δ_{TMS} ($CDCl_3$) 7.0–7.8 (m, 7, olefinic) and −0.4 (AB pattern, J = 10 Hz, 2, bridgehead protons).

Anal. Calcd for $C_{12}H_9N$: C, 86.20; H, 5.43. Found: C, 85.96; H, 5.48.

Amide **17c** was purified either by sublimation (90°, 0.05 mm) or recrystallization from ether or methylene chloride–pentane: mp 108–109°; ν_{max} (KBr) 3340, 3160, 1640, and 1610 cm^{-1}; δ_{TMS} ($CDCl_3$) 7.85 (m, 1, proton α to carbonyl), 6.9–7.7 (m, 6), 6.38 (br s, 2, $-CONH_2$), and −0.41 (br s, 2, bridgehead); calcd m/e 185.0840, found 185.0843.

Anal. Calcd for $C_{12}H_{11}NO$: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.35; H, 5.82; N, 7.49.

1,6-Methano[10]annulene-2-carboxamide (17c). A mixture of 1,6-methano[10]annulene-2-carboxylic acid (**17e**, 200 mg, 1.1 mmol), thionyl chloride (250 mg, 2.12 mmol), and benzene (10 ml) was refluxed under nitrogen for 3.5 hr. The benzene was removed in vacuo and the residue dissolved in methylene chloride was

added dropwise at −78° to dry liquid ammonia. After 3 hr, this mixture was poured onto ice and methylene chloride. The aqueous layer was extracted with methylene chloride and the combined organic phases were washed with 10% potassium hydroxide solution and water, dried, and evaporated. The yellow solid (200 mg, 100%) was recrystallized from methylene chloride–pentane to give 90 mg of **17c**, mp 107–109°, which proved to be identical by ir, ^{1}H NMR, and mixture melting point with the sample isolated above.

2-Cyano-1,6-methano[10]annulene (17d). A room-temperature solution of **17c** (94 mg, 0.51 mmol), 2,6-lutidine (200 mg, 1.9 mmol), and benzene (10 ml) was treated with thionyl chloride (180 mg, 1.5 mmol) and an immediate precipitate was observed. After 5 hr at reflux, the mixture was partitioned between water and methylene chloride. The aqueous phase was reextracted with CH_2Cl_2 (2 × 25 ml) and the combined organic layers were washed with saturated sodium bicarbonate solution and water, dried, and evaporated. The resulting red oil (100 mg) was chromatographed on Florisil (25 g) to give upon elution with 50% chloroform–pentane 48 mg (57%) of nitrile, identical in all respects with the sample isolated above.

Electrochemical Measurements. Chemicals. The tetrahydrofuran was prepared by predrying over calcium hydride and storing in vacuo over sodium–potassium alloy. The supporting electrolyte, tetra-*n*-butylammonium perchlorate (TBAP, Southwestern Analytical, Austin, Tex.), was dried by heating in vacuo at 90°. Acetonitrile was purified by distillation from phosphorus pentoxide and storage over calcium hydride.

Apparatus. The electrochemical instrumentation, cells, and procedures for achieving measurements under rigorously aprotic conditions have been previously described.[33] All measurements were made at ambient laboratory temperature, 23 ± 1°. Potentials were measured against a silver wire/0.1 *M* Ag^+ (THF) reference electrode, but are reported herein vs. the aqueous saturated calomel electrode and are not corrected for *iR* drop. The Ag/Ag^+ (0.1 *M*) reference electrode was measured to be +0.49 vs. SCE. From previous work,[5] the *iR* drop is estimated to be between 1 and 5 mV for the concentrations employed herein; the effect on the potentials is considered to be negligible.

Alkali Metal Reduction of 5. Into a dry 100-ml three-necked flask which had been fitted with a gas inlet tube, a Dry Ice condenser, a rubber septum, and a glass-encased magnetic stirring bar was placed a solution of **5** (208 mg, 1.04 mmol) in 6 ml of anhydrous tetrahydrofuran (freshly distilled from $LiAlH_4$). Liquid ammonia (55 ml) was distilled from sodium metal directly into this flask cooled to −78°. With stirring, there was introduced under a dry oxygen-free atmosphere 350 mg (9.0 mg-atoms) of potassium metal (as fine chips) during 10 min. The blue-green solution was stirred at −78° for 8 hr, whereupon 3 ml of methanol was introduced and the contents allowed to warm to room temperature. After 1 hr most of the ammonia had evaporated and the green residue was taken up in water (200 ml) and ether (3 × 100 ml). The combined organic layers were washed with water, dried, and concentrated to leave a green oil. Chromatography on silica gel (elution with 50% benzene–hexane) returned 3 mg (1.7%) of **5** and gave 50 mg (24%) of **19** and 37 mg (18%) of **20**.

In an alternative work-up procedure, the reaction mixture was quenched with methanol (2 ml) and ammonium chloride (amount equivalent to K used) at −78° followed by rapid pouring into ice water (200 ml) and ether (150 ml), immediate work-up, and chromatography.

For **19:** ν_{max} (neat) 2930, 1665, 1610, and 1210 cm^{-1}; δ_{TMS} ($CDCl_3$) 5.9–6.7 (m, 4, H_6–H_9), 6.35 and 5.50 (AB, J = 13 Hz, 2, $H_{3,4}$), 3.70–4.10 (m, 1, H_{12}), 2.60–3.05 (m, 3, H_{11} and H_{12}), 3.76 (s, 3, methoxyl), 3.24 (d with additional fine splitting, 1, H_{13a} or H_{13b}), and 1.10 (d with additional fine splitting, 1, H_{13a} or H_{13b}).

The perchlorate salt was obtained as yellow crystals, mp 194–195° (from methylene chloride–ether).

Anal. Calcd for $C_{13}H_{16}ClNO_5$: C, 51.75; H, 5.35; N, 4.64. Found: C, 52.09; H, 5.61; N, 4.46.

For **20:** ν_{max} (neat) 3010, 2950, 2860, 1670, and 1600 cm^{-1}; δ_{TMS} ($CDCl_3$) 6.0–6.7 (m, 4, H_6–H_9), 6.25 and 5.52 (AB, J = 10 Hz, 2, H_{11}, H_{12}), 3.74 (s, 3, methoxyl), 2.98 (d with additional fine coupling, J = 12 Hz, 1, H_{13a} or H_{13b}), 1.6–2.95 (m, 4, H_3, H_4), and 0.95 (d, J = 12 Hz, 1, H_{13a} or H_{13b}). Calcd for $C_{13}H_{15}NO$: *m/e* 201.1153. Found: 201.1157.

The perchlorate salt of **20** was found to decompose upon standing at room temperature.

Bicyclo[5.4.1]dodeca-2,7,9,11-tetraen-4-one Oxime (21b). A solution of ketone **21a**[9] (100 mg, 0.58 mmol) and hydroxylamine hydrochloride (70 mg, 1 mmol) in 1 ml of pyridine and 1 ml of ethanol was refluxed under nitrogen for 4 hr. Work-up in the predescribed manner left a yellow oil which was crystallized from chloroform–hexane and sublimed (100°, 0.05 mm) to give 100 mg (90%) of **21b**: mp 104–106°; ν_{max} (KBr) 3100, 1620, 1590, 1440, and 1000 cm^{-1}. Calcd for $C_{12}H_{13}NO$: *m/e* 187.0997. Found: 187.0998.

Beckmann Rearrangement of 21b. A solution of **21b** (390 mg, 2.1 mmol) in 6 ml of pyridine cooled to 0° was treated with tosyl chloride (450 mg, 2.4 mmol) and allowed to stir for 20 min at 0° and 2.5 hr at 25° before pouring into water (300 ml) and methylene chloride (4 × 100 ml). From the processed organic layers there was isolated a brown solid which was dissolved in aqueous dioxane (1:1, 18 ml) containing 300 mg of 2,6-lutidine. After 15 hr at the reflux temperature, the solution was diluted with water (200 ml) and extracted with methylene chloride (4 × 75 ml). The yellow solid (230 mg) so obtained was chromatographed on silica gel (ether elution) and furnished 30 mg of crude lactam **23** and 120 mg of isomeric lactam **22**.

Pure **22** (95 mg, 25%) was obtained by sublimation at 110–115° (0.05 mm) and recrystallization from ether–pentane: mp 147–148°; ν_{max} ($CHCl_3$) 3420, 3400, 2950, 1660, and 1640 cm^{-1}; δ_{TMS} ($CDCl_3$) 5.5–7.3 (m, 7, olefinic and >NH), 3.60 (d with additional fine splitting, J = 12.5 Hz, bridgehead), 2.2–4.3 (m, 4, methylenes), and 2.05 (d with fine splitting, J = 12.5 Hz, bridgehead); calcd *m/e* 187.0997, found 187.1000.

Anal. Calcd for $C_{12}H_{13}NO$: C, 76.97; H, 7.00; N, 7.48. Found: C, 76.59; H, 7.02; N, 7.15.

Pure **23** (22 mg, 5%) was obtained by sublimation at 100–110° (0.05 mm) followed by recrystallization from ether–pentane: mp 143–144°; ν_{max} ($CHCl_3$) 3380, 1660, and 1625 cm^{-1}; δ_{TMS} ($CDCl_3$) 6.44–6.70 (m, 2, olefinic), 5.95–6.36 (br m, 2, olefinic), 5.83 (br s, 2, olefinic), 3.12 (br d, J = 13 Hz, 1, bridgehead), and 1.6–3.0 (m, 5, bridgehead and methylenes); calcd *m/e* 187.0997, found 187.0998.

Anal. Calcd for $C_{12}H_{13}NO$: C, 76.97; H, 7.00; N, 7.48. Found: C, 76.81; H, 7.00; N, 7.44.

4-Aza-5-methoxybicyclo[6.4.1]trideca-4,6,8,10,12-pentaene (19). A solution of **22** (36 mg, 0.20 mmol) and triethyloxonium fluoroborate (46 mg, 0.30 mmol) in 2 ml of methylene chloride was stirred under nitrogen for 20 hr at room temperature. A solution of sodium bicarbonate (50 mg) in water (2 ml) was added and the mixture was partitioned between methylene chloride and water. The organic phase was washed with water, dried, and concentrated to produce **19** (40 mg, 99%) as a yellow oil which was homogeneous to vpc (6 ft × 0.25 in. 5% SE-30) and spectroscopically identical with the material isolated above.

4-Aza-5-methoxybicyclo[6.4.1]trideca-2,4,8,10,12-pentaene (20). Reaction of 22 mg (0.12 mmol) of **23** with 35.5 mg (0.24 mmol) of trimethyloxonium fluoroborate in 1.5 ml of methylene chloride as before gave 20 mg (90%) of **20**, the spectra of which were superimposable upon those of the imino ether obtained earlier.

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Registry No.—**5**, 54004-04-5; **7**, 30234-91-4; **8**, 54004-05-6; (*E*)-**12**, 54004-06-7; (*Z*)-**12**, 54004-07-8; **13**, 54004-08-9; **17a**, 2443-46-1; **17c**, 54004-09-0; **17d**, 54004-10-3; **17e**, 5873-56-3; **19**, 54004-11-4; **19** perchlorate, 54004-12-5; **20**, 54004-13-6; **20** perchlorate, 54004-14-7; **21a**, 54004-15-8; **21b**, 54004-16-9; **22**, 54004-17-0; **23**, 54004-18-1; 4,9-methano[11]annulenone, 30234-90-3; hydroxylamine hydrochloride, 5470-11-1; tosyl chloride, 98-59-9; trimethyloxonium fluoroborate, 420-37-1; 3,8-methano[11]annulenone, 40563-46-0; chlorosulfonyl isocyanate, 1189-71-5; potassium, 7440-09-7.

References and Notes

(1) Unsaturated Heterocyclic Systems. XCII. For the previous paper in this series, see L. A. Paquette, M. J. Broadhurst, C. Lee, and J. Clardy, *J. Am. Chem. Soc.*, **95**, 4647 (1973).
(2) Review: L. A. Paquette, *Angew. Chem.*, **83**, 11 (1971); *Angew. Chem., Int. Ed. Engl.*, **10**, 11 (1971).
(3) (a) L. A. Paquette and T. Kakihana, *J. Am. Chem. Soc.*, **90**, 3897 (1968); (b) L. A. Paquette and J. C. Philips, ibid., **90**, 3898 (1968); (c) L. A. Paquette, T. Kakihana, J. F. Kelly, and J. R. Malpass, *Tetrahedron Lett.*, 1455 (1969); (d) L. A. Paquette, T. Kakihana, J. F. Hansen, and J. C. Philips, *J. Am. Chem. Soc.*, **93**, 152 (1971); (e) L. A. Paquette, T. Ka-

kihana, and J. F. Kelly, *J. Org. Chem.*, **36**, 435 (1971); (f) L. A. Paquette, L. B. Anderson, J. F. Hansen, S. A. Lang, Jr., and H. Berk, *J. Am. Chem. Soc.*, **94**, 4907 (1972); (g) D. W. McNeil, M. E. Kent, E. Hedaya, P. F. D'Angelo, and P. O. Schissel, ibid., **93**, 3817 (1971).
(4) (a) L. A. Paquette, T. Kakihana, and J. F. Hansen, *Tetrahedron Lett.*, 529 (1970); (b) L. A. Paquette, J. F. Hansen, and T. Kakihana, *J. Am. Chem. Soc.*, **93**, 168 (1971); (c) L. A. Paquette and T. Kakihana, ibid., **93**, 174 (1971).
(5) (a) L. A. Paquette, J. F. Hansen, T. Kakihana, and L. B. Anderson, *Tetrahedron Lett.*, 533 (1970); (b) L. B. Anderson, J. F. Hansen, T. Kakihana, and L. A. Paquette, *J. Am. Chem. Soc.*, **93**, 161 (1971).
(6) E. Vogel, M. Mann, Y. Sakata, K. Müllen, and J. F. M. Oth, *Angew. Chem.*, **86**, 231 (1974); *Angew. Chem., Int. Ed. Engl.*, **13**, 283 (1974).
(7) The prevailing state of affairs in methoxyazabullvalene serves as a useful analogy: L. A. Paquette and T. J. Barton, *J. Am. Chem. Soc.*, **89**, 5480 (1967); L. A. Paquette, T. J. Barton, and E. B. Whipple, ibid., **89**, 5481 (1967); L. A. Paquette and G. R. Krow, ibid., **90**, 7149 (1968); L. A. Paquette and J. R. Malpass, ibid., **90**, 7151 (1968); L. A. Paquette, J. R. Malpass, G. R. Krow, and T. J. Barton, ibid., **91**, 5296 (1969); L. A. Paquette, G. R. Krow, and J. R. Malpass, ibid., **91**, 5522 (1969).
(8) W. Grimme, J. Reisdorff, W. Jünemann, and E. Vogel, *J. Am. Chem. Soc.*, **92**, 6335 (1970).
(9) E. Vogel, *Proc. XXIIIrd Int. Congr. Pure Appl. Chem.*, **1**, 275 (1971), and private communication.
(10) W. E. Volz, unpublished observations. For the response of β-lactams to thermal activation, see L. A. Paquette, M. J. Wyvratt, and G. R. Allen, Jr., *J. Am. Chem. Soc.*, **92**, 1763 (1970).
(11) R. E. Rondeau and R. E. Sievers, *J. Am. Chem. Soc.*, **93**, 1522 (1971).
(12) P. V. Demarco, T. K. Elzey, R. B. Lewis, and E. Wenkert, *J. Am. Chem. Soc.*, **92**, 5734 (1970).
(13) G. Pifferi, P. Consonni, G. Pelizza, and E. Testa, *J. Heterocycl. Chem.*, **4**, 619 (1967); D. Bormann, *Justus Liebigs Ann. Chem.*, **725**, 124 (1969).
(14) M. G. Ahmed, R. W. Alder, G. H. James, M. C. Sinnott, and M. C. Whiting, *Chem. Commun.*, 1533 (1968); R. W. Alder, *Chem. Ind. (London)*, 983 (1973).
(15) E. Vogel and W. A. Böll, *Angew. Chem.*, **76**, 784 (1964); *Angew. Chem., Int. Ed. Engl.*, **3**, 642 (1964); E. Vogel, *Chem. Soc., Spec. Publ.*, **No. 21**, 123–126 (1967).
(16) T. Durst and M. J. O'Sullivan, *J. Org. Chem.*, **35**, 2043 (1970).
(17) (a) D. R. Thielen and L. B. Anderson, *J. Am. Chem. Soc.*, **94**, 2521 (1972); (b) A. J. Fry and M. A. Mitnick, ibid., **91**, 6207 (1969); (c) A. J. Fry and R. G. Reed, ibid., **91**, 6448 (1969).
(18) J. F. M. Oth, K. Müllen, H. Königshofen, M. Mann, Y. Sakata, and E. Vogel, *Angew. Chem., Int. Ed. Engl.*, **13**, 284 (1974); *Angew. Chem.*, **86**, 232 (1974).
(19) (a) C. W. Shoppee and G. Krüger, *J. Chem. Soc.*, 3641 (1961); C. W. Shoppee, G. Krüger, and R. N. Mirrington, ibid., 1050 (1962); C. W. Shoppee, R. Lack, R. N. Mirrington, and L. R. Smith, ibid., 5868 (1965); F. Kohen, *Chem. Ind. (London)*, 1378 (1966); M. Kroner, *Chem. Ber.*, **100**, 3162 (1967); M. S. Ahmad and A. H. Siddiqui, *Aust. J. Chem.*, **21**, 1371 (1968); T. Sato, H. WaKatsuka, and K. Amano, *Tetrahedron*, **27**, 5381 (1971); Y. Tamura et al., *Chem. Pharm. Bull.*, **19**, 529 (1971); P. Catsoulacos, *Chim. Chronika*, **1**, 147 (1972); I. Fleming and R. B. Woodward, *J. Chem. Soc., Perkin Trans. 1*, 1653 (1973); Y. Tamura, H. Fujiwara, K. Sumoto, M. Ikeda, and Y. Kita, *Synthesis*, 215 (1973). (b) See also F. J. Donet and A. J. Nelson, *J. Org. Chem.*, **22**, 1107 (1957); R. H. Mazur, ibid., **26**, 1289 (1961).
(20) L. A. Paquette, S. V. Ley, R. H. Meisinger, R. K. Russell, and M. Oku, *J. Am. Chem. Soc.*, **96**, 5806 (1974); S. V. Ley and L. A. Paquette, ibid., **96**, 6670 (1974).
(21) Quenching experiments involving the use of CH_3OD were expectedly not revealing because of rapid D–H exchange with NH_3 solvent prior to proton (deuteron) transfer to the reduced species. Levels of deuterium incorporation as high as 20% were observed in **19** and **20**.
(22) G. Ewing, unpublished observations.
(23) P. H. Gebert, R. W. King, R. A. LaBar, and W. M. Jones, *J. Am. Chem. Soc.*, **95**, 2357 (1973).
(24) R. A. LaBar and W. M. Jones, *J. Am. Chem. Soc.*, **95**, 2359 (1973).
(25) G. C. Farrant and R. Feldmann, *Tetrahedron Lett.*, 4979 (1970).
(26) J. Reisdorf and E. Vogel, *Angew. Chem.*, **84**, 208 (1972); *Angew. Chem., Int. Ed. Engl.*, **11**, 218 (1972).
(27) E. Vogel, R. Feldmann, and H. Düwel, *Tetrahedron Lett.*, 1941 (1970).
(28) L. A. Paquette, R. E. Wingard, Jr., and R. K. Russell, *J. Am. Chem. Soc.*, **94**, 4739 (1972).
(29) E. Vogel, U. H. Brinker, K. Nachtkamp, J. Wassen, and K. Müllen, *Angew. Chem.*, **85**, 760 (1973); *Angew. Chem., Int. Ed. Engl.*, **12**, 758 (1973).
(30) E. Vogel, R. Feldmann, H. Düwel, H.-D. Cremer, and H. Günther, *Angew. Chem.*, **84**, 207 (1972); *Angew. Chem., Int. Ed. Engl.*, **11**, 217 (1972).
(31) Others seem to be of the opinion that the level of homoaromaticity in charged and uncharged systems should be equally pronounced.[29] It should be clear that neutral homoaromatic structures will partake of less delocalization in their ground states with the obvious result that the prevailing stabilizing contributions will be more difficultly detectable by the usual spectroscopic methods. Direct spectral comparison of neutral homoaromatic with Hückel-type aromatic systems is consequently not conveniently workable because of the large numerical gap separating the delocalization energies in these two classes of compounds.
(32) E. Ciganek, *J. Am. Chem. Soc.*, **87**, 1149 (1965).
(33) J. Mills, R. Nelson, S. Shore, and L. B. Anderson, *Anal. Chem.*, **43**, 157 (1971).

Synthesis and Photolysis of 2-Acylpyrazolidin-3-ones. A Model for the Photochemical Syntheses of 6-Azapenicillin Isomers[1]

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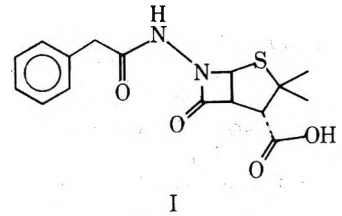
A series of 2-acyl-5,5-dimethylpyrazolidin-3-ones (**5a–e**) was prepared by two routes and shown to rearrange photochemically under a variety of conditions to *N*-acylamino-4,4-dimethylazetidin-2-ones (**9a–e**). Photolysis of the parent systems, 5,5-dimethylpyrazolidin-3-one (**1**), to give 1-amino-4,4-dimethylazetidin-2-one (**20**), which was acylated to give **9a**, is also discussed. A plausible reaction scheme is presented to account for the observed photochemistry.

Strong interest in the synthesis of β-lactam (azetidin-2-one) containing molecules,[2] particularly those of the penicillin and cephalosporin classes of antibiotics,[3] has continued unabated since the original discovery and structure determination of penicillin.[4] Although a large number of original syntheses of β-lactams have been reported since that period, very few of these approaches have employed either thermal[5] or photochemical[6] ring contraction steps. As a part of our approach to the synthesis of penicillin isomers containing nitrogen in the 6 position (such as I), we hope to use a photochemically induced ring contraction reaction to generate the β-lactam moiety. As a model system for such a step we have investigated the photochemistry of a series of 2-acyl-5,5-dimethylpyrazolidin-3-ones, one of which contains the side chain of penicillin G.[7] We report at this time some interesting aspects of the syntheses of these 2-acylpyrazolidin-3-ones[8] and our studies on their photochemical rearrangements to give *N*-acylamino β-lactams.



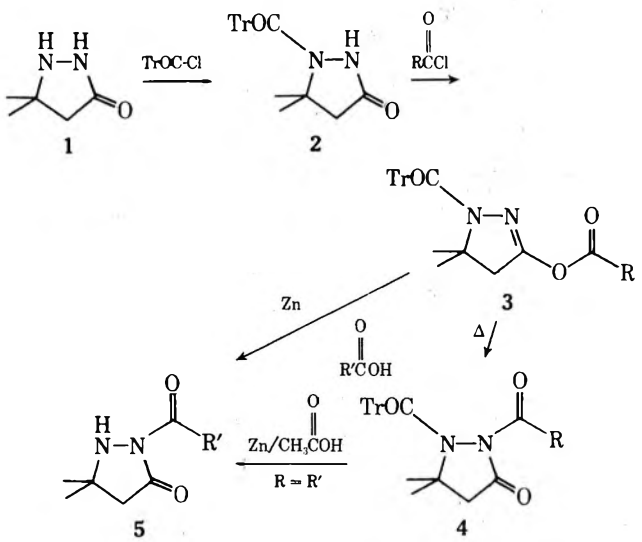
I

Preparation of 2-Acyl-5,5-dimethylpyrazolidin-3-ones. After several attempts to condense acylhydrazides with 3,3-dimethylacrylic acid[9] or its ethyl ester resulted only in the isolation of 1,2-diacylhydrazides, a different approach involving functionalization of the preformed ring

system, 5,5-dimethylpyrazolidin-3-one (1), was undertaken. While 1-acyl derivatives of 5,5-dimethylpyrazolidin-3-ones can be prepared easily, our attempts to form 2-acyl isomers by reaction of the anion of **1**, generated in situ, with a variety of electrophilic species led only to complex mixtures containing no isolatable products with the properties expected for the 2-acylpyrazolidin-3-ones. When the amine nitrogen of 1 was protected using a removable acyl blocking group, however, the desired 2-acyl isomers were obtained in good yields.

The protected ring system, 1-(2,2,2-trichloroethoxycarbonyl[10])-5,5-dimethylpyrazolidin-3-one (**2**, Scheme I)

Scheme I



a, R = CH_3; **b**, R = CH_2CH_3; **c**, R = $CH(CH_3)_2$; **d**, R = $C(CH_3)_3$; **e**, R = CH_2Ph; **f**, R = Ph

a, R′ = CH_3; **b**, R′ = CH_2CH_3; **c**, R′ = $CH(CH_3)_2$; **d**, R′ = $C(CH_3)_3$

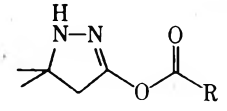
TrOC = $Cl_3CCH_2OC(=O)$-

was prepared from 1[11] using Schotten–Baumann conditions. Reaction of **2** with 1 equiv of acetyl chloride and triethylamine in tetrahydrofuran solvent at room temperature gave exclusively **3a**, the *O*-acetyl derivative of **2**. Heating of **3a** neat for 3 hr at 110° resulted in a high yield of **4a**, the *N*-acetyl isomer of **3a**. This thermal rearrangement could be followed very easily, since the *O*-acetyl (**3a**) and *N*-acetyl (**4a**) derivatives of **2** were readily distinguished by their NMR spectra. The NMR spectrum of the *O*-acetyl derivative showed a singlet due to the ring methylene protons at δ 3.10 while the *N*-acetyl derivative showed a singlet for these protons at δ 2.70. Consequently, integration of the δ 2.5–3.5 region gave the relative ratio of the two isomers.

When compounds **4b–e** were prepared from **2** using reaction conditions similar to those used to prepare **4a** from **2**, two deviations were noted: first, heating at 110° for 3 hr of **3d**, which contains a bulky *tert*-butyl group, resulted in a mixture of **3d** and **4d** of which **4d**, the *N*-acyl derivative of **2**, comprised only about 40% as determined by NMR (in our hands further heating did not alter the above ratio); second, acylation of **2** with phenylacetyl chloride gave an appreciable amount of **4e**, the *N*-acyl derivative of **2**, along with the expected *O*-acyl derivative **3e**. Since no *N*-acyl derivatives of **2** were obtained during the similar acylations of **2** to give **3a–d**, we postulate that O-acylation of **2** occurred to give **3e** which subsequently partially isomerized to **4e** under the reaction conditions. The more facile isomerization of **3e**, relative to **3a–d**, is reasonable because the electron-withdrawing inductive effect of the phenyl group makes the side-chain carbonyl more reactive to nucleophilic attack.

It appears that acylation using the conditions described gives the less stable *O*-acyl derivatives of **2**, namely **3**, and the heating of **3** results in equilibration[12] of it with the *N*-acyl derivatives **4**. The position of the equilibrium appears to be influenced by several factors, including the nature of the 1 substituent[13] and steric and electronic factors relating to the added acyl group. The thermal equilibration of the *O*-acyl and *N*-acyl derivatives of this system possibly occurs through a stepwise biomolecular transacylation process.[16]

When the TrOC protecting group was removed from the *N*-acyl derivatives of **2** (**4a–e**) using zinc dust in acetic acid at room temperature, good yields of the desired 2-acyl-5,5-dimethylpyrazolidin-3-ones (**5a–e**), 2-acyl derivatives of **1**, were obtained. As part of the structure proof of compounds **5a–e**, attempts were made to isolate **6a**, the *O*-acetyl derivative of **1**, by careful removal of the protecting group from **3a**. In all cases, however, we obtained only **5a**, the 2-acetyl derivative of **1**. In hopes of obtaining a stable *O*-acyl derivative of **1**, compound **3f**, the *O*-benzoyl derivative of **2**, was prepared. Interestingly, removal of the protecting group from **3f** using zinc in acetic acid at room temperature did not give **6f**, the desired *O*-benzoyl derivative of **1**, or its 2-benzoyl isomer **5f**, but instead gave a good yield of the 2-acetyl derivative **5a** where the acetyl moiety appears to have been derived from the carboxylic acid solvent (acetic acid). This interesting "exchange–rearrangement" reaction of **6f** also occurred when either propionic acid, isobutyric acid, or a mixture of pivalic acid and tetrahydrofuran (50:50 by volume) was used as the solvent, giving respectively **5b–d**. Several attempts to obtain **6f** from **3f** by removal of the protecting group under conditions not involving a carboxylic acid solvent were unsuccessful.

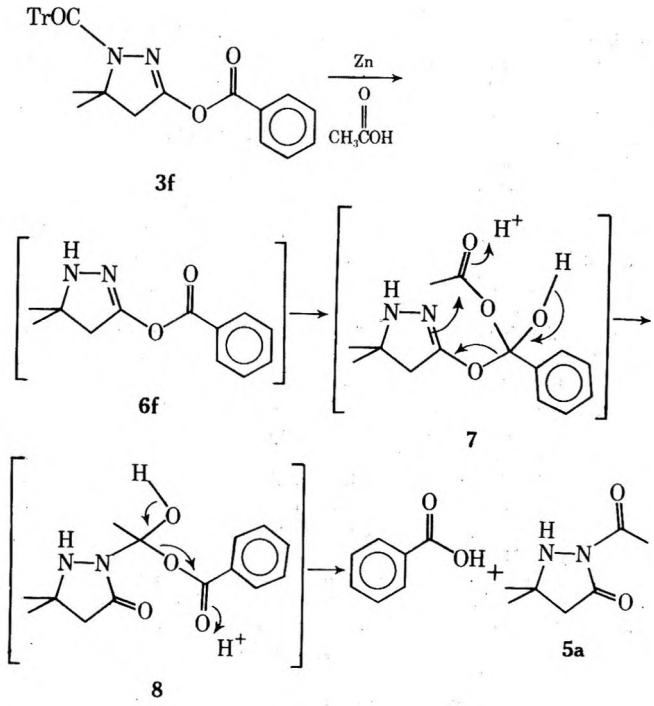


6a, R = CH_3; **f**, R = Ph

Formation of **5a** upon treatment of **3f** with zinc in acetic acid seems to involve two steps: one, loss of the protecting group; and two, acyl exchange–rearrangement. It appears that loss of the protecting group must occur before the exchange–rearrangement reaction, since treatment of **3f**, the *O*-benzoyl derivative of **2**, with either acetic acid or acetic acid containing zinc acetate resulted only in the slow formation of **2**. No *O*-acetyl (**3a**), *N*-acetyl (**4a**), or *N*-benzoyl (**4f**) derivatives of **2** could be isolated in the absence of metallic zinc. A mechanism[17] consistent with our observations for the conversion of **3f** to **5a** is shown in Scheme II. We postulate that **6f** is an intermediate in the reaction and that **6f** reacts with the solvent to form species **7** which breaks down as shown to give the observed products. Protonation of the imidic nitrogen of **7** instead of intramolecular transacylation would give **2**, which was detected as a minor product in these acyl exchange–rearrangement reactions. Our failure to isolate either **6a**, the *O*-acetyl derivative of **1**, or **6f**, the *O*-benzoyl derivative of **1**, is not surprising in light of our inability to prepare a 1-benzyl *O*-acyl derivative of this system.[13] The stabilization provided by a 1-acyl substituent is apparently necessary for the isolation under normal conditions of any *O*-acyl derivatives of pyrazolidin-3-ones.

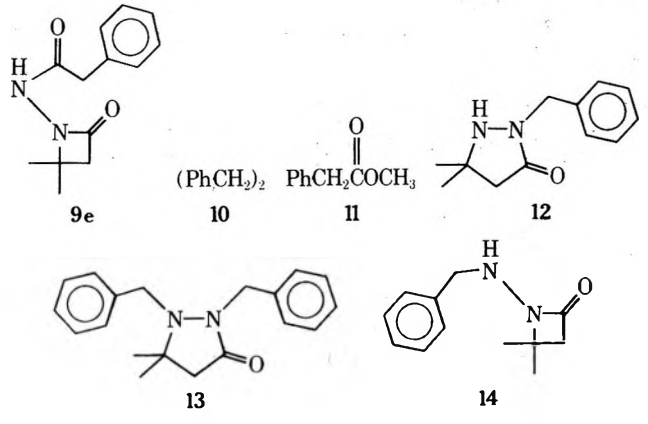
Irradiation of 2-Acyl-5,5-dimethylpyrazolidin-3-ones. Photolysis of 2-acyl-5,5-dimethylpyrazolidin-3-ones

Scheme II



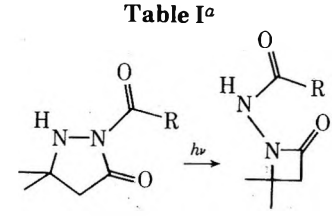
5a–e led to 1-acylamino-4,4-dimethylazetidin-2-ones[18] **9a–e** in yields ranging from 20 to 65%, depending on the starting material and conditions as shown in Table I. In all the photolyses reported here loss of starting material was followed by TLC using silicic acid plates. In the acetyl (**5a**) and propionyl (**5b**) cases TLC analysis indicated the formation of one new product with a slightly smaller R_f value than that of starting material. For **5c–e**, however, the TLC plates of the crude reaction mixtures were badly streaked and irradiation times for these molecules were arbitrarily set at 2 hr on the basis of the **5a** and the **5b** photolysis results. Irradiation of compounds **5a–d** gave β-lactams **9a–d** as the only isolated products, while irradiation of compound **5e** gave the series of products shown in Scheme III

Scheme III



which included **9e**. The yields of the various products were highly condition dependent.[7] It is interesting to note that for the nonaromatic series **5a–d** the pyrazolidin-3-ones show significant uv absorption while the respective azetidin-2-ones show only end absorption. This accounts for the photostability of **9a** when irradiated in methanol through a Vycor filter. In contrast to **9a**, **9e** has a uv absorption similar to that of benzene. Irradiation of **9e** in methanol through a Vycor filter for 2 hr led to 15–20% decomposition of the β-lactam.

Table I[a]

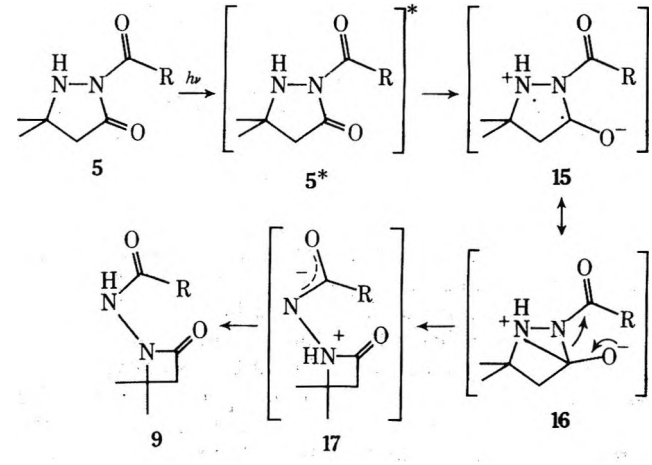


Compd		R	Solvent[b]	Filter	Yield, %[c]
5a	9a	CH_3	CH_3OH	Vycor	65
5b	9b	CH_2CH_3	CH_3OH	Vycor	36
5c	9c	$CH(CH_3)_2$	CH_3OH	Vycor	30
5d	9d	$C(CH_3)_3$	CH_3OH	Vycor	20
5e	9e	CH_2Ph	$(CH_3)_3COH$ (non-degassed)	Corex	45

[a] All irradiations were carried out at 0.1–1% w/v concentration for 2 to 3 hr with a Hanovia 450-W immersion lamp. [b] All solutions were degassed with a stream of nitrogen for 2 hr unless noted. [c] Yield of **9** which was isolated by column chromatography on silicic acid.

In order to explain the photochemical ring contraction of **5** to give **9**, the sequence shown in Scheme IV is proposed.

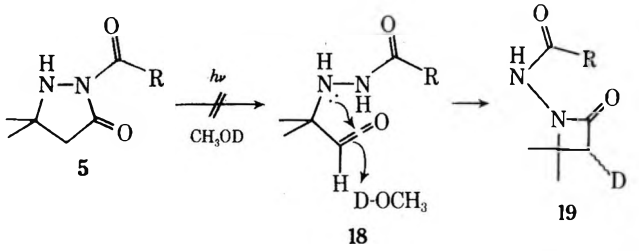
Scheme IV



Formation of radical anion–radical cation species **15** via intramolecular electron transfer deactivation of **5*** followed by bond formation would give **16**.[19] Bond reorganization to give **17** followed by proton transfer would lead to photoproduct **9**. The decrease in the yield of β-lactam in the series **5a–d** (see Table I) can be accounted for by the presence of a photochemical Norrish type I reaction pathway which competes with β-lactam formation. The increasing stability of the radicals formed from type I processes as the substitution of the 2-acyl moiety increases and the decreasing rate of recombination of those radicals once formed can explain the lowered observed yield of β-lactam. Similarily, formation of β-lactam **9e** from **5e** is in competition with type I processes. With **5e**, however, the type I processes are significantly enhanced, giving rise to **10**, **12**, **13**, and **14** as a result of phenyl-assisted cleavage of the same bond to give stable benzyl radicals. The difference between the yield of **9e** from the photolysis of **5e** in degassed methanol through a Vycor filter (15% of **9e**) and the yield of **9e** from the photolysis of **5e** in nondegassed *tert*-butyl alcohol through a Corex filter (45% of **9e**) probably resulted from quenching of the radical (i.e., type I) processes in the latter case.[20]

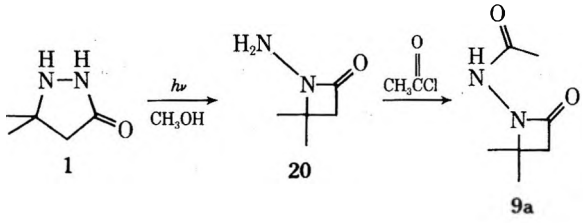
In addition to the sequence proposed in Scheme IV, formation of **9** from **5** might be postulated to occur via formation, probably by a Norrish type II process, of a ketene in-

termediate such as **18** followed by closure to the four-membered ring compound **19**.[22] This possibility was ruled out



by photolysis of **5a** in MeOD. Under these conditions the β-lactam product (**19**) would be expected to contain a deuterium in the 3 position. The β-lactam isolated from this photolysis, under conditions which would not cause loss of deuterium from the 3 position, contained no deuterium as determined by mass spectral analysis.

In order to compare the photochemistry of the 2-acylpyrazolidin-3-ones with other derivatives of this ring system, photolysis of the unsubstituted parent compound **1** was undertaken. Irradiation of a degassed methanolic solution of **1** through a Vycor filter for 20 hr, followed by column chromatography of the oil obtained upon evaporation of the solvent, led to a 15% isolated yield of 1-amino-4,4-dimethylazetidin-2-one (**20**).[23] As an internal check **20** was acetylated to give **9a** in good yield. The low yield and long reac-



tion time required for the formation of **20** from **1** supports the proposed sequence (see Scheme IV) for the formation of β-lactams **9** from the 2-acylpyrazolidin-3-ones **5**. From examination of Scheme IV it can be determined that the presence of a functional group (i.e., an acyl moiety) at the 2 position which can stabilize a negative charge (as in **17**) should strongly enhance β-lactam formation relative to the parent system or a 2-alkyl[15] system. This is, in fact, what is observed.

Further work to expand our understanding of the photochemistry of pyrazolidin-3-ones and the application of these results to the syntheses of penicillin-like bicyclic systems is under way, and will be reported at a later date.

Experimental Section

Melting points were taken in capillary tubes on a Thomas-Hoover Unimelt and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 457 A spectrometer. The NMR spectra were taken either on a Varian A-60 spectrometer or on a Perkin-Elmer Jeol MH-100 spectrometer and are reported in parts per million downfield from tetramethylsilane. Mass spectra were determined on a Perkin-Elmer Hitachi RMU-6D spectrometer. Ultraviolet spectra were taken on a Cary 14 recording spectrophotometer. Gas chromatography was carried out using programmed temperature control on a Hewlett-Packard 5750 B instrument equipped with 8-ft and 10-ft stainless steel columns packed with SE-30 on 80–100 mesh Chromosorb P. Mallinckrodt AR 100 mesh silicic acid was used for all column chromatography. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

5,5-Dimethylpyrazolidin-3-one (1). Cyclic hydrazide **1** was prepared in 75% yield and has been described previously.[11] For **1**: bp 100° (0.5 mm) [lit.[11] bp 115° (2 mm)]; mass spectrum (70 eV) *m/e* (rel intensity) 114 (21, M^+), 99 (48), 83 (26), 72 (27), 58 (22), 57 (16), 56 (44), 55 (38), 42 (96), 41 (100); uv (EtOH) 202 nm (ε 3750), shoulder 220 (2200).

1-(2,2,2-Trichloroethoxycarbonyl)-5,5-dimethylpyrazolidin-3-one (2). To a solution of 5,5-dimethylpyrazolidin-3-one (**1**, 23.0 g, 0.20 mol) in aqueous 2 *N* NaOH (100 ml) cooled to 10–20° under a nitrogen atmosphere was added dropwise 2,2,2-trichloroethoxycarbonyl chloride (42.5 g, 0.20 mol). After the addition was complete, the mixture was allowed to warm to room temperature and was stirred for 2 hr. The precipitate which formed during the reaction was filtered off and washed with water and a little cold Et_2O. Recrystallization of the solid from EtOH gave 30.2 g (52%) of pure **2**: mp 212.0–212.5°; ir (CCl_3H) 3680, 3400, 1710, 1600, 1372, 1332, 1282, 1120, 1105 cm^{-1}; NMR (CCl_3D) δ 1.65 (s, 6), 2.72 (s, 2), 4.88 (s, 2); mass spectrum (70 eV) *m/e* (rel intensity) 288 [10, isotope ratio shows three chlorines (3-Cl), M^+], 273 (4, 3-Cl), 253 (2, 2-Cl), 141 (20), 131 (30, 3-Cl), 113 (57), 99 (38), 98 (16), 97 (16), 96 (23), 95 (24), 83 (100), 82 (18), 71 (31), 63 (15), 61 (45), 56 (41), 55 (60), 44 (40), 41 (66).

Anal. Calcd for $C_8H_{11}N_2O_3Cl_3$: C, 33.19; H, 3.83; N, 9.68. Found: C, 33.34; H, 3.89; N, 9.74.

2-Acetyl-1-(2,2,2-trichloroethoxycarbonyl)-5,5-dimethylpyrazolidin-3-one (4a) via 3-Acetoxy-1-(2,2,2-trichloroethoxycarbonyl)-5-5-dimethyl-2-pyrazoline (3a). To a solution of 1-(2,2,2-trichloroethoxycarbonyl)-5,5-dimethylpyrazolidin-3-one (**2**, 25.0 g, 0.087 mol) and triethylamine (8.8 g, 0.087 mol) in tetrahydrofuran (475 ml) at room temperature under a nitrogen atmosphere was added dropwise over a period of 30 min acetyl chloride (6.9 g, 0.087 mol). The mixture was stirred for an additional 6 hr and the precipitated triethylamine hydrochloride salt was filtered off. Concentration of the filtrate left a solid which was dried under high vacuum. NMR analysis revealed this to be the O-acylated product **3a**: nmr (CCl_3D) δ 1.68 (s, 6), 2.22 (s, 3), 3.10 (s, 2), 4.89 (s, 2).

Without further purification the O-acylated material was heated neat under a nitrogen atmosphere at 110° for 3 hr. To the solid obtained on cooling was added Et_2O (50–100 ml). A small amount of insoluble material was filtered off and recrystallized from EtOH. Spectral comparisons showed it to be **2**. The Et_2O was stripped to leave a solid which upon recrystallization from Et_2O gave 19.5 g (67% based on **2**) of pure **4a**: mp 83.5–84.5°; ir (CCl_4) 2960, 1750 (broad), 1375, 1340, 1290, 1245, 1210, 1160, 1125, 1105, 1060 cm^{-1}; NMR (CCl_3D) δ 1.60 (s, 6), 2.58 (s, 3), 2.72 (s, 2), 4.82 (s, 2); mass spectrum (70 eV) *m/e* (rel intensity) 330 (trace, 3-Cl, M^+), 288 (45, 3-Cl), 273 (24, 3-Cl), 253 (6, 2-Cl), 183 (8), 141 (11), 131 (15, 3-Cl), 113 (37), 99 (62), 97 (10), 95 (14), 83 (63), 82 (12), 71 (9), 61 (8), 56 (31), 55 (22), 43 (100), 41 (21).

Anal. Calcd for $C_{10}H_{13}N_2O_4Cl_3$: C, 36.22; H, 3.95; N, 8.45. Found: C, 36.16; H, 3.89; N, 8.57.

1-(2,2,2-Trichloroethoxycarbonyl)-5,5-dimethyl-2-propionylpyrazolidin-3-one (4b) via 1-(2,2,2-Trichloroethoxycarbonyl)-5,5-dimethyl-3-propionoxy-2-pyrazoline (3b). Pyrazoline **3b** was prepared in a manner similar to that described for the preparation of **3a**. For **3b**: NMR (CCl_3D) 1.20 (t, J = 7 Hz, 3), 1.68 (s, 6), 2.53 (q, J = 7 Hz), 3.10 (s, 2), 4.89 (s, 2).

Heating of **3b** (110° for 3 hr) followed by recrystallization of the crude product from Et_2O resulted in 53% yield (based on **2**) of pure **4b**: mp 53.0–54.5°; ir (CCl_4) 2970, 1745 (broad), 1385, 1235, 1205, 1130, 1105, 1055 cm^{-1}; NMR (CCl_3D) δ 1.20 (t, J = 7 Hz, 3), 1.60 (s, 6), 2.73 (s, 2), 2.94 (q, J = 7 Hz, 2), 4.81 (s, 2); mass spectrum (70 eV) *m/e* (rel intensity) 344 (1, 3-Cl, M^+) 288 (49, 3-Cl), 273 (21, 3-Cl), 253 (5, 2-Cl), 197 (5), 155 (4), 149 (6), 141 (6), 131 (13, 3-Cl), 113 (25), 99 (40), 97 (10), 95 (13), 83 (42), 71 (8), 61 (9), 57 (100), 56 (38), 55 (19), 43 (10), 42 (10), 41 (22).

Anal. Calcd for $C_{11}H_{15}N_2O_4Cl_3$: C, 38.24; H, 4.38; N, 8.11. Found: C, 38.54; H, 4.51; N, 8.39.

1-(2,2,2-Trichloroethoxycarbonyl)-2-isobutyryl-5,5-dimethylpyrazolidin-3-one (4c) via 1-(2,2,2-Trichloroethoxycarbonyl)-3-isobutyroxy-5,5-dimethyl-2-pyrazoline (3c). Pyrazoline **3c** was prepared in a manner similar to that described for the preparation of **3a**. For **3c**: NMR (CCl_3D) δ 1.28 (d, J = 7 Hz, 6), 1.68 (s, 6), 3.12 (s, 2), 3.25 (septet, J = 7 Hz, 1), 4.90 (s, 2).

Heating of **3c** (110° for 3 hr) followed by recrystallization of the crude product from Et_2O resulted in a 48% yield (based on **2**) of pure **4c**: mp 81–82°; ir (CCl_4) 2970, 1740 (shoulder 1760), 1390, 1235, 1200, 1130, 1105, 1050 cm^{-1}; NMR (CCl_3D) δ 1.24 (d, J = 7 Hz, 6), 1.59 (s, 6), 2.25 (s, 2), 3.65 (septet, J = 7 Hz, 1), 4.82 (s, 2); mass spectrum (70 eV) *m/e* (rel intensity) 358 (trace, 3-Cl, M^+), 288 (19, 3-Cl), 273 (7.5, 3-Cl), 253 (2, 2-Cl), 211 (2.5), 169 (1.5), 149 (2), 141 (4.5), 131 (8, 3-Cl), 113 (13), 99 (22), 97 (6), 95 (8), 83 (23), 82 (4), 71 (61), 61 (5), 56 (18), 55 (12), 43 (100), 41 (33).

Anal. Calcd for $C_{12}H_{17}N_2O_4Cl_3$: C, 40.08; H, 4.77; N, 7.79. Found: C, 40.03; H, 4.70; N, 7.80.

1-(2,2,2-Trichloroethoxycarbonyl)-5,5-dimethyl-2-pivaloylpyrazolidin-3-one (4d) via 1-(2,2,2-Trichloroethoxycarbonyl)-

5,5-dimethyl-3-pivaloxy-2-pyrazoline (3d). Pyrazoline **3d** was prepared in a manner similar to that described for the preparation of **3a**. For **3d:** NMR (CCl_3D) δ 1.31 (s, 9), 1.78 (s, 6), 3.09 (s, 2), 4.89 (s, 2).

Heating of **3d** (120° for 10 hr) resulted in partial conversion (40% as determined by the appearance of new signals in the NMR) to **4d:** NMR (CCl_3D) δ 1.39 (s, 9), 1.60 (s, 6), 2.72 (s, 2), 4.79 (s, 2).

1-(2,2,2-Trichloroethoxycarbonyl)-5,5-dimethyl-2-phenylacetylpyrazolidin-3-one (4e) via 1-(2,2,2-Trichloroethoxycarbonyl)-5,5-dimethyl-3-phenylacetoxy-2-pyrazoline (3e). Treatment of **2** with phenylacetyl chloride, under conditions similar to those used for the preparation of **3a**, gave a 30:60 mixture of **3e** and **4e**. The signals assigned to **3e** follow: NMR (CCl_3D) δ 1.59 (s, 6), 3.00 (s, 2), 3.72 (s, 2), 4.82 (s, 2), 7.26 (s, 5).

Heating of the mixture (110° for 3 hr) followed by recrystallization of the crude product from Et_2O resulted in a 60% yield (based on **2**) of pure **4e:** mp 74–75°; ir (CCl_4) 2960, 1750 (broad), 1450, 1410, 1390, 1380, 1340, 1225, 1205, 1125, 1095, 1055 cm^{-1}; NMR (CCl_3D) δ 1.52 (s, 6), 2.65 (s, 2), 4.28 (s, 2), 4.75 (s, 2), 7.29 (s, 5); mass spectrum (70 eV) *m/e* (rel intensity) no parent ion, 308 (2), 288 (5, 3-Cl), 273 (3, 3-Cl), 253 (1), 204 (2), 203 (3), 159 (2), 141 (8), 136 (24), 131 (12, 3-Cl), 119 (25), 105 (40), 99 (19), 97 (11), 92 (23), 91 (100), 83 (43), 77 (11), 71 (12), 65 (18), 63 (11), 61 (19), 56 (26), 55 (28), 44 (56), 41 (44).

Anal. Calcd for $C_{16}H_{17}N_2O_4Cl_3$: C, 47.14; H, 4.20; N, 6.87. Found: C, 47.31; H, 4.18; N, 6.96.

3-Benzoxy-1-(2,2,2-trichloroethoxycarbonyl)-5,5-dimethyl-2-pyrazoline (3f). Pyrazoline **3f** was prepared in 70% yield in a manner similar to that described for the preparation of **3a**. For **3f:** mp 124–125° ir (CCl_4) 3050, 2960 (shoulder 2940), 1755, 1720, 1425, 1325, 1250 (shoulder 1240), 1210, 1175, 1110, 1075, 1055, 1020, 960 cm^{-1}; NMR (CCl_3D) δ 1.72 (s, 6), 3.28 (s, 2), 4.91 (s, 2), 7.50–7.80 (m, 3), 8.05–8.30 (m, 2); mass spectrum (70 eV) *m/e* (rel intensity) 392 (1, 3-Cl, M^+), 357 (0.5, 2-Cl), 288 (0.5, 3-Cl) 273 (trace, 3-Cl), 245 (1.5), 266 (trace), 218 (trace), 307 (0.7), 198 (trace), 159 (trace), 141 (0.8), 133 (1), 131 (1), 122 (2.5), 113 (1.5) 106 (8), 105 (100), 99 (0.5), 97 (1), 95 (1.5), 86 (1), 83 (4), 78 (1.5), 72 (24), 71 (1), 61 (1.2), 56 (4), 55 (2.5), 51 (5), 50 (1), 43 (2), 42 (2.5), 41 (3).

Anal. Calcd for $C_{15}H_{15}N_2O_4Cl_3$: C, 45.77; H, 3.84; N, 7.11. Found: C, 45.88; H, 3.71; N, 7.22.

2-Acetyl-5,5-dimethylpyrazolidin-3-one (5a). Method I. To a solution of 2-acetyl-1-(2,2,2-trichloroethoxycarbonyl)-5,5-dimethylpyrazolidin-3-one (**4a,** 5.0 g, 0.015 mol) in acetic acid (25 ml) under a nitrogen atmosphere was added all at once an equal quantity by weight of zinc dust. Cooling with an ice bath was applied as necessary to prevent any warming. After stirring for 2 hr at room temperature, the mixture was carefully poured into ice-cold water (100 ml) containing K_2CO_3 (70 g). The heterogeneous mixture was extracted well with chloroform which was dried over K_2CO_3. Evaporation of the solvent left an oil which slowly crystallized under high vacuum. Recrystallization of the solid from Et_2O gave 1.40 g (60%) of pure **5a:** mp 67–68°; ir (CCl_4) 3220, 2960, 1750, 1695, 1415, 1375, 1310, 1265, 1240, 1110, 985, 960, 935 cm^{-1}; NMR (CCl_3D) δ 1.31 (s, 6), 2.41 (s, 3), 2.61 (s, 2) 5.22 (broad s, 1, NH); mass spectrum (70 eV) *m/e* (rel intensity) 156 (7, M^+), 115 (4), 114 (47), 100 (7), 99 (100), 83 (8), 82 (2), 72 (7), 71 (3), 56 (8), 55 (6), 43 (22), 42 (8), 41 (9), metastable ion 86; uv (EtOH) 224 nm (ϵ 4290), 248 (2380) shoulder 274 (1290).

Anal. Calcd for $C_7H_{12}N_2O_2$: C, 53.83; H, 7.75; N, 17.94. Found: C, 53.91; H, 7.65; N, 18.02.

Method II. To a solution of 3-benzoxy-1-(2,2,2-trichloroethoxycarbonyl)-5,5-dimethyl-2-pyrazoline (**3f,** 5.00 g, 0.0128 mol) in acetic acid (40 ml) under a nitrogen atmosphere was added all at once an equal quantity by weight of zinc dust. Occasional cooling with an ice bath was necessary to prevent warming. After stirring for 2 hr at room temperature, the mixture was carefully poured into ice-cold water (200 ml) containing K_2CO_3 (150 g). The heterogeneous mixture was then extracted with chloroform which was dried over K_2CO_3 and evaporated to leave a solid. Recrystallization of the solid from Et_2O gave 1.30 g (65%) of pure **5a,** mp 67–68°.

5,5-Dimethyl-2-propionylpyrazolidin-3-one (5b). Method I. Pyrazolidin-3-one **4b** was converted into **5b** in a manner similar to that described for the reaction of **4a** to give **5a.** Recrystallization of the crude product from Et_2O gave a 52% yield of pure **5b:** mp 83.5–84.5°; ir (CCl_4) 3280, 2960, 1750, 1700 (shoulder 1720), 1420, 1380, 1310, 1260, 1225, 1100, 1020, 960, 905 cm^{-1}; NMR (CCl_3D) δ 1.15 (t, J = 8 Hz, 3), 1.35 (s, 6), 2.60 (s, 2), 2.83 (q, J = 8 Hz, 2), 4.95 (broad s, 1, NH); mass spectrum (70 eV) *m/e* (rel intensity) 170 (5, M^+), 115 (3), 114 (32), 100 (5), 99 (100), 83 (6), 72 (5), 57 (13), 56 (5), 55 (3), 42 (5), 41 (6), metastable ion 86; uv (EtOH) 225 nm (ϵ 3900), 246 (2450), shoulder 270 (1500).

Anal. Calcd for $C_8H_{14}N_2O_2$; c, 56.45; H, 8.29; N, 16.46. Found: C, 56.47; H, 8.25; N, 16.25.

Method II. Pyrazoline **3f** in propionic acid was treated with zinc and worked up in a manner similar to the preparation of **5a** by method II. Recrystallization of the crude product from Et_2O gave a 56% yield of pure **5b,** mp 83.5–84.5°.

2-Isobutyryl-5,5-dimethylpyrazolidin-3-one (5c). Method I. Pyrazolidin-3-one **4c** was converted into **5c** in a manner similar to that described for the reaction of **4a** to give **5a.** Column chromatography of the crude product on silicic acid with Et_2O eluent gave a 43% yield of pure **5c:** mp 36–37°; ir (CCl_4) 3260, 2960, 1750, 1690 (shoulder 1710), 1470, 1410, 1390, 1310, 1240, 1220, 1185, 1100, 1050, 995, 970, 910 cm^{-1}; NMR (CCl_3D) δ 1.18 (d, J = 7 Hz, 6), 1.35 (s, 6), 2.66 (s, 2), 3.63 (septet, J = 7 Hz, 1), 5.00 (broad s, 1, NH); mass spectrum (70 eV) *m/e* (rel intensity) 184 (10, M^+), 115 (7), 114 (63), 100 (7), 99 (100), 83 (8), 72 (6), 71 (12), 56 (8), 55 (5), 43 (41), 42 (8), 41 (16), metastable ion 86; uv (EtOH) 226 nm (ϵ 3400), 232 (3000), 250 (2200), shoulder 270 (1450).

Anal. Calcd for $C_9H_{16}N_2O_2$: C, 58.67; H, 8.75; N, 15.21. Found: C, 58.49; H, 9.00; N, 14.98.

Method II. Pyrazoline **3f** in isobutyric acid was treated with zinc and worked up in a manner similar to the preparation of **5a** by method II. Column chromatography of the crude product on silicic acid with Et_2O eluent gave a 40% yield of pure **5c,** mp 36–37°.

5,5-Dimethyl-2-pivaloylpyrazolidin-3-one (5d). Method I. A 60:40 mixture of **3d** and **4d** was converted to **5c** in a manner similar to that described for the reaction of **4a** to give **5a** but using as the solvent a 50:50 mixture of pivalic acid and tetrahydrofuran. Recrystallization of the crude product from Et_2O gave a 34% yield of pure **5d:** mp 97–98°; ir (CCl_4) 3250, 2950, 1750, 1670 (shoulder 1700), 1400, 1310, 1260, 1215, 1175 cm^{-1}; NMR (CCl_3D) δ 1.33 (s, 15), 2.52 (s, 2), 5.06 (broad s, 1, NH); mass spectrum (70 eV) *m/e* (rel intensity) 198 (5, M^+), 183 (2), 127 (2), 115 (5), 114 (61), 100 (7), 99 (100), 85 (3), 83 (7), 72 (5), 57 (35), 56 (8), 55 (5), 42 (7), 41 (19), metastable ion 86; uv (EtOH) 231 nm (ϵ 3300), 239 (2800), 248 (2300), shoulder 275 (1800).

Anal. Calcd for $C_{10}H_{18}N_2O_2$: C, 60.58; H, 9.15; N, 14.13. Found: C, 60.80; H, 8.97; N, 14.32.

Method II. Pyrazoline **3f** in a 50:50 mixture of pivalic acid and tetrahydrofuran was treated with zinc and worked up in a manner similar to the preparation of **5a** by method II. Recrystallization of the crude product from Et_2O gave a 31% yield of pure **5d,** mp 97–98°.

5,5-Dimethyl-2-phenylacetylpyrazolidin-3-one (5e). Pyrazolidin-3-one **4e** was converted into **5e** in a manner similar to that described for the reaction of **4a** to give **5a.** Recrystallization of the crude product from Et_2O gave a 64% yield of pure **5e:** mp 62–63°; ir (CCl_4) 3260, 2960, 1750, 1695, 1420, 1315, 1275, 1235, 1165 cm^{-1}; NMR (CCl_3D) δ 1.29 (s, 6), 2.52 (s, 2), 4.20 (s, 2), 4.90 (broad s, 1, NH), 7.29 (s, 5); mass spectrum (70 eV) *m/e* (rel intensity) 232 (4, M^+, this ion disappears rapidly with time), 214 (2), 149 (2), 118 (6), 115 (7), 114 (100), 113 (5), 100 (5), 99 (86), 91 (37), 83 (23), 72 (28), 71 (9), 65 (7), 56 (20), 55 (15), 42 (9), 41 (17), metastable ion 86; uv (EtOH) end absorption 200 nm (ϵ 11,200), 227 (4400), 248 (2700), shoulder 275 (1350).

Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.01; H, 6.93; N, 12.06.

1-Acetamido-4,4-dimethylazetidin-2-one (9a). From Irradiation of 5a. A solution of 2-acetyl-5,5-dimethylpyrazolidin-3-one (**5a,** 1.56 g, 0.010 mol) in methanol (250 ml) was degassed with a stream of nitrogen for 2 hr, after which it was irradiated for 2 hr with a Hanovia 450-W immersion lamp equipped with a Vycor filter. TLC analysis [silicic acid plates with Et_2O–EtOH (90:10) developer] showed the loss of starting material (detected by uv and I_2) and the appearance of a new spot of slightly smaller R_f (detected by I_2). Stripping of the solvent left an oil which slowly crystallized. Column chromatography of the solid on silicic acid with Et_2O–EtOH (90:10) solvent resulted in the isolation of 1.01 g (65%) of pure **9a:** mp 107–108°; ir (CCl_3H) 3280, 3225 (broad), 2995, 1765, 1705, 1370, 1280, 1225, 1155, 1045, 915, 905 cm^{-1}; NMR (CCl_3D) δ 1.41 (s, 6), 2.01 (s, 3), 2.69 (s, 2); mass spectrum (70 eV) *m/e* (rel intensity) 156 (9, M^+), 138 (4), 115 (7), 114 (93), 101 (14), 100 (30), 99 (45), 83 (32), 82 (18), 72 (53), 57 (15), 56 (61), 55 (55), 44 (15), 43 (100), 42 (12), 41 (75); uv (EtOH) end absorption 200 nm (ϵ 2000).

Anal. Calcd for $C_7H_{12}N_2O_2$: C, 53.83; H, 7.75; N, 17.94. Found: C, 54.03; H, 7.83; N, 17.86.

From Acylation of 22. To a solution of 1-amino-4,4-dimethyl-

azetidin-2-one (22, 0.120 g, 1.05 mmol) and triethylamine (0.106 g, 1.05 mmol) in benzene (5 ml) under a nitrogen atmosphere and cooled to 10° was added over a period of 30 min acetyl chloride (0.081 g, 1.05 mmol) in benzene (1 ml). The mixture was then stirred for an additional 30 min at 10° and 5 hr at room temperature. Additional benzene (10 ml) was then added, the mixture was filtered, and the solvent was evaporated to leave 0.145 g (89%) of an oil which was shown to be 90% 1-acetamido-4,4-dimethylazetidin-2-one (**9a**) by TLC and NMR comparison to **9a** obtained from irradiation of **5a**.

4,4-Dimethyl-1-propionylaminoazetidin-2-one (9b). Irradiation of **5b** in methanol, similar to the irradiation described for **5a**, gave after work-up a 36% yield of pure **9b**: mp 100–101°; ir (CCl_3H) 3400, 3250 (broad), 2975, 1765, 1710, 1465, 1375, 1275, 1170 cm^{-1}; NMR (CCl_3D) δ 1.14 (t, J = 8 Hz, 3), 1.42 (s, 6), 2.29 (q, J = 8 Hz, 2), 2.70 (s, 2); camphor depression determined mol wt 189; mass spectrum (70 eV) m/e (rel intensity) 170 (6, M^+), 115 (15), 114 (71), 113 (18), 99 (35), 83 (35), 72 (64), 57 (100), 56 (32), 55 (40), 41 (32); uv (EtOH) end absorption 200 nm (ϵ 2400).

Anal. Calcd for $C_8H_{14}N_2O_2$: C, 56.45; H, 8.29; N, 16.46. Found: C, 56.28; H, 8.16; N, 16.44.

1-Isobutyrylamno-4,4-dimethylazetidin-2-one (9c). Irradiation of **5c** in methanol, similar to the irradiation described for **5a**, gave after work-up a 30% yield of pure **9c**: mp 91–92°; ir (CCl_3H) 3410, 3280 (broad), 2970, 1768, 1706, 1465, 1390, 1375, 1275, 1160 cm^{-1}; NMR (CCl_3D) δ 1.19 (d, J = 7 Hz, 6), 1.42 (s, 6), 2.55 (septet, J = 7 Hz, 1), 2.70 (s, 2); mass spectrum (70 eV) m/e (rel intensity) 184 (7, M^+), 129 (7), 127 (7), 114 (41), 99 (20), 83 (22), 72 (38), 71 (49), 56 (13), 55 (17), 43 (100), 41 (19); uv (EtOH) end absorption 200 nm (ϵ 2200).

Anal. Calcd for $C_9H_{16}N_2O_2$: C, 58.67; H, 8.75; N, 15.21. Found: C, 58.75; H, 8.62; N, 15.25.

4,4-Dimethyl-1-pivaloylaminoazetidin-2-one (9d). Irradiation of **5d** in methanol, similar to the irradiation described for **5a**, gave after work-up a 20% yield of pure **9d**: mp 165.0–165.5°; ir (CCl_3H) 3430, 3290 (broad), 2960, 1768, 1707, 1480, 1460, 1375, 1270, 1160, 1130 cm^{-1}; NMR (CCl_3D) δ 1.28 (s, 9), 1.40 (s, 6), 2.69 (s, 2); mass spectrum (70 eV) m/e (rel intensity) 198 (8, M^+), 183 (1), 167 (1), 155 (1), 143 (5), 141 (4), 114 (19), 99 (21), 85 (13), 83 (28), 72 (43), 57 (100), 56 (11), 55 (12), 42 (5), 41 (21); uv (EtOH) end absorption 200 nm (ϵ 3200).

Anal. Calcd for $C_{10}H_{18}N_2O_2$: C, 60.58; H, 9.15; H, 14.13. Found: C, 60.71; H, 9.40; N, 14.05.

4,4-Dimethyl-1-phenylacetamidoazetidin-2-one (9e). Irradiation of **5e** in methanol, similar to the irradiation described for **5a**, followed by removal of the solvent under reduced pressure at room temperature gave an oil which was shown by VPC analysis to be a complex mixture. Isolated by VPC were **9e, 10, 11, 12, 13,** and **14.** Products **9e, 12, 13,** and **14** are described below while **10** and **11** were identified by comparison of their mass spectra with those of known samples. Products **9e** and **11** were also isolated by column chromatography in yields of 15 and 5%, respectively. Based on an isolated yield of **9e** of 15%, VPC yields of the other products were determined: **10,** 1–2%; **11,** 1–5%; **12,** 10–12%; **13,** 1–2%; **14,** 5–7%.

Irradiation of a nondegassed *tert*-butyl alcohol solution of **5e** through a Corex filter for 3 hr gave, after removal of the solvent, an oil which was shown by VPC to contain mainly **9e** with only small amounts of other products. Column chromatography of the crude reaction mixture gave a 45% isolated yield of **9e.** These conditions represent the best yield of **9e** obtained by us. For **9e**: mp 137–138°; ir (CCl_3H) 3390, 3230 (broad), 2960, 1769, 1700, 1600, 1475, 1370, 1270, 1150 cm^{-1}; NMR (CCl_3D) δ 1.31 (s, 6), 2.61 (s, 2), 3.49 (s, 2), 7.29 (s, 5); mass spectrum (70 eV) m/e (rel intensity) 232 (trace, M^+, this ion disappears rapidly with time), 215 (3), 214 (22), 213 (4), 199 (3), 174 (12), 149 (5), 114 (15), 99 (14), 91 (26), 88 (11), 86 (25), 84 (100), 83 (11), 72 (9), 59 (33), 57 (15), 56 (52), 55 (30), 49 (15), 47 (18), 44 (27), 43 (18), 41 (83); uv (EtOH) end absorption 200 nm (ϵ 12,500), 258 with fine structure (188).

Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.01; H, 6.82; N, 11.73.

2-Benzyl-5,5-dimethylpyrazolidin-3-one (12). Pyrazolidin-3-one **12** was isolated by VPC from the photolyses of **5e** described above. It was identified by comparison of its mass spectrum to that of a sample independently synthesized in our laboratory.[15] For **12:** mass spectrum (70 eV) m/e (rel intensity) 204 (36, M^+), 189 (8), 113 (25), 111 (8), 105 (9), 100 (13), 91 (100), 85 (5), 83 (10), 77 (8), 71 (12), 65 (12), 57 (12), 56 (12), 55 (12), 46 (29), 45 (64), 43 (21), 41 (18).

1,2-Dibenzyl-5,5-dimethylpyrazolidin-3-one (13). Pyrazolidin-3-one **13** was isolated by VPC from the photolyses of **5e** described above. It was identified by comparison of its mass spectrum to that of a sample independently synthesized in our laboratory.[15] For **13:** mass spectrum (70 eV) m/e (rel intensity) 294 (45, M^+), 204 (16), 203 (100), 100 (30), 91 (84), 83 (6), 77 (5), 65 (20), 57 (8), 56 (15), 55 (9), 41 (17).

1-Benzylamino-4,4-dimethylazetidin-2-one (14). β-lactam **14** was isolated by VPC from the photolyses of **5e** described above. It was assigned the structure shown from its mass spectrum. For **14:** mass spectrum (70 eV) m/e (rel intensity) 204 (3, M^+), 190 (28), 175 (12), 118 (19), 113 (6), 99 (7), 92 (14), 91 (100), 90 (10), 72 (40), 41 (8), 65 (20), 57 (7), 56 (10), 55 (12), 42 (7), 41 (10).

1-Amino-4,4-dimethylazetidin-2-one (20). Irradiation of a solution of freshly distilled 5,5-dimethylpyrazolidin-3-one (**1**) in methanol for 20 hr, in a manner similar to the irradiation of **5a** described above, gave, after removal of the solvent at room temperature, an oil. Column chromatography of the oil resulted in the isolation of one product in 15% yield which was identified by its spectra to be **20:** ir (CCl_3H) 3360, 2960, 2940, 1755, 1390, 1385, 1285 cm^{-1}; NMR (CCl_3D) δ 1.38 (s, 6), 2.54 (s, 2), 4.30 (broad s, 2, $-NH_2$); mass spectrum (70 eV) m/e (rel intensity) 114 (15, M^+), 99 (7), 83 (35), 72 (100), 57 (74), 56 (66), 55 (93), 44 (34), 43 (20), 42 (20), 41 (70).

Compound **20** was acetylated to give **9a** for which a correct analysis was obtained (see above, **9a**).

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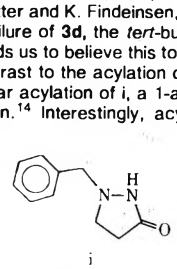
Registry No.—**1,** 42953-82-2; **2,** 49629-15-4; **3a,** 53992-35-1; **3b,** 53992-36-2; **3c,** 53992-37-3; **3d,** 53992-38-4; **3e,** 53992-39-5; **3f,** 49629-16-5; **4a,** 49661-81-6; **4b,** 53992-40-8; **4c,** 53992-41-9; **4d,** 53992-42-0; **4e,** 53992-43-1; **5a,** 49629-18-7; **5b,** 49629-19-8; **5c,** 49629-20-1; **5d,** 49629-21-2; **5e,** 53992-44-2; **9a,** 53992-45-3; **9b,** 53992-46-4; **9c,** 53992-47-5; **9d,** 53992-48-6; **9e,** 53992-49-7; **12,** 53992-50-0; **13,** 53992-51-1; **14,** 53992-52-2; **20,** 53992-53-3.

References and Notes

(1) Presented in part at the 5th Northeast Regional Meeting of the American Chemical Society, Rochester, N.Y., Oct 17, 1973.
(2) For a comprehensive review of synthesis of β-lactams see A. K. Mukerjee and R. C. Srivastava, *Synthesis*, 327 (1973).
(3) (a) E. H. Flynn, "Cephalosporins and Penicillins", Academic Press, New York, N.Y., 1972; (b) M. Manhas and A. K. Bose, "Synthesis of Penicillin, Cephalosporin C and Analogs", Marcel Dekker, New York, N.Y., 1972.
(4) H. T. Clarke, J. R. Johnson, and R. Robinson, "The Chemistry of Penicillin", Princeton University Press, Princeton, N.J., 1949.
(5) (a) D. R. Bender, L. F. Bjeldanes, D. R. Knapp, D. R. McKean, and H. Rapoport, *J. Org. Chem.*, **38,** 3439 (1973); (b) M. F. Chasle and A. Foucaud, *C. R. Acad. Sci., Ser. C,* 2034 (1969).
(6) (a) D. S. C. Black and A. B. Boscacci, *J. Chem. Soc., Chem. Commun.*, 129 (1974); (b) G. Lowe and D. Ridley, *J. Chem. Soc., Perkin Trans. 1,* 2024 (1973); (c) G. Stork and R. Szajewski, *J. Am. Chem. Soc.*, **96,** 5787 (1974); (d) S. N. Ege, *Chem. Commun.*, 759 (1968).
(7) A preliminary account of the photolysis of **9e** has been reported: C. E. Hatch and P. Y. Johnson, *Tetrahedron Lett.*, 2719 (1974).
(8) C. E. Hatch and P. Y. Johnson, *Tetrahedron Lett.*, 2153 (1973).
(9) This reaction with phenylhydrazine gives 2-phenyl-5,5-dimethylpyrazolidin-3-one: B. Prentice, *Justus Liebigs Ann. Chem.*, **292,** 273 (1896).
(10) Abbreviated as TrOC; see T. B. Windholz and D. B. R. Johnson, *Tetrahedron Lett.*, 2555 (1967).
(11) H. Stetter and K. Findeinsen, *Chem. Ber.*, **98,** 3228 (1965).
(12) The failure of **3d,** the *tert*-butyl case, to convert any more than 40% to **4d** leads us to believe this to be an equilibrium process.
(13) In contrast to the acylation of 2, a 1-acyl-5,5-dimethylpyrazolidin-3-one, a similar acylation of i, a 1-alkylpyrazolidin-3-one, occurs exclusively on nitrogen.[14] Interestingly, acylation under similar conditions of ii, a 1-alkyl-5,5-dimethylpyrazolidin-3-one, gave no apparent reaction: unpublished results from our laboratories.[15]



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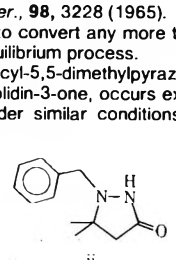

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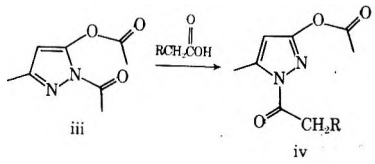
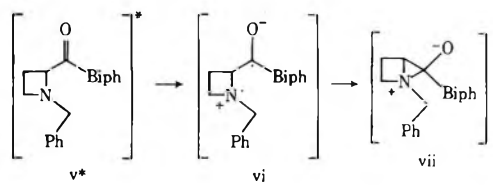
(14) H. Dorn and D. Arndt, *J. Prakt. Chem.*, **313,** 115 (1971).
(15) The synthesis and photolysis of several alkylpyrazolidin-3-ones will be the subject of a forthcoming paper.

(16) This type of mechanism was demonstrated by labeling experiments for the interconversion of *O*- and *N*-acyl isomers in another heterocycle system: A. W. K. Chan and W. D. Crow, *Aust. J. Chem.*, 2967 (1968).
(17) A similar mechanism was set forth for the conversion of iii to iv: K. Arakawa, T. Miyasaka, and H. Ochi, *Chem. Pharm. Bull.*, 214 (1974).



iii iv

(18) *N*-Acylaminoazetidin-2-ones have been previously reported; see E. Testa and L. Fontanella, *Farmaco, Ed. Sci.*, 1017 (1971).
(19) A similar mechanism involving a bicyclo[2.1.0] intermediate, vii, has been proposed in the photolysis of compound v: A. Padwa, F. Albrecht, P. Singh, and E. Vega, *J. Am. Chem. Soc.*, 93, 2928 (1971).



v* vi vii

(20) Another process which might compete with β-lactam formation is radical cleavage of the relatively weak N–N linkage. Although this mode of reaction has been observed for monoacylhydrazides,[21] 1,1-diacylhydrazides (**5** is a 1,1-diacylhydrazide) have been shown not to undergo this type of reaction.[21]
(21) R. S. Davidson and A. Lewis, *Tetrahedron Lett.*, 4679 (1973).
(22) Product **11** from the photolysis of **5e** in methanol probably occurred by a similar type II mechanism.
(23) A similar 1-aminoazetidin-2-one has been synthesized thermally. See F. D. Greene, R. L. Camp, V. P. Abegg, and G. O. Pierson, *Tetrahedron Lett.*, 4091 (1973).

On the Generation and Reactivity of *N*-Pyrazolyl Radicals in Benzene Solution[1]

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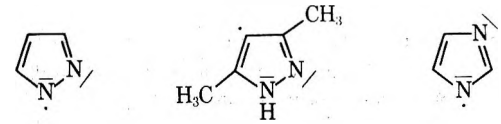
The synthesis of *tert*-butyl 1-pyrazolepercarboxylate (**5a**) and of its 3-methyl derivative **5b** is described. Thermolysis of these compounds in benzene solution at ~140° proceeds predominantly via homolysis and leads to N-phenylated pyrazoles without formation of isomeric *C*-phenyl derivatives. *N*-Pyrazolyl radicals, which are proposed as intermediates, apparently are able to effect homolytic aromatic substitution. Judging from competition with *p*-dichlorobenzene (partial rate factor ~0.25), 1-pyrazolyl (**1**) has a marked electrophilic character. Photolysis of *N*-nitropyrazoles in benzene solution, also leading to N-phenylated derivatives, constitutes an alternative fashion for the generation of *N*-pyrazolyl radicals. Using 3- and 5-substituted pyrazoles as precursors, it is shown that the unpaired electron is delocalized over (at least) the two nitrogen atoms. A σ-type ground state is favored over a π-type electronic structure.

Pyrazolyl radicals—and in general radicals derived from aromatic heterocyclic compounds containing a pyrrole-like nitrogen—can be divided in two classes, viz. (i) radicals which result from homolytic cleavage of a group bound to carbon, and (ii) those formed by such a removal of a substituent on nitrogen. The type i radicals are expected to be closely analogous to homocyclic aryl radicals like phenyl, having the unpaired electron localized in a σ-type orbital.[2] A type ii radical can a priori be compared with both aryl and amino radicals, the latter normally having a π-type electronic ground state.[3]

As an outgrowth of our study on the mechanism of the thermal rearrangement of *N*-nitropyrazoles (resulting in the isomeric 3(5)-nitropyrazoles),[4] we wished to learn about the physical and chemical properties of 1-pyrazolyl (**1**) (Chart I) and its derivatives. To the best of our knowledge **1** is as yet unknown.[5] Recently, Taguchi et al.[6] generated the 4-pyrazolyl radical **2** via decomposition of the parent 4-diazopyrazole in benzene. As anticipated, this type i radical led to the formation of the corresponding 4-phenylpyrazole. A 3,5-diphenyl-1-pyrazolyl radical, thus of type ii, was postulated by Lempert,[7] but there the phenyl rings might strongly influence the character of the radical, as in the well-known polyphenyl substituted pyrryl[8] and imidazolyl[9] radicals.

As regards the electronic ground state of **1**, interaction of the σ orbitals on the two nitrogen atoms has to be considered. Assuming that **1** has C_{2v} symmetry, it may have its unpaired electron in a σ-type orbital, arising from the combination of two N–σ orbitals ($^2B_2$ state); alternatively, the unpaired electron may reside in a π-type orbital involving all five ring atoms ($^2A_2$ or $^2B_1$ state). No information exists about the actual electronic ground state of **1**. For the related 1-imidazolyl (**3**), Evleth et al.[10] predict a $^2B_2$ (σ) ground state, whereas the ESR data of Samuni and Neta[11] strongly point to a π-type electronic structure.

Chart I



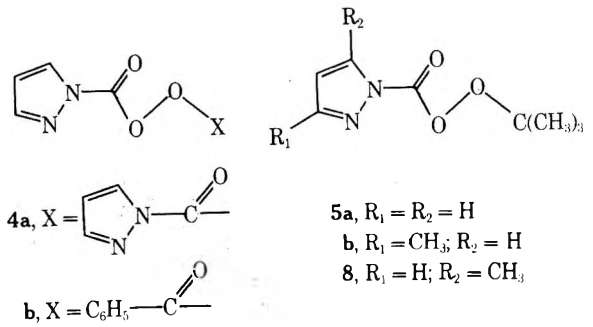
1 2 3

In order to shed light on this matter from a theoretical viewpoint, a series of ab initio SCF calculations is now being performed by Mulder et al. (from the Department of Theoretical Organic Chemistry of our laboratory).[12]

The present paper deals with the generation and reactions of **1** and its 3(5)-methylated analog(s). Several attempts to synthesize the peroxides **4a** and **4b** (Chart II) as precursors for **1** were unsuccessful.[13] The preparation of the *tert*-butyl perester **5a** and of its 3-methyl analog **5b** offered no difficulties, however. Here we report on the thermal decomposition of these novel peresters in benzene solution.

Photolytic decomposition of *N*-nitropyrazoles in benzene has also been considered as a source of **1** and derivatives;

Chart II

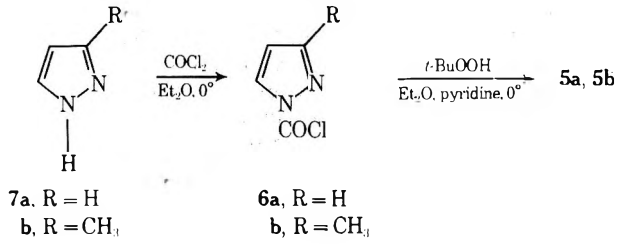


the results are compared with those of the perester decomposition. Finally, the character of the intermediate *N*-pyrazolyl radicals is discussed.

Results and Discussion

The *tert*-butyl perester **5a** and its 3-methyl analog **5b** were prepared via the 1-pyrazolecarbonyl chlorides **6a** and **6b** (Scheme I). The preparation of **6b** by the reaction of 3(5)-methylpyrazole (**7b**) has been described by von Auwers;[15] **6a** was synthesized analogously. The peresters were purified by distillation under reduced pressure and were characterized by their ir and NMR spectra. Compound **5b** appeared to be contaminated with ~4% of its 5-methyl isomer **8**, probably originating from the corresponding acid chloride which may be formed—in addition to **6b**—from **7b**.

Scheme I



Thermolyses of **5a** were performed in sealed tubes, or in an autoclave under nitrogen atmosphere. Typically, a 10% solution of **5a** in benzene was heated in a sealed tube for 1 hr at 135°. As for the fate of the *tert*-butoxy group, NMR

Table I
Products from Thermal Decomposition of 5a in Benzene at 135°

Product	Yield[a] 1 wt % soln	Yield[a] 10 wt % soln
Pyrazole[b]	69	75
1-Phenylpyrazole[b]	17.5	6
(Pyrazolyl group recovery[c]	86.5	81)
tert-Butyl alcohol[d]	*e*	9
Acetone[d]	*e*	51
Isopropenyl methyl ether[d]	*e*	21
(*tert*-Butoxyl group recovery	*e*	81)
Biphenyl[b]	8.5	2
Toluene[d]	*e*	13

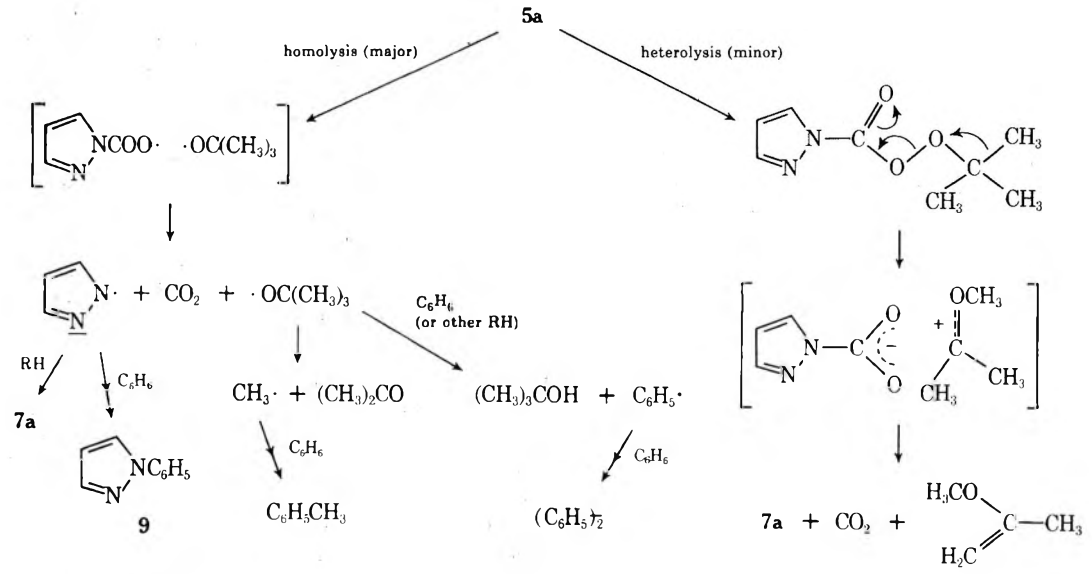
[a] In mole percent on basis of the amount of starting material. [b] Fraction isolated from column chromatography (see text). [c] A number of incompletely separated, unidentified products (mostly pyrazole derivatives) was also obtained. [d] By nmr analysis. [e] Not determined.

spectroscopy showed the formation of *tert*-butyl alcohol, acetone, and toluene, proving the intermediate production of *tert*-butoxy radicals. In addition, isopropenyl methyl ether was found, indicating the occurrence of a competing Criegee-type rearrangement[16] (Scheme II).

Column chromatography was used to isolate derivatives formed from the *pyrazolyl* residue, and other higher boiling products. With the aid of NMR and mass spectroscopy, the formation of pyrazole (**7a**), 1-phenylpyrazole (**9**), and biphenyl was demonstrated, yields being dependent on the perester/benzene intake ratio (Table I). The occurrence of peaks from C_{13} and C_{14} hydrocarbons in the mass spectrum of the biphenyl fraction, and of NMR signals in the 1–3 and 5–6-ppm regions, suggest the presence of methylated and hydrogenated biphenyls in the fraction. Likewise, the pyrazole fraction appeared to contain a few percent of 3(5)-methylpyrazole (**7b**), while the *N*-phenylpyrazole fraction most probably contained 1-cyclohexadienylpyrazole. *No C-phenylated pyrazoles could be detected.*

These observations strongly point to a regular homolytic decomposition of perester **5a** as the major pathway, leading to pyrazolyl radical **1**. *tert*-Butoxy radicals are capable of abstracting H atoms from benzene, giving *tert*-butyl alcohol and phenyl radicals,[17] the latter species leading to bi-

Scheme II



phenyl. At the temperatures used, *tert*-butoxy radicals will decompose partly, the methyl radicals being responsible for the production of toluene via homolytic alkylation of benzene; the other arenes present may be methylated analogously. Pyrazole may be produced *via* both radical and nonradical pathways (cf. Scheme II).

1-Phenylpyrazole (**9**) is thought to be formed via **1** by a normal homolytic substitution reaction involving benzene. An alternative pathway for the formation of **9** could perhaps be homolytic phenylation of pyrazole, *selectively on nitrogen*. As far as we know, homolytic phenylation of *unsubstituted* pyrazole has not yet been investigated. We found that when dibenzoyl peroxide (2 mol %) was thermolyzed at 135° in a 1:10 (molar) mixture of pyrazole and benzene, phenylation of pyrazole mainly took place at the 3(5) position, with a partial rate factor (f) of ~1.5 relative to a position in benzene.[18] The amount of 1-phenylpyrazole corresponds to $f \leq 0.6$, substitution at C-4—if any—having $f < 0.2$. Comparing these results with those of thermal decomposition of **5a** in benzene, leading to only N-phenylated pyrazole, we can exclude the alternative of phenylation of pyrazole as an important pathway in the formation of **9** from **5a**.

On the basis of the rate of decomposition of **5a** (suggesting a half-life of the order of magnitude of 0.1 hr at 135°) one-bond O–O homolysis is not unlikely. Thus, another mechanism for the formation of **9** may obtain, viz. formation of phenyl ester **11** from benzene and intermediately formed *N*-pyrazolecarboxyl radicals, followed by (rather rapid) decarboxylation to give **9**.[19] However, this pathway could be excluded, as independently prepared **11** was found to be stable under the experimental conditions for perester thermolysis.

Information as regards the *polar character* of **1** was obtained through the thermal decomposition of **5a** in a mixture of benzene and *p*-dichlorobenzene.[20] From the product ratio 1-(2,5-dichlorophenyl)pyrazole/1-phenylpyrazole (**9**), the partial rate factor for a position in *p*-dichlorobenzene was calculated to be ~0.25.

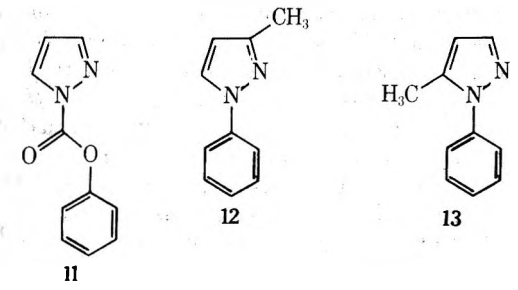
Unfortunately, NMR analysis during decomposition of **5a** in C_6D_6 or in hexachloroacetone at 140° did not reveal any CIDNP effects.

More insight into the electronic structure of *N*-pyrazolyl radicals can be obtained when studying asymmetrically substituted analogs of **1**. If **1** has a σ-type ground state, it either has its unpaired electron localized on N-1, or—more likely—has equal spin densities on N-1 and N-2; for a π-type structure the latter situation also holds. Introduction of asymmetry (by a substituent in the 3 or 5 position) may result in unequal spin densities on both nitrogens in the case of delocalization.

In the first case (localization on N-1), thermolysis of a 3-substituted perester in benzene would result in the 3-substituted 1-phenylpyrazole only; analogously, a 5-substituted derivative would give the isomeric 5-substituted 1-phenylpyrazole. In the second case, that of delocalization, both substrates would give the same result, a mixture of 3 and 5 derivatives in the same ratio.

When a 2% solution of the 3-methyl substituted perester **5b** in benzene was heated for 1 hr at 150°, the products isolated by column chromatography were 3(5)-methylpyrazole (**7b**, 80%), biphenyl (~4%), and both 3-methyl-1-phenylpyrazole (**12**) (Chart III) and 5-methyl-1-phenylpyrazole (**13**), ~10%, in a 4:1 ratio. Essentially the same isomer ratio was found by GLPC analysis of the crude reaction product from thermolysis of **5b** in benzene; moreover, *no C-phenylated pyrazoles could be detected in this fashion*. A control run showed that no mutual isomerization of the *N*-phenylpyrazoles **12** and **13** took place under the experimental conditions of thermolysis.

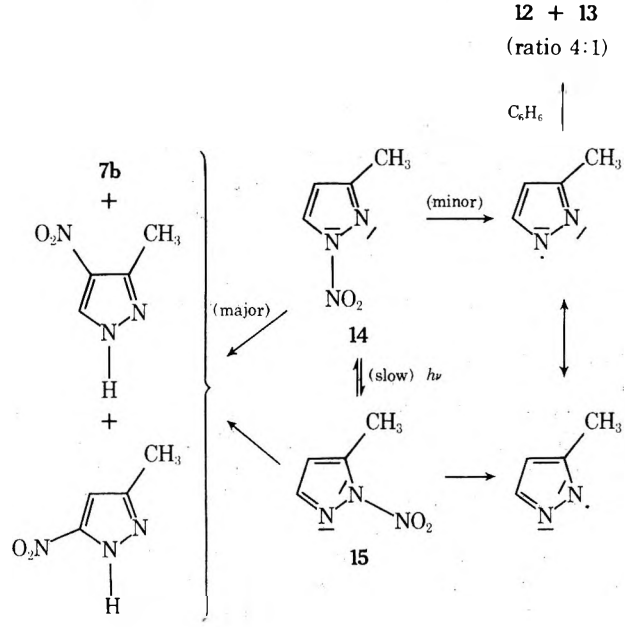
Chart III



11 **12** **13**

In itself, this result on **5b** already points to a delocalization of the unpaired electron in *N*-pyrazolyl radicals; of course, generation of the radical from a 5-methylpyrazole derivative would be of interest. As the synthesis of reasonably pure **8** seemed to be very cumbersome (e.g., synthesis via **7b** and phosgene only gave ≤5% of **8**; vide supra), we considered the alternative pathway of photolyzing the isomeric 3- and 5-methyl-1-nitropyrazoles **14** and **15** (Scheme III), which can easily be obtained pure.[4] Indeed, preliminary experiments involving photolysis of 1-nitropyrazole in benzene showed the formation of both 1-phenylpyrazole (**9**) and biphenyl.[21] Hence, 5% solutions of **14** and **15** in benzene were irradiated with a Philips HP 125 lamp through a copper sulfate filter. The reactions were followed by GLPC. After 4 days, and a conversion of the *N*-nitropyrazoles of ~35%, in both solutions ~0.3 mol % of *N*-phenylpyrazoles was found. Though the yields were fairly low—thwarting accurate analysis—it can be stated that the ratio of isomeric *N*-phenylpyrazoles (**12**:**13**) was essentially the same in all samples, namely 4 ± 1.

Scheme III



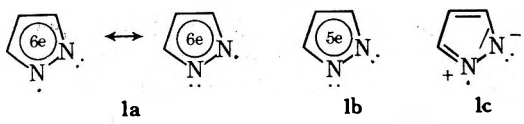
Other observations follow: the formation of **7b** as main reaction product; formation of nitrobenzene and of biphenyl; isomerization of the *N*-nitropyrazoles to *C*-nitropyrazoles (for both *N*-nitropyrazoles in a comparable isomer ratio); some isomerization **14** → **15** and **15** → **14**, respectively, much too slow, however, to account for the production of the two isomeric *N*-phenylpyrazoles **12** and **13** with the same ratio in both experiments.

As mutual isomerization of the *N*-*phenylpyrazoles* **12** and **13** is also very slow compared with their rates of formation (see Experimental Section), it appears that *N*-phenylpyrazoles are formed via the same intermediate. Considering the isomer ratio of 4:1, *which is equal to that obtained via perester decomposition*, this intermediate is most probably (again) the *N*-pyrazolyl radical.

Photolysis of *tert*-butyl 1-pyrazolepercarboxylates in benzene solution appeared to be very inefficient for the formation of *N*-phenylpyrazoles; e.g., irradiation of **5b** for 4 days only yielded ~0.1% of *N*-phenylpyrazoles. The use of a copper sulfate filter increased the yields somewhat, but the concentrations were still too low to permit an accurate analysis of the ratio of **12** and **13** formed.

On the basis of the interpretation given above we may conclude that the unpaired electron in an *N*-pyrazolyl radical is delocalized over at least the two nitrogen atoms. It is not yet possible, however, to say anything definitive about the electronic structure in more detail. The exclusive formation of N-arylated pyrazoles, of course, tallies well with a σ-type structure **1a** (Chart IV). However, it cannot be ex-

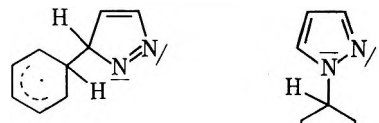
Chart IV



1a **1b** **1c**

cluded that a π-type structure **1b** obtains. A possible selective substitution reaction involving N only might be rationalized on thermodynamic grounds: attack by **1** on benzene via a C atom (exemplified in Scheme IV) must be followed by migration of an H atom, while attack with N directly gives the aromatic pyrazole ring, probably making the latter reaction more favorable. On the other hand, it is known that dialkylamino radicals do not react with benzene,[22] and give addition reactions with a relatively high activation energy;[23] hence we believe that *N*-pyrazolyl radicals are more aryl- (σ)- like.[24,25]

Scheme IV



C-attack N-attack

From its competitive reaction with benzene and *p*-dichlorobenzene, it is seen that **1** has a pronounced electrophilic character. This is as might be expected, the reactive center being an electronegative atom. Moreover, resonance structure **1c** may contribute significantly to the polar properties of **1**, at least when it approaches the transition state involving a localized unpaired electron.

An ESR spectrum of **1** could be conclusive about its electronic structure, but as yet we were unsuccessful in obtaining a signal that can be ascribed to a pyrazolyl radical.[26]

It is clear that more work has to be done on the chemistry of *N*-pyrazolyl and related species like *N*-imidazolyl radicals, in order to elucidate their possible role as reacting intermediates, the possible occurrence of one-electron transfer processes, and their synthetic capabilities.

Experimental Section

General. NMR spectra were recorded on a JEOL-PS 100 or on a JEOL-Minimar 60-MHz instrument; unless otherwise stated, chemical shifts (δ) are expressed in parts per million relative to tetramethylsilane. Ir spectra were recorded on a Unicam SP 1200 or on a Beckman IR-10 spectrophotometer; mass spectra on an AEI-MS 902 apparatus. GLPC analyses were performed on Hewlett-Packard HP 5700 and on Varian Aerograph 1400 instruments, using a 44-m capillary OV-17 and a 2-m 4% OV-17 column, respectively. Elemental analyses were performed by Mr. W. J. Buys, TNO Laboratories of Organic Chemistry, Utrecht, The Netherlands. All melting points were uncorrected. For column chromatographic separations, the short-column technique of Hunt and Rigby[27] was used. Orienting thermolyses were carried out in sealed melting point tubes, inserted in the oil bath of a Büchi melting point apparatus; reaction products were analyzed by TLC and/or GLPC. Irradiations were performed on a cuvette scale; where indicated, a 1-cm copper sulfate (30% $CuSO_4 \cdot 5H_2O$) filter, which transmitted light with $\lambda > 320$ nm, was used.

Materials. Pyrazole (**7a**) and 3(5)-methylpyrazole (**7b**) were prepared by standard procedures; the synthesis of the *N*-nitropyrazoles **14** and **15** has been described in ref 15. The reference pyrazoles were either from the collection of Dr. Habraken, or prepared by standard procedures [e.g., 1-(2,5-dichlorophenyl)pyrazole from 2,5-dichlorophenylhydrazine and 1,1,2-trimethoxy-2-ethoxypropane[28]]. Other reference substances (e.g., isopropenyl methyl ether) were commercial products. *tert*-Butyl hydroperoxide was distilled under reduced pressure before use; dibenzoyl peroxide was recrystallized from chloroform. All other chemicals, being high-grade commercial products, were used as such.

1-Pyrazolecarbonyl Chloride (6a).[29,30] Phosgene was passed through a solution of pyrazole (**7a**, 10 g) in sodium-dried diethyl ether (150 ml) at 0°, until the initially formed white precipitate had disappeared (~2 hr). Dry nitrogen was passed through to remove the excess of phosgene; the solution was filtered and the major part of the solvent evaporated. The acid chloride, a white, crystalline solid, was isolated by filtration (14–18 g). Recrystallization from ether gave mp 53–54.5° (sealed melting point capillary); ir (Nujol) 1775 cm^{-1} (C=O); NMR ($CDCl_3$) δ 8.2 (d, 1, J = 3.0 Hz, 5-H), 7.85 (d, 1, J = 1.5 Hz, 3-H) and 6.55 (m, 1, 4-H).

The presence of an active Cl atom was substantiated by its immediate reaction with silver nitrate solution. The acid chloride appeared to be very reactive toward water and alcohols.

***tert*-Butyl 1-Pyrazolepercarboxylate (5a).** While stirring, solutions of **6a** (14.4 g) and of *tert*-butyl hydroperoxide (9.2 g), each in ~80 ml of sodium-dried ether, were added, slowly and simultaneously, to a cooled solution of pyridine (8.3 g) in ether (~50 ml); the temperature was kept at ca. −5°. The reaction mixture was stirred for 4 hr at room temperature and then filtered. The filtrate was washed successively with dilute hydrochloric acid and sodium carbonate solutions, dried over magnesium sulfate, and concentrated in vacuo, giving ~18 g of a colorless oil. The perester was purified by distillation under reduced pressure: bp 50° (0.10 mm); ir (liquid film) 1790 cm^{-1} (C=O); NMR ($CDCl_3$) δ 8.22 (d, 1, J = 3.0 Hz, 5-H), 7.83 (d, 1, J = 1.5 Hz, 3-H), 6.46 (m, 1, 4-H), and 1.42 [s, 9, $C(CH_3)_3$].

Anal. Calcd for $C_8H_{12}N_2O_3$: C, 52.16; H, 6.57; N, 15.21. Found: C, 51.88; H, 6.58; N, 15.37.

***tert*-Butyl 3-Methyl-1-pyrazolepercarboxylate (5b).** 3-Methyl-1-pyrazolecarbonyl chloride (**6b**) was prepared from 3(5)-methylpyrazole (**7b**) and phosgene according to von Auwers,[15] and was recrystallized from benzene: NMR ($CDCl_3$) δ 8.05 (d, 1, J = 3.0 Hz, 5-H), 6.38 (d, 1, J = 3.0 Hz, 4-H), and 2.39 (s, 3, CH_3).

From this acid chloride and *tert*-butyl hydroperoxide, perester **5b** was prepared as described above for **5a**. The residual colorless oil was distilled under reduced pressure: bp 60° (0.05 mm); ir (liquid film) 1785 cm^{-1} (C=O); NMR ($CDCl_3$) δ 7.99 (d, 1, J = 3.0 Hz, 5-H), 6.23 (d, 1, J = 3.0 Hz, 4-H), 2.26 (s, 3, CH_3), and 1.41 [s, 9, $C(CH_3)_3$]; signals at 7.59 and 2.59 ppm pointed to the presence of ~4% of the 5-methyl isomer **8**.

Anal. Calcd for $C_9H_{14}N_2O_3$: C, 54.53; H, 7.12; N, 14.13. Found: C, 54.58; H, 7.11; N, 14.25.

Thermal Decomposition of 5a in Benzene. A. An ampoule containing a weighed amount (~0.2 g) of **5a** dissolved in a tenfold quantity of benzene was degassed and sealed. The tube was placed in an oven at 135° for 1 hr; a known amount of hexamethyldisiloxane (HMDS) was added to the cooled contents and a quantitative NMR analysis was then made for *tert*-butyl alcohol (1.07 ppm relative to HMDS), acetone (1.47 ppm), toluene (2.00 ppm) and isopropenyl methyl ether (1.65 and 3.10 ppm). The identity of the compounds mentioned was ascertained by adding small amounts of the authentic materials, and by GLPC.

B. Solutions of **5a** in benzene (1 and 10%, respectively) were

thermolyzed in an autoclave under a nitrogen atmosphere. After heating at 135° for at least 1 hr, benzene was carefully removed by distillation; the products were then separated by column chromatography on silica gel (H, according to Stahl), eluting with benzene–ethyl acetate–methanol mixtures of increasing polarity. Collected fractions were compared with reference materials on TLC, concentrated, and investigated further with the aid of NMR and mass spectrometry; in addition, GLPC on a packed OV-17 column was used to test the possible presence of C-phenylated pyrazoles.

Thermal Decomposition of 5a in a Benzene–*p*-Dichlorobenzene Mixture. A solution of 52 mg of perester **5a** in 0.90 g of a 1:10 molar mixture of *p*-dichlorobenzene and benzene was heated in a sealed tube for 1.5 hr at 135°. The formation of 1-(2,5-dichlorophenyl)pyrazole and of 1-phenylpyrazole (**9**) was demonstrated, and their ratio was determined by GLPC analysis on a packed OV-17 column.

Phenylation of Pyrazole (7a) with the Aid of Dibenzoyl Peroxide. An ampoule containing a mixture of dibenzoyl peroxide (0.25 mmol), **7a** (1.13 mmol), and benzene (11.3 mmol) was degassed, sealed, and heated (0.3 hr at 135°). GLPC analysis on a packed OV-17 column revealed the presence of biphenyl (~0.4 mol/mol dibenzoyl peroxide), 3(5)-phenylpyrazole (0.025 mol/mol biphenyl), and 1-phenylpyrazole (**9**, 0.010 mol/mol biphenyl), in addition to several other products. As the presence of 4-phenylpyrazole could not be detected, the partial rate factor given for the 4 position must be considered as an upper limit.

Phenyl 1-Pyrazolecarboxylate (11). Preparation and Thermal Stability. Pyrazole (**7a**, 2.3 g) was slowly added to 5.3 g of phenyl chloroformate; the mixture was then heated at 110° for 1.5 hr, diluted with water, and neutralized with sodium carbonate, and the phenyl ester was isolated via extraction with ether, crude yield 5.3 g (83%). Crystallization from hexane gave pure **11**: white crystals; mp 47–48.5°; ir (KBr) 1780 cm^{-1} (C=O); NMR ($CDCl_3$) δ 8.5 (d, 1, J = 3 Hz, 5-H), 8.0 (d, 1, J = 1.5 Hz, 3-H), 7.5 (m, 5, C_6H_5), and 6.6 (m, 1, 4-H).

Anal. Calcd for $C_{10}H_8N_2O_2$: C, 63.82; H, 4.29; N, 14.89. Found: C, 63.89; H, 4.37; N, 14.91.

This phenyl ester appeared to be stable upon heating at 200° for 5 min (TLC analysis).

Thermal Decomposition of *tert*-Butyl 3-Methyl-1-pyrazolepercarboxylate (5b) in Benzene. A. A solution of 3.0 g of **5b** in 150 ml of benzene was heated in an autoclave at 150° for 1 hr. The resulting solution was carefully concentrated and the reaction products were separated by column chromatography as described for the thermolysis of **5a**. The fractions were analyzed with the aid of TLC and NMR spectroscopy. In this way, the *N*-phenylpyrazoles **12** and **13** (eluted in that order) were obtained in a reasonably pure form.

B. In a sealed tube, a 2.4% solution of **5b** in benzene (containing 0.01% of *p*-di-*tert*-butylbenzene as internal standard) was heated at 150° for 1 hr; the reaction products were analyzed by GLPC. A capillary OV-17 column was used for the separation of the two *N*-phenylpyrazoles **12** and **13**; their ratio was calculated to be 5:1. In addition, a packed OV-17 column was used in searching for C-phenylated pyrazoles: no detectable amounts of 3(5)-methyl-4-phenyl- or of 3(5)-methyl-5(3)-phenylpyrazole were present.

C. Control Experiment. A benzene solution of a mixture of **12** and **13** was heated in a sealed tube at 150° for 1 hr; NMR analysis showed that the composition of the mixture remained unchanged.

Photolysis of the *N*-Nitropyrazoles 14 and 15 in Benzene Solution. A. In 1.0-cm quartz cuvettes, solutions of 3-methyl-1-nitropyrazole (**14**) and of 5-methyl-1-nitropyrazole (**15**), respectively (both 5% in benzene, and containing 0.01% of *p*-di-*tert*-butylbenzene as internal standard), were irradiated through a copper sulfate filter employing a 175-W Philips HP lamp. Samples were taken at 6, 24, and 96 hr, and analyzed by GLPC using a capillary OV-17 column. In addition, a packed OV-17 column was used for the analysis of C-nitropyrazoles; in order to prevent thermal isomerization of the residual *N*-nitropyrazoles, the injection port had to be kept at ≤130°.

B. Control Experiment. A benzene solution of a mixture of the *N*-phenylpyrazoles **12** and **13** was irradiated (copper sulfate filter) for 96 hr; NMR analysis showed that their molar ratio had changed from 0.44 to 0.74.

Photolysis of the *tert*-Butyl Peresters 5a and 5b in Benzene Solution. A. Photolysis of the unsubstituted perester **5a** was studied qualitatively by following the reaction by TLC: when a 2.5% solution of **5a** in benzene was irradiated, small amounts of 1-phenylpyrazole (**9**) and of biphenyl could be detected. After 3 days a considerable amount of starting material **5a** was still present.

B. Photolysis of a 2.4% solution of the 3-methyl substituted perester **5b** in benzene (containing 0.01% of *p*-di-*tert*-butylbenzene as internal standard) was performed both with and without a copper sulfate filter. After 96 hr, the resulting solutions were analyzed by GLPC on a capillary OV-17 column. In either case biphenyl was found and, in only small quantities, the isomeric *N*-phenylpyrazoles **12** and **13** (molar ratios ca. 9:1).

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Registry No.—**5a**, 53881-36-0; **5b**, 53881-37-1; **6a**, 53355-55-8; **6b**, 53881-38-2; **7a**, 288-13-1; **7b**, 1453-58-3; **9**, 1126-00-7; **11**, 53881-39-3; **12**, 1128-54-7; **13**, 6831-91-0; **14**, 31163-84-5; **15**, 31163-85-6; phosgene, 75-44-5; *tert*-butyl hydroperoxide, 75-91-2; phenyl chloroformate, 1885-14-9; 1-(2,5-dichlorophenyl)pyrazole, -53881-40-6.

References and Notes

(1) This research was supported by the Netherlands Foundation for Chemical Research (SON) with financial aid from the Netherlands Organization for the Advancement of Pure Research (ZWO).
(2) P. H. Kasai, E. Hedaya, and E. B. Whipple, *J. Am. Chem. Soc.*, **91**, 4364 (1969).
(3) S. F. Nelsen in "Free Radicals," Vol. II, J. K. Kochi, Ed., Wiley, New York, N.Y., 1973, p 527.
(4) (a) J. W. A. M. Janssen and C. L. Habraken, *J. Org. Chem.*, **36**, 3081 (1971); (b) J. W. A. M. Janssen, H. J. Koeners, C. G. Kruse, and C. L. Habraken, ibid., **38**, 1777 (1973).
(5) The unspecific ESR signal, recorded when photolyzing an aqueous solution of pyrazole with hematoporphyrin and phosphate buffer [S. Tu and J. H. Wang, *Biochemistry*, 9, 4505 (1970)], cannot, in our view, be considered as evidence for the formation of **1**.
(6) G. Fukata, Y. Kawazoe, and T. Taguchi, *Tetrahedron Lett.*, 1199 (1973).
(7) Professor K. Lempert, personal communication.
(8) W. Brosen, H. Kurreck, D. Rennoch, and J. Reusch, *Tetrahedron*, **29**, 3959 (1973).
(9) R. D. Allendoerfer and A. S. Pollock, *Mol. Phys.*, **22**, 661 (1971), and references cited therein.
(10) E. M. Evleth, P. M. Horowitz, and T. S. Lee, *J. Am. Chem. Soc.*, **95**, 7948 (1973).
(11) A. Samuni and P. Neta, *J. Phys. Chem.*, **77**, 1629 (1973).
(12) Neglecting configuration interaction, both **1** and **3** are calculated to have a $^2B_1$-π-type ground state, albeit with rather small energy differences between the "best" π and σ states (e.g., 0.023 au in a RHF calculation on **1**). More detailed results, including a study of asymmetric geometries, will be published separately (J. J. C. Mulder and K. van der Meer).
(13) Attempts were made to prepare these compounds via the carbonyl chloride **6a**. However, e.g., reaction of **6a** with hydrogen peroxide–urea complex[14] led to 4-chloropyrazole, while reaction with perbenzoic acid led to 1-benzoylpyrazole, 1-benzoyl-4-chloropyrazole, and 4-chloropyrazole.
(14) C.-S. Lu, E. W. Hughes, and P. A. Giguère, *J. Am. Chem. Soc.*, **63**, 1507 (1941).
(15) K. von Auwers and W. Daniel, *J. Prakt. Chem.*, **110**, 235 (1925).
(16) Thermolysis of the comparable perester *tert*-butyl *N*-succinimidepercarboxylate proceeds predominantly via a Criegee rearrangement: (a) E. Hedaya, R. L. Hinman, V. Schomaker, S. Theodoropulos, and L. M. Kyle, *J. Am. Chem. Soc.*, **89**, 4875 (1967); (b) T. Koenig and W. Brewer, ibid., **86**, 2728 (1964).
(17) J. H. T. Brook and W. Snedden, *Tetrahedron*, **20**, 1043 (1964).
(18) Assuming that only the C-3 position in pyrazole is involved, in line with the data on 1-methylpyrazole, its phenylation resulting in the product ratio 3-:4-:5- = 94:1:5: B. M. Lynch and H. S. Chan, *Tetrahedron Lett.*, 617 (1964).
(19) Decarboxylation of aliphatic 1-pyrazolecarboxylic esters has been observed by von Auwers.[15] After the present manuscript had been finished, a publication concerning the mechanism of this thermally induced reaction appeared. Probably an intermolecular nucleophilic substitution by pyrazole anions is involved; hence a fast decarboxylation of *phenyl* ester **11** is very unlikely. J. J. Wilczynski and H. W. Johnson, *J. Org. Chem.*, **39**, 1909 (1974).
(20) Thermal decomposition of **5a** in nitrobenzene or in a benzene–nitrobenzene mixture proceeded predominantly via nonradical pathways.
(21) Other products found were the denitrated pyrazole **7a** and the isomerization products 4-nitro- and 3(5)-nitropyrazole. The photochemistry of *N*-nitropyrazole in other solvents (e.g., methanol) is also investigated in these laboratories. Here, isomerization to 4- and 3(5)-nitropyrazole also occurs: J. Cornelisse et al., unpublished observations. This isomerization, which also takes place on photolyzing 3- and 5-methyl substituted *N*-nitropyrazoles (vide infra), can be regarded as a counterpart of the thermally induced *N*-nitropyrazole rearrangement. The latter reaction most probably involves a sigmatropic migration of NO_2;[4b] the mechanism of the novel photochemical rearrangement is not clear as yet.
(22) D. Mackay and W. A. Waters, *J. Chem. Soc. C*, 813 (1966).
(23) S. Shih, R. J. Buenker, S. D. Peyerimhoff, and C. J. Michejda, *J. Am. Chem. Soc.*, **94**, 7620 (1972).

(24) Another nitrogen-centered free radical that reacts with benzene is the *N*-succinimidyl radical;[25] Hedaya et al. showed that this radical most probably has a σ-type electronic ground state.[16a]
(25) D. R. Howton, *J. Am. Chem. Soc.*, **69**, 2060 (1947).
(26) When a frozen solution of **5a** in methylcyclohexane (77 K) was irradiated in the cavity of an ESR apparatus, only signals of methyl radicals and (probably) *t*-BuOO · radicals were observed.
(27) B. J. Hunt and W. Rigby, *Chem. Ind. (London)*, 1868 (1967).
(28) J. D. Kendall and G. F. Duffin, British Patent 797,144 (1958); *Chem. Abstr.*, **53**, 4983 (1959).
(29) Very recently, the synthesis of 1-pyrazolecarbonyl chloride has also been described by Peterson et al.;[30] these authors reported mp 52–54°, and pointed out the extremely lachrymatory character of this compound, a property also observed by us.
(30) L. K. Peterson, E. Kiehlmann, A. R. Sanger, and K. I. Thè, *Can. J. Chem.*, **52**, 2367 (1974).

Ion-Pair Return Associated with Solvolysis of 1,2-Dimethyl-*exo*-2-norbornyl *p*-Nitrobenzoate-^{18}O[1]

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Solvolysis of 1,2-dimethyl-*exo*-2-norbornyl *p*-nitrobenzoate (I-OPNB) in 90% aqueous acetone involves exclusive alkyl–oxygen cleavage and is accompanied by ion-pair return which results in racemization of optically active I-OPNB and randomization of the carboxyl oxygen atoms of ^{18}O-labeled I-OPNB. In this system the carbonium ion is not symmetrical and k_{rac} corresponds to an upper limit of 37% of the total return from product-forming intermediates. The relative rates of racemization and carboxyl oxygen equilibration indicate that k_{eq} corresponds to ~20% of the total return.

Several methods for detecting ion-pair return associated with SN1 solvolytic reactions have been reported. These include salt effects,[2,3] isomerization of the cation[2b,4,5] or anion,[6] racemization of the unsolvolyzed substrate,[2b,5,7] randomization of carboxyl or sulfoxyl oxygen atoms,[5,8] and secondary deuterium isotope effects.[9] To determine the amount of return requires an independent measure of (a) the total rate of ionization or (b) the rate of re-formation of substrate by ion-pair return.

With optically active substrates that give symmetrical (bridged[2b,8b] or allylic[7,10]) carbonium ions, the rate of loss of optical activity (eq 1) corresponds to the total rate of ionization providing that the ion pair, as well as the unperturbed cation, is symmetrical. With systems that do not isomerize, ion-pair return does not disturb the rate of solvolysis (eq 2) and the rate of return, which corresponds to rate of racemization (eq 3), is obtained indirectly as the difference between rates of ionization (k_α) and solvolysis (k_t), i.e., $k_{rac} = k_\alpha - k_t$.[10] Alternatively, the rate of racemization can be obtained directly by isolating samples of unsolvolyzed substrate throughout the reaction and determining k_{rac} from the rotations.[8a]

Another direct method for measuring return is determining the rate of randomization of carboxyl or sulfonate oxygen atoms (k_{eq}) starting with discretely ^{18}O-labeled *p*-nitrobenzoate[8a,10] (eq 4) or arylsulfonate.[8b] Providing the oxygen atoms in the anion are equivalent in the ion-pair intermediate, k_{eq} corresponds to total return. The distinguishing feature of this method is that it is applicable to achiral as well as chiral nonrearranging systems.

$$(+)\text{-RX} \xrightarrow{k_\alpha} \text{inactive products} \quad (1)$$

$$\text{R–X} \xrightarrow{k_t} \text{solvolysis products} \quad (2)$$

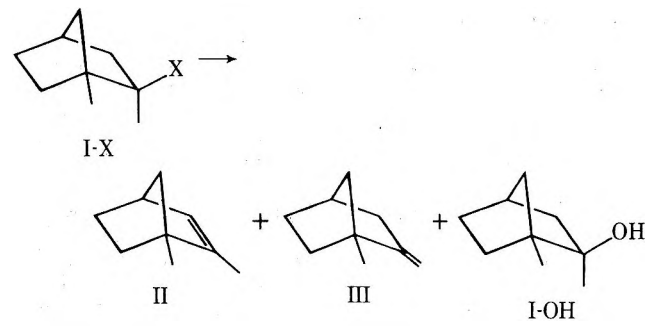
$$(+)\text{-RX} \xrightarrow{k_{rac}} (\pm)\text{-RX} \quad (3)$$

$$\text{R—}^{18}\text{OCOAr} \xrightarrow{k_{eq}} \text{R—}^{18}\text{OC}^{18}\text{OAr} \quad (4)$$

Since the oxygen atoms in the intermediate are not always equivalent,[12] k_{eq} is a lower limit for return—excess rebonding of the original oxygen and carbon atoms is undetected. Similarly, k_α is a lower limit for ionization (or k_{rac} for return) because even though the unperturbed bridged or allylic cation is symmetrical the ion pair may not be. Indeed, there is evidence that this is the case in some allylic systems.[13]

To obtain information regarding the fraction of return detected by oxygen equilibration we have compared k_{eq} with return measured by independent methods in allylic systems and systems involving symmetrical bridged cations.[8b] For *p*-nitrobenzoates the amount of equilibration associated with return ranges from nil for a case involving rearrangement to a strained carbonium ion[14] to partial for several allylic systems[10] and one rearranging system in which the anion migrates a considerable distance,[15] and evidently to complete in systems that give relatively stable (delocalized) carbonium ions.[5,10b,12]

We now report a comparison of k_{eq} with an independent measure of a lower limit of return for solvolysis of 1,2-dimethyl-*exo*-2-norbornyl *p*-nitrobenzoate (I-OPNB), a system which does not involve a symmetrical bridged ion but one in which ion-pair return results in racemization of the unsolvolyzed ester.[11]



The pertinent rate constants for solvolysis of I-OPNB in 90% aqueous acetone at 78° are shown in Table I. The titrimetric rate constants (k_t) were steady up to 80% solvolysis, which shows that the structure of the substrate is preserved throughout the reaction. A control experiment with ether-^{18}O labeled I-OPNB showed that solvolysis involves exclusive alkyl–oxygen cleavage.

For the polarimetric experiments the solvent contained a 50% excess of 2,6-lutidine to neutralize the acid produced

Table I
Rate Constants for Solvolysis of 1,2-Dimethyl-*exo*-2-norbornyl *p*-Nitrobenzoate in 90% (v/v) Aqueous Acetone at 78.45°

Rate constant	10^6 k, sec^{-1} [a]
k_α	17.2 ± 0.1
k_t	12.4 ± 0.1
k_{rac}	5.2 ± 0.4
k_{eq}	2.6 ± 0.3
k_{exc} [b]	6.0[b,c]

[a] Average (and average deviations) of two to six independent experiments. [b] Second-order rate constant, 10^6 l. M^{-1} sec^{-1}. [c] Average value for one kinetic experiment.

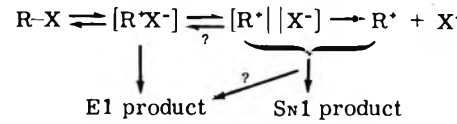
by solvolysis. Under these conditions the products are optically stable—final rotations and product distributions remained constant for periods of several solvolytic half-lives. Since product distributions, final rotations, and k_α are independent of the 2,6-lutidine concentration over the range 0.08–0.6 *M*, it appears that the lutidine has no important effect on the solvolysis. Under these conditions solvolysis gives 14% I-OH, 50% 1,2-dimethyl-2-norbornene (II), and 36% 1-methyl-2-methylenenorborene (III). As can be seen in Table I, $k_\alpha > k_t$, which means that ion-pair return results in racemization of the unsolvolyzed ester.

The rate of racemization (eq 3) was determined directly from rotations of isolated samples of unsolvolyzed ester. Control experiments showed that isolation of active samples did not alter the optical purity. It is noteworthy that k_{rac} obtained directly is in good agreement with $k_\alpha - k_t$. This is further evidence that 2,6-lutidine has no important effect on k_α.

The rate constant for equilibration of the carboxyl oxygen atoms (k_{eq}) was determined with carbonyl-^{18}O labeled I-OPNB. Because of the high k_t/k_{eq} ratio this reaction could only be followed to ~22% reaction (75% solvolysis). The value in Table I is the average of three independent determinations.

The second-order rate constant for exchange (k_{exc}) between I-OPNB and *p*-nitrobenzoic acid was determined by the method used earlier.[16] Only 0.14% exchange resulted when a solution of 0.007 *M* I-OPNB and 0.0035 *M* *p*-nitrobenzoic acid-^{14}C was heated for one solvolytic half-life. This shows that exchange between unsolvolyzed ester and acid produced by solvolysis is insignificant and establishes that reactions 3 and 4 are intramolecular.

As reported earlier,[11] optically active I-OPNB gives active products; the E1 product (III) is formed with ~63% and the SN1 product (I-OH) with ~9% retention of configuration. The other E1 product (II) is also active; however, the optical purity has not been determined. The formation of active products shows that ionization gives the asymmetric classical ion instead of a symmetrical bridged ion. The partial loss of optical configuration evidently results from interconversion of enantiomeric classical ions (Wagner–Meerwein rearrangement) in competition with the product-forming steps. The different optical purities of the E1 and SN1 products shows that they are derived from different intermediates. The interpretation proposed earlier[11,17] is summarized in the accompanying scheme. This suggests that most, or all, of the E1 product is derived from the initially formed intimate ion pair and the SN1 product is formed from a solvent-separated ion pair or the dissociated carbonium ion. The additional dissociation required for substitution is accompanied by additional racemization. The absence of exchange suggests that there is no external ion-pair return and establishes that there is no external return. This is not surprising because the equilibrium constant for protonation of the basic anion ($1/K_A$) is very large and consequently the anion concentration remains low throughout the solvolysis.



The rate of carboxyl oxygen equilibration (eq 4) is about half that of racemization (eq 3) and thus corresponds to the rate of interconversion of enantiomers. This is apparently a coincidence because we cannot imagine a plausible process (consistent with the principle of microscopic reversibility) that would give complete equilibration only when one enantiomer is converted to the other.[18]

In this system racemization detects more return than oxygen equilibration; however, k_{rac} does not correspond to total return. Clearly, substrate re-formed by ion-pair return must be at least as optically active as the E1 product (~63%). This is a lower limit because some E1 product may be formed from intermediates that are more racemic than the intimate ion pair. This means that k_{rac} corresponds to an upper limit of 37% of the total return. Thus, k_{eq} corresponds to an upper limit of 20% of the return. Or, to put it another way, at least 90% of the re-formed substrate has the original labeling pattern and 10% has inverse labeling. From this we conclude that in trialkylcarbinyl *p*-nitrobenzoates, oxygen equilibration correspond to only a fraction of the total return from product-forming intermediates.

Experimental Section

Oxygen-18 contents and distributions were determined as described earlier.[10,12] The solvent, 90% aqueous acetone (v/v), was prepared as described earlier.[16a]

Compounds. The samples of racemic I-OH, mp 104–106°, (−)-I-OH, mp 104–105°, $[\alpha]^{30}D$ −22.6° (*c* 7.3, $CHCl_3$), and (+)-I-OPNB, mp 143–144°, $[\alpha]^{30}D$ 37.3° (*c* 5.5, $CHCl_3$), used in this work were described earlier.[20] Less active samples of (+)-I-OPNB and samples of (−)-I-OPNB were also used. Racemic I-OPNB, mp 128–129.5° (lit. mp 132.5–133°),[21] was prepared by the method[20] used to prepare optically active I-OPNB.

I-OPNB-*carbonyl*-^{18}O, mp 127–128.5°, 3.704% excess ^{18}O, was prepared from I-OH and *p*-nitrobenzoyl-*carbonyl*-^{18}O chloride[19] in the usual manner[20] and obtained in 42% yield after purification by several recrystallizations from ether–pentane. A sample of this labeled ester was reconverted to I-OH by reduction with lithium aluminum hydride.[19] The resulting I-OH contained only 0.034% excess ^{18}O, which shows that >99% of the label was in the carbonyl position of the I-OPNB.

I-OPNB-*ether*-^{18}O was prepared as follows. A solution of 3.9 g of I-OH in a mixture of 102 ml of purified dioxane containing 25 ml of ^{18}O-enriched water (1.5% excess ^{18}O) and 4.96 g of 60% perchloric acid was warmed to 30° for 20 hr. Under these conditions (i.e., $[HClO_4]$ = 0.23 *M*, [I-OH] = 0.22 *M*), the half-life for oxygen exchange is about 2 hr and exchange is about 10^3 times faster than exo → endo isomerization.[22] The solution was cooled, neutralized, diluted with 100 ml of water, and extracted with 200 ml of pentane. The pentane extracts were combined, shaken with 10% aqueous sodium carbonate, and dried. The resulting extract was concentrated to near dryness and the residue was purified by GC (20% KOH and 1% Carbowax 20M on firebrick). This preparation gave 2.3 g (59% recovery) of ^{18}O-labeled I-OH. Another preparation, using the same amounts but with more enriched ^{18}O water, gave 2.6 g (67%) of ^{18}O-labeled I-OH. Sublimation of the combined preparations gave 4.35 g (56%) of ^{18}O-labeled I-OH, mp 109–111°, 1.590% excess ^{18}O.

The above labeled I-OH was converted[20] to **I-OPNB-*ether*-^{18}O** in 60% yield, mp 130–131°, 1.691% excess ^{18}O.[23]

Kinetic Experiments. A. Titrimetric Rates. These reactions were followed as described earlier.[10,12] Rate constants (k_t) were independent of initial concentration over the range 0.026–0.07 *M*.

B. Polarimetric Rates. The polarimetric rate constants (k_α) were determined as described earlier.[5] In these experiments the I-

OPNB concentration varied from 0.06 to 0.12 *M* and in all cases 50% excess 2,6-lutidine was present. The change in rotation was at least 0.7° and individual readings were obtained with a precision of ±0.002°. Good first-order behavior was observed and rate constants determined from rotations for 589 and 436 nm were indistinguishable. Over the indicated concentration range 50% excess 2,6-lutidine has no effect on the observed rate of change of rotation.

That the presence of the lutidine does not affect the product distribution and that the initially formed products are stable under these conditions was established as follows. 2,6-Lutidine was added to four samples of a 0.067 *M* solution of (+)-I-OPNB, $[\alpha]^{25}D$ +27.14° (*c* 5.6, $CHCl_3$), in 90% acetone so that the final lutidine concentrations were 0.08, 0.14, 0.28, and 0.56 *M*. After heating for 8 half-lives for solvolysis (12 hr), the observed rotations of the four solutions varied only 0.007° (from 0.113° to 0.120°). Capillary GC showed that the product distributions were the same for the four samples. It was also shown that a synthetic mixture of optically active II, III, and I-OH in 90% acetone containing 0.07 *M* *p*-nitrobenzoic acid and 0.14 *M* 2,6-lutidine does not undergo change in rotation or composition when heated for a period corresponding to 8 half-lives for solvolysis (k_t).

C. Rates of Racemization. The rate constant for racemization of the unsolvolyzed I-OPNB (k_{rac}) during solvolysis can be determined from the constants for solvolysis (k_t) and mutarotation (k_α), i.e., $k_{rac} = k_\alpha - k_t$.[10] In the present work the rate of racemization was determined directly from rotations of isolated samples of unsolvolyzed ester.[8a] In this case, unlike for the polarimetric rates, 2,6-lutidine was not present. In a typical experiment 7-ml portions of 0.046 *M* (−)-I-OPNB, $[\alpha]^{25}D$ −11.35° (*c* 10, $CHCl_3$), in 90% acetone were sealed in ampoules that had been previously flushed with nitrogen. The ampoules were placed in a thermostat and quenched at appropriate times by chilling in ice water. Each ampoule was treated as follows. The contents were transferred to a 50-ml flask and neutralized with 0.03 *M* sodium hydroxide and the flask was attached to a vacuum line (10^{-5} mm) for 24 hr. The solid residue was extracted with 10 ml of dry ether and the filtered extract was concentrated to dryness under reduced pressure (10^{-2} mm) to remove all traces of I-OH, II, and III. The residue, pure I-OPNB, was transferred to a tared 1-ml volumetric flask, weighed, and diluted to exactly 1 ml with chloroform. The chloroform solution was transferred to a 1-dm microcell and rotations were determined at 40° and 436 nm. The rate constant (k_{rac}) was calculated in the usual way from the rotations of the samples. The value of k_{rac} in the table is the average of four independent experiments in which initial I-OPNB concentrations varied from 0.046 to 0.072 *M*. The initial rotation was at least 1° and the reaction was followed to about 25% racemization, which corresponds to >50% solvolysis.

That the isolation procedure does not alter the optical purity of the unsolvolyzed ester was established as follows. Racemic I-OPNB was completely solvolyzed (16 half-lives) in 90% acetone. A solution of (−)-I-OPNB in 90% acetone was prepared and mixed with the above solvolysis mixture to give solutions with (−)-I-OPNB concentrations corresponding to 0, 25, 50, and 75% solvolysis. The (−)-I-OPNB was isolated from the racemic solvolysis products as described above and the specific rotations of the four samples of recovered (−)-I-OPNB were $[\alpha]^{25}_{436}$ −25.97, −26.15, −25.99, and −26.12°. This shows that the isolation and separation gives recovered I-OPNB without alteration of optical activity.

D. Rates of Carboxyl-Oxygen Equilibration. The equilibration rate constant (k_{eq}) was determined as described earlier.[10,12,16a] The samples of unsolvolyzed ester were isolated as described above. The residual recovered I-OPNB (~1 g) was converted to about 150 mg of I-OH, which was purified by two sublimations, and the ^{18}O content of the resulting I-OH[23] was determined in the usual manner.[12,19] The rate constant for equilibration (k_{eq}) was calculated as described earlier.[10,12,16a]

That isolation of the unsolvolyzed ^{18}O-labeled I-OPNB does not alter the ^{18}O content was established as follows. Unlabeled I-OPNB was solvolyzed completely (10 half-lives) and to this solution was added a solution containing an equal amount of I-OPNB-*carbonyl*-^{18}O, 3.704% excess ^{18}O. This corresponds to 50% solvolysis. The I-OPNB isolated as described above contained 3.684% excess ^{18}O.

The ^{18}O content of the unsolvolyzed labeled I-OPNB after 75% solvolysis was 3.638%. This shows that there is no loss of label, or enrichment due to an isotope effect,[10b] during solvolysis.

E. Rates of Exchange. A 25-ml solution of 0.0069 *M* I-OPNB and 0.0035 *M* of ^{14}C-labeled *p*-nitrobenzoic acid in 90% acetone was placed in a 78.45° thermostat for 16 hr, which corresponds to 50% solvolysis. The unreacted I-OPNB was isolated as described above. The specific activities (dpm/mmol) for the ^{14}C-labeled acid, recovered I-OPNB, and original I-OPNB were 111,500, 584, and 448. From these data the rate constant for exchange (k_{exc}) and percentage exchange at any stage of the reaction can be determined as described earlier.[16a]

Control Experiments Demonstrating Alkyl–Oxygen Cleavage. Solvolysis of optically active I-OPNB in 90% acetone gives I-OH with 9% retention of optical configuration.[11] That the excess retention in the SN1 product does not result from acyl oxygen cleavage was established by the following experiments.

A 0.07 *M* solution of the above I-OPNB-*ether*-^{18}O and 0.1 *M* 2,6-lutidine in 90% acetone was placed in a 100° thermostat for 10 solvolytic half-lives. The resulting I-OH was isolated by extraction with pentane, concentration of the dried ($MgSO_4$) pentane extract, and separation from other volatile products by preparative GC (10-ft column packed with 20% KOH and 1% Carbowax M-40 on firebrick 30/60 at 80°). The isolated alcohol was sublimed four times, the last time from powdered potassium hydroxide. Capillary GC showed the product to be 99% pure. The observed ^{18}O content was 0.014% excess ^{18}O. The ^{18}O content would be 0.11% excess ^{18}O if the excess retention of optical configuration resulted from acyl–oxygen cleavage.

In another experiment 2.4 g of unlabeled I-OPNB was solvolyzed under the above conditions in the presence of 11.4 mg of ^{18}O-labeled I-OH, 1.59% excess ^{18}O. The added labeled I-OH corresponds to 9.2 ± 0.7% of the total I-OH after complete solvolysis and the expected ^{18}O content of the isolated alcohol is 0.15 ± 0.01 providing that there is no loss of ^{18}O during solvolysis or the subsequent isolation and purification. The observed ^{18}O content of the I-OH isolated and purified as above (44 mg) was 0.132% excess ^{18}O. This shows that the loss of ^{18}O from the initially formed I-OH during solvolysis, isolation, and purification is negligible.

Registry No.—I-OPNB, 13351-32-1; (+)-I-OPNB, 18366-97-7; (−)-I-OPNB, 53993-65-0; I-OPNB-*ether*-^{18}O, 53993-66-1.

References and Notes

(1) This work was supported by the National Institutes of Health (GM 14134), the National Science Foundation (GP-21116X), and the Research Council of Croatia.
(2) (a) S. Winstein et al., *J. Am. Chem. Soc.*, **80**, 459 (1958), and earlier papers; (b) S. Winstein, B. Appel, R. Baker, and A. Diaz, *Chem. Soc., Spec. Publ.*, **No. 19**, 109 (1965).
(3) R. A. Sneen, *Acc. Chem. Res.*, **6**, 46 (1973).
(4) A. F. Diaz and S. Winstein, *J. Am. Chem. Soc.*, **91**, 4300 (1969); I. L. Reich, A. F. Diaz, and S. Winstein, ibid., **94**, 2256 (1972).
(5) H. L. Goering, G. S. Koermer, and E. C. Linsay, *J. Am. Chem. Soc.*, **93**, 1230 (1971).
(6) A. Fava, "The Chemistry of Sulfur Compounds", Vol. II, N. Kharasch and C. Meyers, Ed., Pergamon Press, Oxford, 1966, p 73; L. A. Spurlock and T. E. Peaks, *Mech. React. Sulfur Compd.*, **3**, 161 (1968); S. G. Smith and J. P. Petrovich, *J. Org. Chem.*, **30**, 2882 (1965).
(7) H. L. Goering, *Rec. Chem. Prog.*, **21**, 109 (1960).
(8) (a) H. L. Goering and H. Hopf, *J. Am. Chem. Soc.*, **93**, 1224 (1971); (b) H. L. Goering and R. W. Thies, ibid., **9**, 2968, 2967 (1968).
(9) K. Humski, V. Sendijarević, and V. J. Shiner, Jr., *J. Am. Chem. Soc.*, **95**, 7722 (1973).
(10) (a) H. L. Goering, M. M. Pombo, and K. D. McMichael, *J. Am. Chem. Soc.*, **85**, 965 (1963); (b) H. L. Goering, J. T. Doi, and K. D. McMichael, ibid., **86**, 1951 (1964).
(11) H. L. Goering and K. Humski, *J. Am. Chem. Soc.*, **90**, 6213 (1968).
(12) H. L. Goering and E. C. Linsay, *J. Am. Chem. Soc.*, **91**, 7435 (1969).
(13) H. L. Goering and J. T. Doi, *J. Am. Chem. Soc.*, **82**, 5850 (1960); R. P. Anderson, Ph.D. Thesis, University of Wisconsin, Madison, Wisconsin, 1966.
(14) W. G. Dauben and J. L. Chitwood, *J. Org. Chem.*, **34**, 726 (1969).
(15) H. L. Goering and R. F. Myers, *J. Am. Chem. Soc.*, **91**, 3386 (1969).
(16) (a) H. L. Goering and J. F. Levy, *J. Am. Chem. Soc.*, **84**, 3853 (1962); **86**, 120 (1964); (b) H. L. Goering and M. J. Degani, ibid., **91**, 4506 (1969).
(17) H. L. Goering and J. V. Clevenger, *J. Am. Chem. Soc.*, **94**, 1010 (1972).
(18) Formation of the enantiomer with inverse labeling, i.e., (*d*)-ROC^{18}OAr ⇄ (*l*)-R^{18}OCOAr, would result in $k_{rac} = k_{exc}$.
(19) H. L. Goering and M. M. Pombo, *J. Am. Chem. Soc.*, **82**, 2515 (1960).
(20) H. L. Goering, C. Brown, S. Chang, J. V. Clevenger, and K. Humski, *J. Org. Chem.*, **34**, 624 (1969).
(21) H. Toivonen, *Suom. Kemistil. B*, **33**, 66 (1960).
(22) H. L. Goering, C. Brown, and C. Schewene, *J. Am. Chem. Soc.*, **90**, 6214 (1968).
(23) It should be noted that the apparent ^{18}O content of I-OPNB is 5.7% larger than that of the I-OH from which it was derived. As noted earlier (footnote 13, ref 10), different derivatives with the same ^{18}O content often give different apparent ^{18}O contents. However, for each derivative the apparent ^{18}O contents are reproducible. For this reason, to determine accurate relative ^{18}O contents (such as required for kinetic experiments), the same derivative should be used for all determinations.

The Synthetic Utility and Mechanism of the Reductive Deoxygenation of α,β-Unsaturated p-Tosylhydrazones with Sodium Cyanoborohydride

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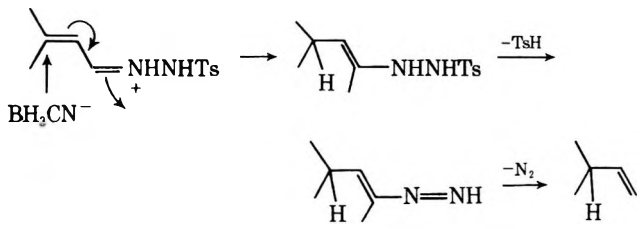
The combination of sodium cyanoborohydride in acidic dimethylformamide–sulfolane provides an effective and convenient system for the reduction of α,β-unsaturated carbonyl tosylhydrazones specifically to the corresponding alkenes with migration of the double bond most probably via a 1,5-sigmatropic rearrangement of an intermediate diazene. Furthermore, the reduction proceeds stereoselectively to furnish the *E* geometric isomer as the predominant product. Applications include (a) conversion of endocyclic to exocyclic double bonds; (b) transformation of alkenes which are conjugated to aromatic rings to unconjugated isomers; (c) deconjugation of certain 1,3-diene systems to 1,4-dienes; (d) synthesis of (*E*)-alkenes. Cyclohexenones and multiply conjugated systems are less successful, giving primarily saturated hydrocarbons in the former case and isomer mixtures in the latter.

During a recent exploration of the reductive deoxygenation of carbonyl tosylhydrazones with $NaBH_3CN$, we observed that α,β-unsaturated systems cleanly afforded alkenes resulting from migration of the double bond from the α,β position to the site formerly occupied by the carbonyl, even in the event that such a migration removed the double bond from conjugation with an aromatic ring.[2] The potential utility of this procedure prompted the present, more thorough investigation of the reaction with respect to synthetic scope and limitations, regio- and stereoselectivity of the alkenes produced, and the mechanistic possibilities.

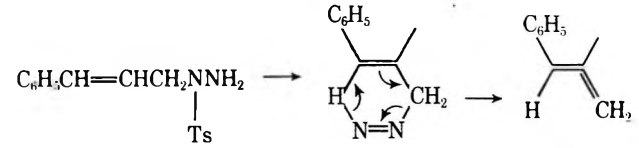
The preparation of the requisite tosylhydrazones and reduction procedure has been described previously and is briefly outlined in the Experimental Section. A variety of α,β-unsaturated tosylhydrazones representing a wide range of structural types were chosen for study and the results are presented in Table I. Synthetically, several features of the reductions are particularly noteworthy. Paramount, the specific formation of the *less* stable positional isomers of alkenes in several examples (entries 1–3, 5, 8–12) appears to offer general and reliable synthetic possibilities such as converting endocylic to exocyclic alkenes (entry 5), moving double bonds out of conjugation with aromatic rings (entries 1–3) and deconjugating certain 1,3-dienes to the 1,4 isomers (entries 8–10). In all such examples the migrations are clean with only a trace, if any, of the unrearranged olefin observed. In addition, the double-bond migration appears to occur stereoselectively to give the trans alkene as the major product, as illustrated by the conversions of benzalacetone and β-ionone (entries 2, 8) predominantly to the corresponding trans alkenes. With α,β,α′,β′-dienones, the procedure proved less successful and led to partial concomitant alkene reduction or mixtures of isomers (entries 13, 14). Furthermore, 9-anthraldehyde tosylhydrazone afforded only 9-methylanthracene (entry 15) with no evidence for products resulting from migration of the conjugate double bond. Cyclohexenones also apparently give anomalous reductions. Thus, isophorone gave principally (in low yield) the saturated hydrocarbon 1,1,3-trimethylcyclohexane in addition to a lesser amount of the alkene (entry 7).[3]

Ostensibly, the most straightforward mechanism for the reductive migration involves initial attack by cyanoborohydride in a 1,4-Michael type addition to give the rearranged tosylhydrazine intermediate, which subsequently decomposes to the alkene as shown in Scheme I.[2] The propensity for cyanoborohydride[4] (and borohydride)[7] to add in a 1,4 fashion to α,β-unsaturated ketones has been noted and $LiAlH_4$ reduces carvone tosylhydrazone to the unsaturated hydrocarbon limonene with preponderant migration of the double bond and initial attack at the conjugate position.[8]

Scheme I

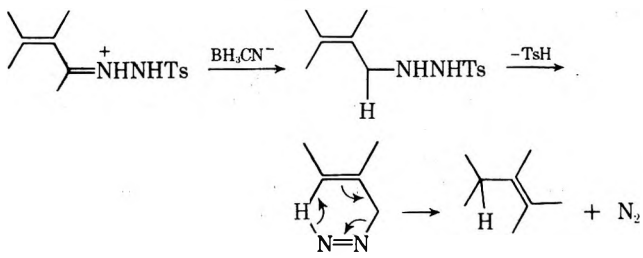


On the other hand, an alternative mechanistic possibility was suggested by the recent report[9] that *N*-allyl-*N*-tosylhydrazines, including cinnamyl tosylhydrazine (1), fragment under acidic conditions to the corresponding rearranged alkenes (i.e., 1 affords 3-phenylpropene uncontaminated with the 1 isomer). The mechanism of this tranformation apparently involves initial elimination of *p*-toluenesulfinic acid to the diazene intermediate 2 followed by a 1,5-sigmatropic rearrangement with transfer of hydrogen to the β carbon and π-bond migration. This points to the



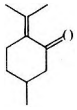
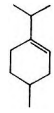
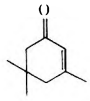
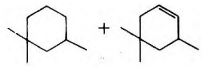
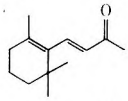
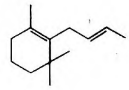
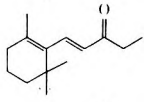
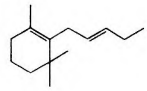
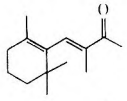
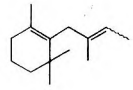
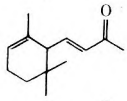
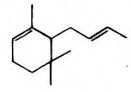
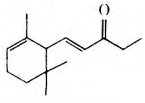
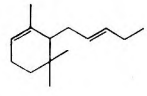
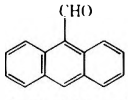
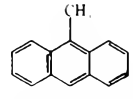
strong possibility that an analogous pathway may operate in the present case, as illustrated in Scheme II. Thus, the

Scheme II



initial step may consist of reduction of the imminium ion to the tosylhydrazine by cyanoborohydride followed by elimination of *p*-toluenesulfinic acid and a subsequent 1,5-sigmatropic shift to the observed rearranged alkene. Evidence for this latter mechanism was provided by the observation that the tosylhydrazine 1 gave 3-phenylpropene under the reaction conditions used successfully for reduction of tosylhydrazones (entry 16), again with no evidence for the un-

Table I
Reduction of Conjugated Carbonyl Compounds with Sodium Cyanoborohydride

Entry	Tosylhydrazone	Time,[a] hr	Product	Yield,[b] % (isolated)
1	$C_6H_5CH{=}CHCHO$	3.0	$C_6H_5CH_2CH{=}CH_2$	98
2	(E)-$C_6H_5CH{=}CHCOCH_3$	2.5	$C_6H_5CH_2CH{=}CHCH_3$	68.5[d] (54)[e]
3	p-$CH_3OC_6H_4CH{=}CHCOCH_3$	3.0	p-$CH_3OC_6H_4CH_2CH{=}CHCH_3$	67 (57)
4	$C_6H_5CH{=}CHCOC_6H_5$	4.0	$C_6H_5CH_2CH{=}CHC_6H_5$	60
5		2.0 4.0[c]		79 (84)
6		6.0		(70)
7		2.0		36 (19)[f]
8		3.0[c]		85 (65–70)
9		3.0[c]		(63–76)
10		5.0[c]		(45)
11		5.0[c]		(81)
12		6.0[c]		(77)
13	$(C_6H_5CH{=}CH)_2CO$	4.0	$C_6H_5CH_2CH{=}CH(CH_2)_2C_6H_5$	45 (38)
14	$[C_6H_5(CH{=}CH)_2]_2$	5.0	$C_6H_5(CH{=}CH)_2(CH_2)_3CH{=}CHC_6H_5$ + other isomers	(ca. 54)
15		7.0		(70)
16	$C_6H_5CH{=}CHCH_2\underset{\text{TS}}{\overset{\displaystyle NNH_2}{|}}$	3.0[c]	$C_6H_5CH_2CH{=}CH_2$	79

[a] Solutions were 0.2 M in tosylhydrazone, 0.8 M in $NaBH_3CN$ in 1:1 DMF-sulfolane, acidified with concentrated HCl to pH < 3.8 (Bromocresol Green indicator). [b] Yields were determined by GLC using internal standards and detector response factors; isolated yields are for purified products. [c] An additional portion of Bromocresol Green and concentrated HCl added after half the specified time. [d] Composed of 61.5% E and 7.0% Z geometric isomers. [e] Composed of 47.8% E and 6.2% Z geometric isomers. [f] NMR indicated an approximate ratio of 9:1 with the alkane predominant.

rearranged alkene. Apparently, the sigmatropic shift is considerably more facile than collapse to the unrearranged isomer.[10] This pathway also explains the reluctance of isophorone tosylhydrazone to give the rearranged products. Inspection of models reveal that the requisite correct positioning of the diazene over the ring is geometrically difficult, especially because of the blocking axial 5-methyl group.[11]

In summary, the reductive deoxygenations of α,β-unsaturated carbonyl tosylhydrazones offer a convenient, clean, and synthetically useful tactic for preparing such otherwise difficult olefins as exocyclic alkenes, unconjugated arenes, and 1,4-dienes. The double-bond migration occurs predominantly to give the more stable E isomer. The procedure is less successful with cyclohexenones. The probable mechanism involves a diazene intermediate which transfers hydrogen to the β carbon with concomitant π-bond migration via a 1,5-sigmatropic rearrangement.[12]

Experimental Section

Materials. $NaBH_3CN$ was obtained from Alfa Inorganics and used without purification. Sulfolane and DMF were distilled from CaH_2 and stored over 4A molecular sieves. The ketones and aldehydes were commercial materials which were purified before use. GLC analyses were performed on a Hewlett-Packard Model 5250B instrument equipped with a Disc Integrator using either 10% OV-1 or 10% Carbowax 20M on 80–100 Chromosorb W (AW-DMCS) columns. Melting points were obtained on a Mel-Temp apparatus and are uncorrected. Elemental analyses were determined by A. Bernhardt, West Germany, or Chemalytics, Inc., Tempe, Ariz. Drying of organic solvents was accomplished with anhydrous $MgSO_4$. In all cases, the nmr and ir spectra were consistent with the assigned structures.

Tosylhydrazone Formation. The carbonyl compound and a

Table II
Carbonyl Tosylhydrazones[a]

Tosylhydrazone	Yield, %	Mp, °C	Registry no.
β-Ionone	80	169–171	53941-08-5
1-Methyl-β-ionone	91	130–131	53941-09-6
3-Methyl-β-ionone	77	149–151	53941-10-9
α-Ionone	83	188–189 dec	53941-11-0
1-Methyl-α-ionone	80	144–146 dec	53941-12-1
1,5-Diphenyl-1,4-pentadien-3-one	94	145–148	538-58-9
(+)-Pulegone	33	145–147	89-82-7
1,9-Diphenyl-1,3,6,8-nonatetraene	68	143–150	622-21-9
9-Anthraldehyde	52	183–184	642-31-9

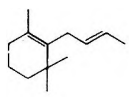
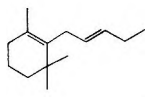
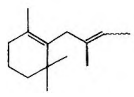
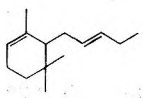
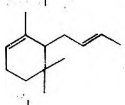
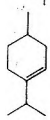
[a] Other tosylhydrazones listed in ref 2. All new tosylhydrazones gave satisfactory elemental analyses the results of which have been provided to the Editor.

10% molar excess of *p*-toluenesulfonylhydrazine in absolute ethanol (ca. 2 ml per gram of carbonyl compound) were heated on a steam bath until a clear solution resulted (15 min). Cooling afforded crystalline products in good to excellent yields (Table II). Recrystallization was accomplished from ethanol or aqueous acetone.

Reduction Procedure. For analytical reductions, the carbonyl tosylhydrazone, a fourfold molar excess of $NaBH_3CN$, and a small amount of Bromocresol Green were dissolved in a 1:1 mixture of sulfolane and DMF such that the solutions were 0.2 *M* in tosylhydrazone and 0.8 *M* in $NaBH_3CN$. The mixtures were heated at 100–105° and concentrated HCl was added cautiously dropwise until a color change was indicated by the indicator (tan). An internal standard and 5–10 ml of cyclohexane were added and the solutions were heated for the appropriate periods indicated in Table I. For several cases, an additional portion of Bromocresol Green and concentrated HCl were added (Table I). After completion, the solutions were diluted with water and the cyclohexane solutions analyzed by GLC to determine yields. For preparative-scale reactions, the aqueous phase was extracted twice with cyclohexane, and the combined cyclohexane solution was washed with water, dried, and concentrated on a rotary evaporator. Purification was accomplished by distillation at reduced pressure or recrystallization. All new products exhibited expected spectral characteristics and provided satisfactory elemental analyses (Table III).

As a representative preparative application, the reduction of (*E*)-1-phenylbuten-3-one to 1-phenyl-2-butene is described. A solution of the tosylhydrazone (6.29 g, 20 mmol), $NaBH_3CN$ (5.02 g, 80 mmol), and a few milligrams of Bromocresol Green in 100 ml of 1:1 DMF–sulfolane was heated to 105° and concentrated HCl was added dropwise cautiously until the pH was <3.8 as indicated by a color change from blue to tan. Approximately 40 ml of cyclohexane was added and the reaction mixture was heated with stirring for 1 hr. A few milligrams of Bromocresol Green and a few drops of concentrated HCl were added to maintain the pH below 3.8 and heating was continued for 1.5 hr; then the solution was diluted with 150 ml of water and the layers were separated. The aqueous phase was extracted twice with cyclohexane, and the cyclohexane solution was washed with three portions of water, dried, and concentrated. The residue was flash distilled at 2.8 mm (Kugelrohr apparatus) to obtain 1.42 g (54%) of 1-phenyl-2-butene. Analysis by GLC (10 ft 10% Carbowax 20M column, 150°) indicated the product to be composed of ca. 47.8% *E* and 6.2% *Z*[13] geometric isomers.

Table III[a]
Physical Data for New Alkene Products

Alkene	Bp, °C (mmHg)	$n^{25}D$	NMR data, Hz[c] (60 MHz, $CDCl_3$)	Registry no.
	58 (0.35)[b]	1.4810[b]	57, s (6 H), $(CH_3)_2C$ 93, broad s (3 H), $CH_3C{=}C$ 163, ind. m (2 H), $(C{=}C)_2CH_2$ 321, m (2 H), $HC{=}CH$[d]	53941-13-2
	76 (0.45)	1.4790	59, s (6 H), $(CH_3)_2C$ ca. 60, ind. t (3 H), CH_3CH_2 164, ind. m (2 H), $(C{=}C)_2CH_2$ 322, m (2 H), $HC{=}CH$	53941-14-3
	61 (0.15)	1.4811	53, 56, two s (6 H), $(CH_3)_2C$ 89, s (ca. 3 H), $CH_3C{=}C$ ca. 95, 96, ind. s and d (ca. 6 H); $CH_3C{=}C$, $CH_3CH{=}C$ 160, ind. m (2 H), $(C{=}C)_2CH_2$ 315, m (1 H), $HC{=}C$[d]	53941-15-4
	*e*	1.4775	53, 56, two s (6 H), $(CH_3)_2C$ 100, broad s (6 H), $CH_3C{=}C$ 322, m (3 H), $HC{=}C$, $HC{=}CH$	53941-16-5
	68 (0.35)	1.4760	52–65, singlets and ind. t (9 H), $(CH_3)_2C$, CH_3CH_2 ca. 321, m (3 H), $HC{=}CH$, $HC{=}C$	53941-17-6
	*e*	1.4510	59, d, J = 6 Hz (6 H), $(CH_3)_2C$ ca. 58, ind. d (3 H), CH_3CH 326, broad m (1 H), $HC{=}C$	619-52-3

[a] Alkene products gave satisfactory elemental analyses the results of which have been provided to the Editor. [b] Lit. bp 91.5–93° (11 mm), $n^{18}D$ 1.4795 (ref 12). [c] Downfield from Me_4Si standard. [d] No signals attributable to conjugated alkene protons were observed. [e] Flash distilled at reduced pressure.

Registry No.—(*E*)-1-Phenylbuten-3-one tosylhydrazone, 53941-18-7; (*E*)-1-phenyl-2-butene, 935-00-2; (*Z*)-1-phenyl-2-butene, 15324-90-0; sodium cyanoborohydride, 25895-60-7.

References and Notes

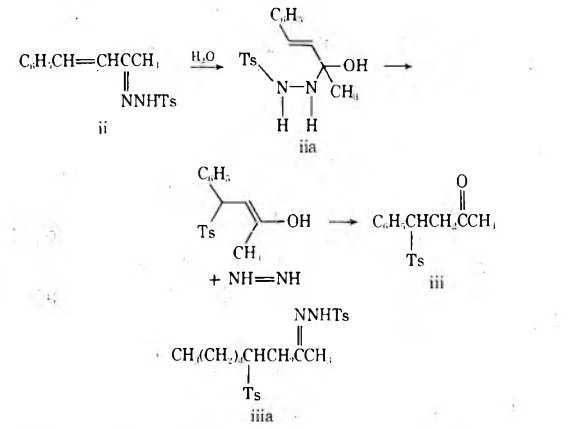
(1) (a) Undergraduate Research Participant, 1972–1973; (b) NDEA Fellow, 1971–1974.
(2) R. O. Hutchins, C. A. Milewski, and B. E. Maryanoff, *J. Am. Chem. Soc.*, **95**, 3662 (1973).
(3) Reference 2 contains an error. The product indicated from isophorone tosylhydrazone was 3,3,5-trimethycyclohexene instead of mostly the

saturated hydrocarbon. This problem arose from the unknown extreme difficulty in separating the two compounds by GLC. NMR spectroscopy confirmed the predominance of the latter. Presumably, 3,5-dimethyl-2-cyclohexen-1-one tosylhydrazone also furnishes the corresponding saturated hydrocarbon in major amount instead of the reported 3,5-dimethylcyclohexene. 4-Cholesten-3-one tosylhydrazone afforded a complex mixture of hydrocarbons and alkenes. Anyway, the procedure does not appear very synthetically useful with cyclohexenones.

(4) Borch and coworkers (ref 5) obtained cyclopentanol upon cyanoborohydride reduction of 2-cyclopentenone. However, a more thorough investigation of the reduction of cholestenone-type systems (ref 6) indicated the major products usually to be the allylic alcohols, leaving the double bonds unmolested.

(5) R. F. Borch, M. Bernstein, and H. D. Durst, *J. Am. Chem. Soc.*, **93**, 2897 (1971).
(6) M.-H. Boutique, R. Jacquesy, and Y. Petit, *Bull. Soc. Chim. Fr.*, 3062 (1973).
(7) See, for example, H. C. Brown and H. M. Hess, *J. Org. Chem.*, **38**, 2206 (1969).
(8) I. Elphimoff-Felkin and M. Verrier, *Tetrahedron Lett.*, 1515 (1968).
(9) T. Sato and I. Homma, *Bull. Chem. Soc. Jpn.*, **44**, 1885 (1971).

(10) This general type of sigmatropic migration has also been suggested (ref 9) to account for the transformation of certain α,β-unsaturated tosylhydrazone intermediates (i.e., ii) to β-tosyl ketones (i.e., iii) by thermolysis in aqueous acetic acid as indicated. We also observed a similar occurrence upon attempted preparation of (*E*)-3-octen-2-one tosylhydrazone. The only isolatable product was the corresponding β-ketotosylhydrazone iiia. Evidently, rearrangement of the intermediate analogous to iia is very facile for this example; further reaction of the β-tosyl ketone with *p*-toluenesulfonylhydrazine would produce the observed product. The reason this example chose to rearrange while all other α,β-unsaturated ketones gave the normal tosylhydrazones is not obvious.



(11) Sato and Homma (ref 9) also noted the failure of 3-methyl-2-cyclohexenone tosylhydrazone to rearrange to the corresponding β-tosyl ketone and offered a similar explanation.

(12) Analogous sigmatropic rearrangements of intermediate diazenes may also account for the production of rearranged alkenes often encountered in Wolff–Kishner reductions of α,β-unsaturated aldehydes and ketones. See, for example, R. Fischer, G. Lardelli, and O. Jegar, *Helv. Chim. Acta*, **34**, 1577 (1951).

(13) An authentic sample of the *Z* isomer was prepared from the epoxide via the procedure of Vedejs; cf. E. Vedejs and P. Fuchs, *J. Am. Chem. Soc.*, **93**, 4070 (1971).

Reaction of Lithium Aluminum Hydride with Hindered Phenols. New Stereoselective Reducing Agents

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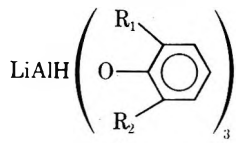
A study involving the reaction of lithium aluminum hydride ($LiAlH_4$) with hindered phenols and alcohols is described. This has resulted in the preparation of a new series of stereoselective reagents for the reduction of substituted cyclohexanones. The most highly selective reagent was formed by the reaction of $LiAlH_4$ with 2 molar equiv of 2,6-di-*tert*-butylphenol followed by 1 molar equiv of neopentyl alcohol. Several experiments involved the reaction of lithium borohydride with hindered phenols in which different results were obtained.

Lithium aluminum alkoxyhydrides have proven to be useful selective reagents in the reduction of organic compounds.[1] The preparation of these reagents by the reaction of lithium aluminum hydride ($LiAlH_4$) with alcohols has been found to be a generally useful and convenient procedure.[1,2] These reagents are of interest not only because of their ease of preparation and useful applications,[1] but also because of their possible role as intermediate species in the reduction of carbonyl compounds with $LiAlH_4$.[3] The stereoselective reducing properties of lithium aluminum alkoxyhydrides and the stabilities of these species (to disproportionation) have recently been discussed.[4] It was also found that the hindered reagent formed from the reaction of 3 mol of di-*tert*-butyl ketone with 1 mol of $LiAlH_4$ reduced 3,3,5-trimethylcyclohexanone to 98% of the trans–axial alcohol.[4] However, this moderately hindered ketone is quite sensitive to stereoselective reduction by bulky reagents,[3,5,6] and a better test substrate for a selective reducing agent is an unhindered ketone such as 4-*tert*-butylcyclohexanone (**1**). Reduction of **1** with the above reagent (in 92 vol % THF, 8% ether) gave 76% of axial *cis*-4-*tert*-butylcyclohexanol (*cis*-**2**). This reagent is thus seen to be more highly stereoselective than other aluminum alkoxyhydrides previously used. For example, reduction of **1** with lithium aluminum tri-*tert*-butoxyhydride gave only 10% of *cis*-**2**.[5a,b,8] Lithium aluminum trimethoxyhydride is generally more highly stereoselective than the tri-*tert*-butoxyhydride owing to its relatively high degree of association;[5c] but it affords only 41% of *cis*-**2** on reduction of **1**.[5a]

In view of the apparent relationship between steric bulk and stereoselectivity of the reagent[3,4] it was thought to be of interest to prepare highly sterically hindered lithium aluminum triaryloxyhydrides by the reaction of $LiAlH_4$ with phenols. It would be of considerable interest to have highly stereoselective reagents easily prepared from relatively inexpensive starting materials. It should be noted that other procedures, most of which do not involve aluminum compounds, have been reported for the synthesis of axial alcohols, in particular the use of lithium tri-*sec*-butylborohydride,[9] potassium triisopropoxyborohydride,[10] iridium tetrachloride–trimethyl phosphite,[11] isobornyloxyaluminum dichloride,[12] and lithium dimesitylborohydride bis(dimethoxyethane).[13]

A study of the stereoselectivities of lithium aluminum triaryloxyhydrides in the reduction of the ketone **1** was undertaken. The general procedure (see Experimental Section for details) involved the addition of a solution of the phenol in tetrahydrofuran (THF) to a standardized solution of $LiAlH_4$ (commercially available in THF or diethyl ether) with measurement of hydrogen evolution. This was followed by addition of **1**. After hydrolysis of the reaction mixture, the concentrated product mixture was analyzed

Table I
Reduction[a] of 4-*tert*-Butylcyclohexanone with A



A

Entry	Reagent R_1	Reagent R_2	Registry no.	Solvent[b]	% yield[c] of alcohols Cis (axial)	% yield[c] of alcohols Trans	% yield[c] ketone[d]	Stereoselectivity, % cis isomer[e]
1	CH_3	CH_3	54081-36-6	THF–ether	11	50	26	21
2	$(CH_3)_2CH$	$(CH_3)_2CH$	54003-97-3	THF	58	42	~0	58
3	$(CH_3)_2CH$	$(CH_3)_2CH$		THF[f]–ether	70	28	0	72
4	$(CH_3)_3C$	H	54003-98-4	THF	9	82	4	10
5	$(CH_3)_3C$[g]	$(CH_3)_3C$[g]	54004-00-1	THF–ether	*h*	*h*	~0	58
6[i]	$(CH_3)_3C$	$(CH_3)_3C$	54003-99-5	THF–ether	49[j]	9[j]	31	85

[a] Reaction times varied, 3–21 hr, reaction temperature ca. 25°. [b] 65–75 vol % tetrahydrofuran (THF) in ether, or 100% THF. [c] Yields determined by GLC analysis using 3,3,5,5-tetramethylcyclohexanone as internal standard. [d] Yield of recovered 4-*tert*-butylcyclohexanone. [e] Cis and trans alcohols normalized to 100%. Best values based on two or more analyses. [f] In 57 vol % THF in ether. [g] The reagent is lithium diaryloxyhydride. [h] Not measured with an internal standard. [i] Reaction mixture heated. [j] Some of the crude reaction product was removed before GLC analysis.

Table II
Reduction[a] of 4-*tert*-Butylcyclohexanone with $LiAlH(OAr)_2(OR)$[b]

Entry	Reagent, R	Registry no.	Solvent[c]	% yield[d] of alcohols Cis (axial)	% yield[d] of alcohols Trans	% yield[e] ketone	Stereoselectivity, % cis (axial) isomer[f]
1	$(CH_3)_2CHCH_2$	54004-01-2	THF–ether	*g*	*g*	26[h]	84
2	$(CH_3)_2CH$	54004-02-3	THF–ether	70	18	12	80
3	$(CH_3)_3C$-CH_2	54004-03-4	THF–ether	64	5	27	93
4	$(CH_3)_3C$-CH_2		THF–ether	*g*	*g*	31[h]	89
5	$(CH_3)_3C$-CH_2		THF	54	34	10	61
6	$(CH_3)_3C$-CH_2		THF	56	36	9	61

[a] Reaction times varied, reaction temperature ca. 25°. [b] Ar = 2,6-di-*tert*-butylphenyl. [c] 65–75 vol % THF in ether or pure THF. [d] Yields determined by GC analysis using 3,3,5,5-tetramethylcyclohexanone as internal standard. [e] Yield of recovered 4-*tert*-butylcyclohexanone. [f] Cis and trans alcohols normalized to 100%. [g] Not measured. [h] Area percent of ketone and alcohol isomers.

by gas chromatography, generally before and after the addition of a suitable internal standard.

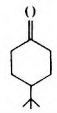
Preparation and Stereoselectivities of Lithium Aluminum Triaryloxyhydride Reagents. Table I summarizes the results of the reaction of $LiAlH_4$ with hindered phenols, and the reduction of 1 with the resulting lithium aluminum triaryloxyhydrides. The 2,6-dimethyl, 2,6-diisopropyl, and 2-*tert*-butylphenols (entries 1–4, Table I) react readily with $LiAlH_4$ in a 3:1 molar ratio at room temperature (ca. 25°) as evidenced by the liberation of 3 molar equiv of hydrogen.

Presumably the reducing species formed is lithium aluminum triaryloxyhydride. In the reaction of 2,6-di-*tert*-butylphenol with $LiAlH_4$ in a 3:1 molar ratio at room temperature (entry 5, Table I) hydrogen evolution ceased before addition of the phenol was complete. After addition of 1 mol of 1, hydrolysis of the reaction mixture led to the evolution of 1 mol of hydrogen. Therefore only 2 molar equiv of hydride was used in the reaction of $LiAlH_4$ with this highly hindered phenol, since at room temperature the placement of the third aryloxy group about the aluminum atom is slow owing to steric hindrance.[14] It is possible to react $LiAlH_4$ with 3 molar equiv of 2,6-di-*tert*-butylphenol on heating. The resulting reagent (entry 6, Table I) is seen to be quite highly stereoselective. The degree of stereoselectivity is measured by the proportion of axial alcohol.

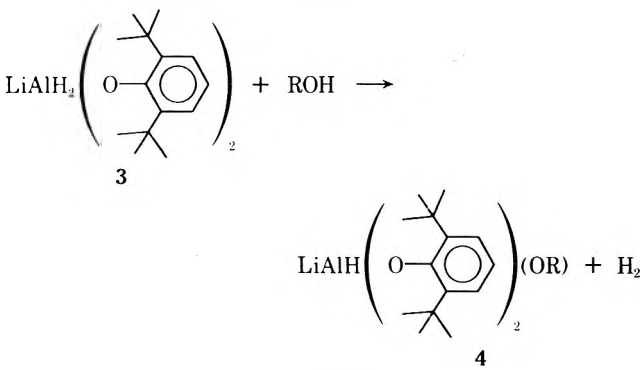
There appears to be a correlation between the size of the ortho substituents in the phenol with the steric requirements of the reducing agent, as long as the solvent remains constant. In THF–ether, stereoselectivity decreases with decreasing size of ortho substituent: $(CH_3)_3C > (CH_3)_2CH > CH_3$ (entries 6, 3, and 1, respectively). There is an interesting solvent effect, in that these reagents prepared from $LiAlH_4$ in ether are consistently more selective than when prepared fron $LiAlH_4$ in THF (compare entries 2 and 3, Table I). This same effect was observed again (vide infra) and was reproducible, although its cause is unknown. With one ortho *tert*-butyl substituent, the aluminum triaryloxyhydride reagent (entry 4, Table I) shows the same selectivity as lithium aluminum tri-*tert*-butoxyhydride, giving predominantly the more stable *trans*-2 alcohol isomer.

Preparation and Stereoselectivities of Lithium Aluminum Diaryloxyalkoxyhydride Reagents. Since 2,6-di-*tert*-butylphenol reacted with $LiAlH_4$ in only a 2:1 molar ratio at room temperature, a series of experiments was carried out in which the third hydride was replaced with an alkoxy group by reaction with an alcohol. The resulting reagents, assumed to be lithium aluminum diaryloxyalkoxyhydrides, were then used to reduce 1 in order to test their stereoselective reducing properties. This approach has led to a number of new, highly selective reagents, as shown in Table II.

Table III
Reduction[a] of Ketones with $LiAlH(OAr)_2(OR)$[b]

Entry	Ketone	Registry no.	Reaction time, hr	% yield[c] of alcohols: Cis	% yield[c] of alcohols: Trans	% yield of ketone[d]	Stereoselectivity, % axial isomer[e]
1		873-94-9	16.5	<1	44	37	>99 (trans)
2		583-60-8	22.5	*f*	*f*	31[g]	89 (cis)
3		591-24-2	17	12	69	17	85 (trans)
4[h]			5	64	5	27	93 (cis)

[a] Reaction temperature ca. 25°, solvent 58–75 vol % THF in ether. [b] Ar = 2,6-di-*tert*-butylphenyl, R = neopentyl. [c] Yields determined by GLC analysis using the following internal standards: 3-methylcyclohexanone for entry 1; cyclohexanone for entry 3; 3,3,5,5-tetramethylcyclohexanone for entry 4. [d] Yield of recovered ketone. [e] Alcohols normalized to 100%. [f] Not measured. [g] Area percent of ketone and isomeric alcohols. [h] See entry 3, Table II.



3

4

The reaction of the diaryloxyhydride species **3** with isobutyl and isopropyl alcohols giving the respective species **4** occurred smoothly, with the reagents **4** showing quite high stereoselectivities (entries 1 and 2, Table II). The greatest stereoselectivity was found with the reagent **4** formed by reaction of **3** with neopentyl alcohol in THF–ether (entry 3, Table II). In all cases, the measured hydrogen evolution corresponded closely with that expected for the conversion of **3** to **4**. The satisfactory reproducibility in stereoselectivities is demonstrated for two cases in Table II (entries 3 and 4, and entries 5 and 6). Again, the same solvent effect on stereoselectivity as noted above was encountered (cf. entries 3 and 5, Table II).

In order to evaluate the scope of these new reagents, the best system was selected (entry 3, Table II) and used to reduce several additional ketones. The results of these reductions are shown in Table III. The reagent shows extremely high stereoselectivity in the reduction of the relatively highly hindered 3,3,5-trimethylcyclohexanone (entry 1, Table III), giving the trans–axial epimer almost exclusively. The reduction of 2-methylcyclohexanone also is highly stereoselective, giving 89% of the cis-axial epimeric alcohol (entry 2, Table III). In contrast $LiAlH_4$ itself affords only 24% of the cis epimer,[7] and lithium aluminum trimethoxyhydride gives 69% of the same epimer. Lithium aluminum tri-*tert*-butoxyhydride gives 27% of the cis epimer.[15] A similar high selectivity (85% trans–axial epimer) is seen for the reduction of 3-methylcyclohexanone (entry 3, Table III). In contrast, $LiAlH_4$ reduction affords only 16% of the trans alcohol epimer[16] while only 10% of the same epimer is formed with lithium aluminum tri-*tert*-butoxyhydride (at −23°).[15] Thus the new reagent is seen to be highly stereoselective in the reduction of these various ketones.

Several further observations should be made regarding the data in Tables I–III. In many of the reductions a considerable amount of ketone was found in the product. This appears to be a problem with the most selective highly hindered reagents. A possible explanation is reduced reactivity of the highly hindered reagents. An alternative explanation is enolization of the ketones. Several attempts to measure the infrared spectra of crude reaction mixtures (prior to hydrolysis) have not been conclusive. Further work will be directed toward improving the actual yields of the axial epimers. Analyses using internal standards (as shown in Tables I–III) have indicated that in almost all cases these are no significant products other than the alcohols and recovered starting ketones. Finally, although the reaction times employed in the reductions varied, equilibration of alcohol epimers did not occur, as was shown by control experiments involving the removal and analysis of aliquots during reaction.

Reaction of Lithium Borohydride with Hindered Phenols. Several experiments were carried out in which lithium borohydride was treated with 2,6-di-*tert*-butylphenol and with 2-*tert*-butylphenol. It was found that lithium borohydride did not react at room temperature (*ca.* 25°) with 2,6-di-*tert*-butylphenol in diethyl ether. On heating in THF, lithium borohydride reacted with 3 molar equiv of either of the above phenols (hydrogen evolution measured). The reduction of **1** in both cases afforded 20–22% of the cis–axial alcohol. It is possible that in these experiments reduction was effected by lithium borohydride itself. The reduction of **1** with lithium borohydride in diglyme at 20° is reported to give 15% of the cis–axial alcohol.[17] It is known that trialkoxyborohydrides are more reactive reducing agents than borohydride itself,[18–21] and the reaction of borohydride with the phenol may produce the tetraaryloxyborohydride species and unreacted lithium borohydride which is available for reduction.

Experimental Section

Solvents and Reagents. Tetrahydrofuran was refluxed over potassium hydroxide, then distilled from $LiAlH_4$ through an 18-in. helix-packed column. 4-*tert*-Butylcyclohexanone was distilled. The phenols were obtained from Aldrich Chemical Co. 2-6-Di-*tert*-butylphenol was distilled and kept refrigerated. Isopropyl and iso-

butyl alcohols were chromatoquality grade obtained from Matheson Coleman and Bell, and neopentyl alcohol (99%) was obtained from Aldrich. Lithium aluminum hydride was obtained from Ventron Corp. as solutions in diethyl ether or THF. The solutions were standardized by reaction with iodine according to the method of Felkin,[22] or by measurement of hydrogen on methanolysis.

Gas chromatographic analyses were done on a Hewlett-Packard Model 5750 instrument using the following columns: 12 ft × 0.125 in. 5% Carbowax 20M at 145° for the separation of *cis*- and *trans*-4-*tert*-butylcyclohexanols; 10 ft × 0.25 in. 10% Carbowax 20M (acid washed, silanized) at 140° for *cis*- and *trans*-3,3,5-trimethylcyclohexanols; 16 ft × 0.25 in. ethylene glycol succinate (acid washed, silanized) at 105° for *cis*- and *trans*-2-methylcyclohexanols; 12 ft × 0.25 in. diethylene glycol succinate (acid washed, silanized) for *cis*- and *trans*-3-methylcyclohexanols.

Apparatus and General Procedure. The reactions were carried out in a 250-ml glass reactor (Ace Glass Co.) stirred magnetically and equipped with a condenser and equilibrated dropping funnel. The apparatus was baked and flushed with dry nitrogen. The general procedure is described in detail for the following two reactions.

Reaction of $LiAlH_4$ with 2,6-Dimethylphenol. Reduction of 1. Fifteen milliliters of 0.90 *M* $LiAlH_4$ in ether was transferred by pipet to the reaction flask. Ten milliliters of THF (distilled freshly from $LiAlH_4$) was added dropwise with the apparatus attached to a wet test meter. No hydrogen evolution occurred. A solution of 2,6-dimethylphenol (4.96 g, 0.0406 mol) in 10 ml of THF was added dropwise over 6 min. The volume of hydrogen was recorded (0.045 mol) by means of a wet test meter. The reaction mixture was clear and colorless. The ketone 1 (1.994 g, 0.0129 mol) was added dropwise as a solution in 10 ml of THF over 4 min. The clear, colorless reaction mixture was stirred overnight under a nitrogen atmosphere. After 23 hr, the reaction mixture was hydrolyzed with 10% sulfuric acid, and hydrogen evolution measured. After washing (saturated sodium bicarbonate and salt solution) and drying over anhydrous $MgSO_4$, the product was concentrated by distillation through a 17-in. helix-packed column, using an oil bath. The concentrated product, 29 g, was clear and colorless, and analyzed by GLC before and after the addition of 3,3,5,5-dimethylcyclohexanone as an internal standard.

Reaction of $LiAlH_4$ with 2,6-di-*tert*-Butylphenol and with Neopentyl Alcohol. Reduction of 1. Twenty milliliters of 1.2 *M* $LiAlH_4$ in ether was transferred by pipet to the reaction flask. Fifteen milliliters of THF was added dropwise with no hydrogen evolution. Distilled 2,6-di-*tert*-butylphenol (9.9155 g, 0.048 mol) in 10 ml of THF was added over 20 min, during which hydrogen evolution (0.045 mol) was measured with a wet test meter. The clear, colorless reaction mixture was then stirred under nitrogen for 35 min, and a solution of neopentyl alcohol (2.1279 g, 0.024 mol) in 15 ml of THF was added over 8 min, again measuring hydrogen evolution (0.021 mol). Hydrogen evolution continued after the addition was complete, indicating a rather slow reaction. After 32 min, a solution of 1 (3.0863 g, 0.020 mol) in 15 ml of THF was added dropwise under nitrogen over 8 min. The reaction mixture was clear and pale yellow. It was stirred under nitrogen for 5 hr, cooled, and hydrolyzed with 10% sulfuric acid, with hydrogen evolution measured with the wet test meter. The aqueous layer was extracted with three portions of ether, and combined organic solution washed twice with saturated sodium bicarbonate, twice with saturated salt solution, and dried over anhydrous magnesium sulfate. The filtered solution was concentrated by distillation through a 17-in. helix-packed column using an oil bath (bath temperature to ~90°, bp ~35°). The concentrated product was clear and colorless and was analyzed by GLC before and after the addition of the internal standard, 3,3,5,5-tetramethylcyclohexanone.

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Registry No.—1, 98-53-3.

References and Notes

(1) For a review, see J. Malek and M. Cerny, *Synthesis*, 217 (1972).
(2) H. C. Brown and C J. Shoaf, *J. Am. Chem. Soc.*, **86**, 1079 (1964).
(3) H. Haubenstock and E. L. Eliel, *J. Am. Chem. Soc.*, **84**, 2363 (1962).
(4) H. Haubenstock, *J. Org. Chem.*, **38**, 1765 (1973).
(5) (a) E. L. Eliel and Y. Senda, *Tetrahedron*, **26**, 2411 (1970); (b) S. Winstein and J. Sonnenberg, *J. Am. Chem. Soc.*, **83**, 3235 (1961); (c) E. C. Ashby, J. P. Sevenair, and F. R. Dobbs, *J. Org. Chem.*, **36**, 197 (1971).
(6) With highly hindered ketones such as norcamphor, camphor, and isopinocamphone, $LiAlH_4$ itself leads to a high proportion of the less stable alcohol epimer.[7]
(7) H. C. Brown and H. R. Deck, *J. Am. Chem. Soc.*, **87**, 5620 (1965).
(8) J. C. Richer, *J. Org. Chem.*, **30**, 324 (1965).
(9) H. C. Brown and S. Krishnamurthy, *J. Am. Chem Soc.*, **94**, 7159 (1972).
(10) C. A. Brown, *Chem. Commun.*, 391 (1973).
(11) E. L. Eliel, T. W. Doyle, R. O. Hutchins, and E. C. Gilbert, *Org. Synth.*, **50**, 13 (1970).
(12) E. L. Eliel and D. Nasipuri, *J. Org. Chem.*, **30**, 3809 (1965).
(13) J. Hooz, S. Akiyama, F. J. Cedar, M. J. Bennett, and R. M. Tuggle, *J. Am. Chem. Soc.*, **96**, 274 (1974).
(14) J. S. Meek and C. Bouboulis, *J. Org. Chem.*, **26**, 1302 (1961).
(15) H. C. Brown and P. M. Weissman, *Isr. J. Chem.*, **1**, 4301 (1963).
(16) H. C. Brown and W. C. Dickason, *J. Am. Chem. Soc.*, **92**, 709 (1970).
(17) W. M. Jones and H. E. Wise, Jr., *J. Am. Chem. Soc.*, **84**, 997 (1962).
(18) H. C. Brown, E. J. Mead, and B. C. Subba Rao, *J. Am. Chem. Soc.*, **77**, 6209 (1955).
(19) H. C. Brown, E. J. Mead, and C. J. Shoaf, *J. Am. Chem. Soc.*, **78**, 3616 (1956).
(20) E. R. Garrett and D. A. Lyttle, *J. Am. Chem. Soc.*, **75**, 6051 (1953).
(21) H. Haubenstock and E. L. Eliel, *J. Am. Chem. Soc.*, **84**, 2368 (1962).
(22) H. Felkin, *Bull. Soc. Chim. Fr.*, 347 (1950).

Observations on the Steric Requirement of Wittig Reactions with Trialkylphosphonoacetates

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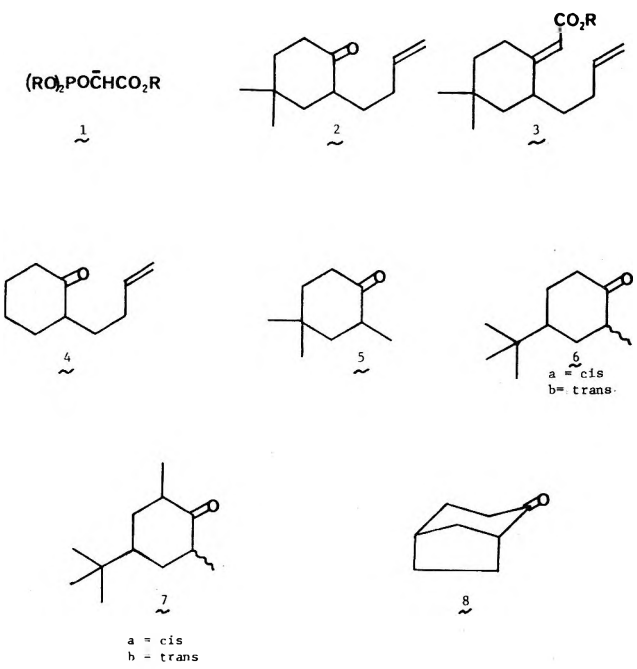
Investigation of the Wittig reaction of trialkylphosphonoacetate anions with several C-2 substituted cyclohexanones has demonstrated the presence of a previously unrecognized steric constraint for this reaction. Cyclohexanones with a C-2 alkyl group constrained to the equatorial orientation proved unreactive to normal treatment with trialkylphosphonoacetate anions. Cyclohexanones which can undergo facile conformational inversion to give an axial C-2 substituent react normally. Conformationally rigid cyclohexanones in which configurational inversion to give an axial C-2 substituent is not energetically prohibitive react slowly and give a mixture of ester products with the alkyl group predominantly axial.

We wish to report some previously unrecognized steric requirements of the Wittig reaction using trialkylphosphonoacetate anions. The observations reported herein further delineate the range of synthetic utility of reactions involving phosphonate anions and substituted cyclohexanones. In the course of another synthetic problem[1] we attempted to convert ketone 2 into the corresponding α,β-unsaturated ester 3 by treatment with anion 1. Attempts to conduct this

reaction under normal conditions (excess phosphonate anion in glyme or dimethylformamide at room temperature) led to recovery of ketone **2** with no condensation product observed. Since 2-methylcyclohexanone reacts readily with 1,[2] we hypothesized that the restriction of the butenyl side chain to the equatorial position[3] in ketone **2** may be responsible for the lack of reactivity. This hypothesis has been tested by examination of the reaction of **1** with several C-2 alkylated ketones. The ketones used in this study were 2-(3-butenyl)cyclohexanone (**4**), 2,4,4-trimethylcyclohexanone (**5**), 2-methyl-4-*tert*-butylcyclohexanone (**6**), *cis,cis*- and *cis,trans*-2,6-dimethyl-4-*tert*-butylcyclohexanone (**7**), and bicyclo[3.2.1]octan-2-one (**8**).



As expected, reaction with ketone **4** proceeded in a manner similar to the reaction with 2-methylcyclohexanone to give a mixture of the *E* and *Z* isomers of the expected α,β-unsaturated ester (**9** and **10**). Ketone **8**, with an axial C-2 substituent, also reacted readily with anion **1** to give a mixture of the two isomers of the expected α,β-unsaturated ester (**11** and **12**). These results show that the reaction is not hindered by the presence of an axial C-2 substituent or an equatorial C-2 substituent if the alternative conformation with the substituent axial is readily obtainable.

Treatment of either ketone **5** or ketone **7** with anion **1** led to recovery of the starting ketones. Each of these ketones is expected to exist in conformations containing an equatorial C-2 methyl group, since the alternative conformations are quite unfavorable.[3,4]

The reactions with ketone **6** proved to be the most complex. Although the *tert*-butyl substituent at C-4 restricts the cyclohexanone to a single chair conformation, the substituent at C-2 can be interconverted between axial and equatorial orientations by base-catalyzed enolization.

The reactions of ketone **6** with an excess of anion **1a** (generated using sodium hydride or potassium *tert*-butoxide as base) in dimethylformamide at room temperature gave a mixture of esters in good yield. Vapor phase chromatographic analysis showed five peaks with the last one as the major peak (~72% of the total peak area). The individual components of the mixture were partially separated by preparative gas chromatography.

The NMR spectra of these products were instrumental in assigning structures to the isomeric products obtained. The key data which allows differentiation of the isomers

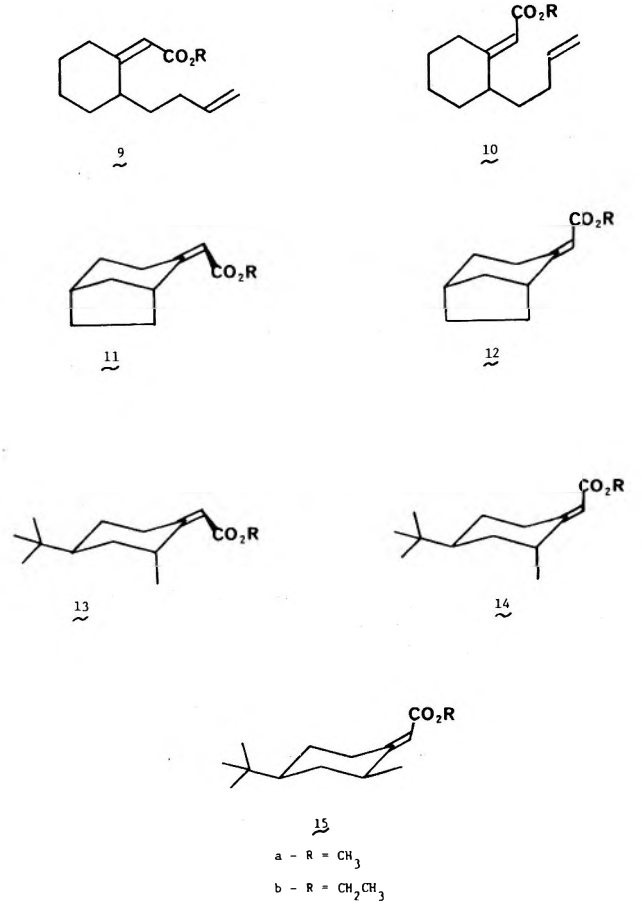
Table I
NMR Assignments for Esters 13, 14, and 15

Compd	δ values: Methyl	Deshielded proton	C-2 methine[a]
13a	1.12	3.84–4.30	~4.0
13b	1.14	~4.01	~3.9–4.0
14a	1.16	3.58–3.98	~2.4
14b		Not isolated pure	
15a	1.05	3.80–4.20	2.18
15b	1.06	~4.01	~2.30

[a] Assigned by determining position of decoupling irradiation which collapsed methyl doublet.

was obtained by use of double-irradiation techniques. The carboalkoxy group of cyclohexylideneacetic acid esters has been shown to strongly deshield the equatorial ring proton which is cis to the carboalkoxy group.[6] In the products from reaction of **1** with ketone **6**, this downfield proton (δ 3.5–4.3) can be established as a C-2 proton (coupled to C-2 methyl) or a C-6 proton (not coupled to C-2 methyl) by double-irradiation techniques.

Specific structural assignments were made for compounds **13, 14,** and **15.** The key spectral parameters for these compounds are shown in Table I. Structure **13** is easily differentiated from **14** and **15** by the observation that the deshielded ring proton is coupled to the C-2 methyl group. Differentiation between **14** and **15** was made by ozonolysis to the corresponding *cis*- and *trans*-2-methyl-4-*tert*-butylcyclohexanones. Although the reaction with ketone **6** was conducted with both **1a** and **1b**, the separation of isomers was more effective with the products from **1a.** The results appeared essentially identical in the cases in which **1a** and **1b** were compared.



Of the five fractions observed for reaction of **1a** with ketone **6**, fractions 1, 4, and 5 could be isolated in reasonable purity. The spectral data for the first component (~4% of total peak area) showed clearly that it was a β,γ-unsaturated ester. The structure and stereochemistry of this component were not pursued further.[7]

The material in the last fraction (~72% of total peak area) was assigned structure **15a** and that in the fourth fraction was assigned structure **14a** on the basis of the spectral properties (Table I and Experimental Section) and on the observation that ozonolysis of the last fraction gave *cis*-2-methyl-4-*tert*-butylcyclohexanone while ozonolysis of fraction 4 gave *trans*-2-methyl-4-*tert*-butylcyclohexanone. Similar ozonolysis conditions have been used in earlier studies for similar stereochemical assignments.[8,9]

The second and third fractions were not completely separated by gas chromatography. The ir spectrum of the mixture showed absorption expected for an α,β-unsaturated ester. The individual components of the mixture could be characterized by comparisons of relative intensities of peaks in the NMR spectrum and in the gas chromatogram, and use of the double-resonance technique. The spectral data for the major component (higher retention time) clearly indicated that it was the ester **13a**. Ozonolysis of a mixture of these two fractions gave *trans*-2-methyl-4-*tert*-butylcyclohexanone. The minor component was not present in sufficiently large amounts to allow characterization in the mixture.

Although the major product (**15a**) observed in the above reaction contained an equatorial C-2 substituent, it was found that the stereochemistry of the product was quite dependent upon reaction conditions. When ketone **6** was treated with excess phosphonate anion, as above, ester **15a** was found to be the major isomer. However, when less than the theoretical molar quantity of anion **1** was used, the esters **13a** and **14a** were found to be the predominant products, and ester **15a** was distinctly a minor component (~7% of total peak area). The relative amount of ester **15a** was increased (still not the major product), when the amount of phosphonate anion was raised to approximately the theoretical molar quantity. It was determined, however, that the product distribution from this reaction was not affected by the strength of the base used to generate the phosphonate anion, because use of either sodium hydride or potassium *tert*-butoxide (using either **1a** or **1b**) was found to give the same result. In all of the above experiments, the phosphonate reagent, $(RO)_2POCH_2CO_2R$, was present in excess over the base used to generate anion **1**. If excess base was used, the major change observed was a significant increase in the relative amount of the β,γ isomer.

A complete rationalization of the stereochemistry of the phosphonate Wittig reaction with cyclic ketones is not possible at this time. However, the above results clearly show the previously unrecognized importance of an equatorial substituent at C-2 upon the course of this reaction.

The key features to be noted from the results of the present study are (a) the lack of reactivity of ketones **2**, **5**, and **7**; (b) the complex stereochemical result obtained with ketone **6**; and (c) the ease of reactivity of ketone **8**. The facile reactions with 2-methylcyclohexanone and ketone **4** suggest that the conformers with an axial C-2 side chain may be important in their reactivity. The two conformations of 2-methylcyclohexanone differ in energy by only 1.60 kcal/mol.[10] Thus the significant amounts of product with *Z* configuration obtained from reaction with this ketone could be readily accounted for by reaction involving intermediates with an axial methyl group.

Ketones **2** and **5** greatly prefer conformations with an equatorial C-2 substituent, since the alternative chair conformation is highly destabilized by a 1,3-diaxial interaction. Thus, any reaction requiring the C-2 substituent to be axial at the transition state would be quite unfavorable.

However, ketone **6a**, in which conformational inversion is blocked by the bulky *tert*-butyl group, can isomerize to its isomer **6b** with an axial C-2 substituent under basic conditions (**6a** $\rightleftarrows$ **6b**, $\Delta G = -1.56$ kcal/mol).[11] Taking into account the aforementioned effect of the reagent ratio on product distribution, one might propose the following mechanism to rationalize this reaction. The condensation reaction to give product is assumed to proceed only after ketone **6a** has isomerized to ketone **6b**. The direct reaction of **6a** to give esters with an equatorial C-2 substituent is assumed to be extremely slow, if it occurs at all. The facile reaction of **6b** would be consistent with the observed reactivity of ketone **8**. The reaction with ketone **6b** then gives as initial products the esters **13** and **14** with an axial methyl group. In the presence of excess anion **1** these are isomerized to ester **15** and other isomers.

Thus the present work demonstrates quite clearly that reaction of phosphonate anion **1** with cyclohexanones is subject to severe steric hindrance by the presence of an equatorial substituent at C-2. Reaction will proceed satisfactorily only if this substituent can readily attain a conformational or configurational (epimerization) conversion to an axial position.

Experimental Section

General Procedures. All compounds in this section containing an asymmetric carbon atom are racemic; the prefix *dl* is omitted. Infrared spectra were determined on a Perkin-Elmer grating infrared spectrophotometer, Model 237B, or a Beckman infrared spectrophotometer, Model IR8. Nuclear magnetic resonance (NMR) spectra were determined on Varian Associates Model HA-100 or T-60 spectrometers. Carbon tetrachloride was used as the solvent unless otherwise stated. Tetramethylsilane (Me_4Si) was used as the internal reference. Chemical shifts are reported as δ values in parts per million (ppm) relative to TMS [$\delta(Me_4Si)$ 0.0 ppm]. High-resolution mass spectra were determined on a CEC Model 21-110 spectrometer under the supervision of Dr. R. Grigsby.

The vapor phase chromatographic analyses (VPC) were performed on a Hewlett-Packard instrument, Model 700, equipped with a thermal conductivity detector with a helium flow rate of ~60 ml/min. All percent-composition values are reported as relative peak areas (disk integrator) without correction for relative detector response. Preparative vapor phase chromatographic separations were performed on the same instrument.

Unless otherwise indicated, the elution order used in column chromatography was hexane (pentane, heptane), ether, ethyl acetate. High-pressure liquid chromatographic analyses were performed on a Waters Associates Model ALC 201 equipped with a refractive index detector.

Microanalyses were performed by Chemalytics, Inc., Tempe, Ariz. Melting points were determined on a Thomas-Hoover capillary melting point apparatus.

Tetrahydrofuran was dried over sodium hydroxide pellets and distilled from lithium aluminum hydride just prior to use. Glyme and *N,N*-dimethylformamide were distilled from lithium aluminum hydride and barium oxide, respectively, just prior to use.

A 19-in. spinning band column, Nester-Faust Corp. Model NFT-51, equipped with a Teflon band and rated at 75 theoretical plates was used for fractional distillations. Evaporative distillations refer to bulb-to-bulb (Kugelrohr), short-path distillations in which the bulb was heated by an oven. The temperatures cited for these distillations refer to the maximum temperature attained by the air chamber during the distillation.

The isolation procedure normally consisted of dilution of the product with water and extraction with the solvent indicated. The extractions were usually three in number. The combined organic extracts were then washed with the stated solutions. "Acid" refers to a 10% aqueous solution of hydrochloric acid. "Bicarbonate" refers to a saturated aqueous solution of sodium bicarbonate.

"Brine" refers to a saturated aqueous solution of sodium chloride. After the solution was dried over the stated drying agent, the solvent was removed at ca. 30 mm using a rotary evaporator (Rinco Co.).

Apparatus similar to that described by Johnson and Schneider[12] was used to maintain a nitrogen atmosphere in reactions requiring an inert atmosphere.

Preparation of Materials. 2,4,4-Trimethylcyclohexanone (5). A solution of 0.42 g (4.2 mmol) of cyclohexylamine in 5 ml of dry benzene was added slowly to a solution of 0.5 g (4.0 mmol) of 4,4-dimethylcyclohexanone[13] in 25 ml of dry benzene at room temperature. The mixture was heated to reflux for 12 hr in a flask with a water-separation head. The solvent was removed and the imine was evaporatively distilled (1.8 mm, 135°) to give 0.712 g (92% yield) of colorless liquid. The imine was dissolved in 8 ml of anhydrous ether and added dropwise to a cold, stirred solution of 20 ml of 1 *M* ethylmagnesium bromide over a period of 5 min. The reaction mixture was then refluxed for 5 hr under nitrogen and cooled in an ice bath, and 0.5 g (3.5 mmol) of methyl iodide in 5 ml of anhydrous ether was added dropwise to the reaction mixture. The mixture was refluxed overnight; then the imine salts were decomposed by slow addition of 20 ml of 10% hydrochloric acid and enough water to dissolve the precipitate. The resulting mixture was extracted with ether. The combined ethereal extracts were washed (water, bicarbonate, and brine), dried over anhydrous sodium sulfate, concentrated, and evaporatively distilled (0.1 mm, 65°) to give 0.27 g (48% yield) of ketone **5** [lit.[14] bp 87–89° (30 mmHg)]: ir (film) 1705 cm^{-1} (C=O); NMR (CCl_4, 60 MHz) δ 0.91 (d, 3 H, J = 7.0 Hz, C-2 methyl), 0.97 (s, 3 H, C-4 axial methyl), 1.27 (s, 3 H, C-4 equatorial methyl), 1.42–2.25 ppm (broad absorption, 6 H).

2-Methyl-4-*tert*-butylcyclohexanone (6). A solution of 1.78 g (18 mmol) of cyclohexylamine in 10 ml of dry benzene was added to a solution of 2.5 g (16 mmol) of 4-*tert*-butylcyclohexanone in 30 ml of dry benzene at room temperature. The mixture was heated to reflux for 12 hr in a flask with a water-separation head. The solvent was removed and the imine, without further purification, was dissolved in 20 ml of tetrahydrofuran and added dropwise to a cold, stirred solution of 32 ml of 1 *M* methylmagnesium bromide over a period of 10 min. The reaction mixture was refluxed for 5 hr under nitrogen. Then 2.56 g (18 mmol) of methyl iodide in 10 ml of tetrahydrofuran was added dropwise to the cooled reaction mixture, and the solution was refluxed overnight. The imine salts were decomposed by dropwise addition of 20 ml of 10% hydrochloric acid and enough water to dissolve the precipitate, and the aqueous layer was extracted with ether. The combined ethereal extracts were washed (water, bicarbonate, and brine), dried over anhydrous sodium sulfate, concentrated, and distilled to give 2.33 g (86% yield) of ketone **6**, bp 130° (0.7 mm). VPC analysis on a 10% SE-30 column at 150° indicated the presence of two components with relative peak areas of 94% (retention time 3.4 min) and 6% (retention time 4.0 min). The former fraction proved to be a mixture of ketone **6a** and **6b**; the latter proved to be the mixture of ketones **7a** and **7b**. The two fractions could be separated preparatively by preparative VPC on a 20-ft 20% SE-30 column at 160° or by liquid chromatography (40:1 hexane–ethyl acetate as the solvent). Spectral data for ketone **6**: ir (film) 1710 cm^{-1} (C=O); NMR (CCl_4, 60 MHz) δ 0.92 (s, 9 H, *tert*-butyl), 0.93 (d, 3 H, J = 8.0 Hz, C-2 equatorial methyl[15,16]), 1.10 ppm (d, 3 H, J = 7.0 Hz, C-2 axial methyl[15,16]).

Enamine Equilibration of 2-Methyl-4-*tert*-butylcyclohexanone (6).[15] A solution of 202 mg (1.2 mmol) of ketones **6a** and **6b** (~18:1) and 142 mg of freshly distilled pyrrolidine in 50 ml of dry benzene was refluxed under nitrogen for 24 hr using a water separator. After removal of the solvent under reduced pressure, the mixture was distilled to give the enamine, bp 80–86° (0.15 mm). Then 10 ml of 50% aqueous acetic acid was added dropwise to a solution of the enamine in 25 ml of dry 1,2-dimethoxyethane with stirring under nitrogen over a period of 2 min. The mixture was stirred for 10 min and poured into a mixture of 100 ml of water and 100 ml of ether. The aqueous layer was extracted with ether, and the combined ethereal extracts were washed (water, bicarbonate, and brine), dried over magnesium sulfate, and concentrated. The residue was evaporatively distilled (0.15 mm, 95°) to give 160 mg of a mixture of ketones **6a** and **6b**. The NMR spectrum indicated that the ratio of the two isomers was about 1:1.

2,6-Dimethyl-4-*tert*-butylcyclohexanone (7).[15] A solution of 1.08 g (15 mmol) of freshly distilled pyrrolidine in 20 ml of dry benzene was added dropwise to a solution of 2.00 g (13 mmol) of 4-*tert*-butylcyclohexanone in 20 ml of dry benzene over a period of 15 min. The reaction mixture was heated to reflux in a 200-ml flask with a phase-separation head under nitrogen for 12 hr. The solvent was removed at reduced pressure and the residue was evaporatively distilled (0.15 mm, 90°) to give 2.4 g of the enamine, *N*-(4-*tert*-butylcyclohex-1-enyl)pyrrolidine. A solution of 2.84 g (20 mmol) of methyl iodide in 20 ml of dry benzene was added slowly to a solution of the aforementioned enamine in 20 ml of dry benzene. The mixture was refluxed overnight; then the enamine salt was decomposed by slow addition of 40 ml of 10% hydrochloric acid and water. The reaction mixture was extracted with ether. The ethereal extracts were washed (water, bicarbonate, and brine), dried over anhydrous sodium sulfate, and concentrated. The residue was evaporatively distilled (0.15 mm, 100°) to give 1.43 g of colorless liquid. VPC analysis on a 10% SE-30 column at 135° showed that the product contained 40% starting ketone, 35% ketone **6**, and 25% ketone **7**. Ketone **7** was isolated by preparative VPC on a 20-ft 20% SE-30 column at 150°.

The NMR spectrum of ketone **7** indicated the presence of both isomers, **7a** and **7b**, in a ratio of 2:1. The structural determination was performed by use of lanthanide shift reagent, $Eu(fod)_3$, and was further confirmed by mass spectra. Spectral data follow: ir (film) 1710 cm^{-1} (C=O); NMR (CCl_4, 60 MHz) δ 2.70–1.20 (broad absorption, 7 H), 1.13 (d, 3, J = 10 Hz, axial CH_3), 1.01 (d, 3, J = 7.0 Hz, equatorial CH_3), and 0.88 ppm [5, 9 H, $C(CH_3)_3$]; mass spectrum (6 kV) *m/e* (rel intensity) 182 (25), 126 (50), 57 (100), and 41 (41). The above spectra are consistent with values reported in the literature.[16]

Triethyl Phosphonoacetate. Freshly distilled ethyl bromoacetate (35 g, 0.21 mol) was added dropwise to 35 g (0.21 mol) of triethyl phosphite. After a 30-min induction period the temperature rose and ethyl bromide began to distil. The remainder of the ethyl bromoacetate was then added at a rate to maintain the reaction. After complete addition, the mixture was refluxed at 170° for 9 hr and distilled to give 37 g (80% yield) of triethyl phosphonoacetate, bp 90° (0.2 mm) [lit. bp 152–153° (20 mm),[17] 109–109.5° (0.8 mm)[18]].

Trimethyl Phosphonoacetate. This material was prepared using the same method as described above but using trimethyl phosphite and methyl bromoacetate as reagents.[19]

Phosphonate Wittig Reactions. Reaction with 2-(3-Butenyl)cyclohexanone (4). A solution of 0.9 g (4 mmol) of triethyl phosphonoacetate in 10 ml of dry 1,2-dimethoxyethane was added in a fast stream of drops to a stirred suspension of 192 mg (4 mmol) of 50% sodium hydride in 5 ml of dry 1,2-dimethoxyethane. The mixture was stirred for 30 min under nitrogen at room temperature; then a solution of 0.5 g (3.3 mmol) of ketone **4** in 10 ml of dry 1,2-dimethoxyethane was added over a period of 5 min at room temperature. The mixture was allowed to stand for 30 hr; then 300 ml of water was added to the mixture and the reaction mixture was extracted with ether. The ethereal extracts were washed (water and brine), dried over anhydrous sodium sulfate, and concentrated. The crude product was eluted through a column (silica gel) using the mixture of hexane–ether (4:1) as the eluting solvent to remove excess phosphonate. The resulting material was evaporatively distilled (0.4 mm, 120°) to give 0.51 g (70% yield) of α,β-unsaturated ester. VPC analysis on a 10% SE-30 column at 165° indicated the presence of two components with relative peak areas of 30% (retention time 6.3 min) and 70% (retention time 7.6 min). The two components were separated by preparative VPC. Spectral analysis showed that the former is ester **9** with Z stereochemistry and the latter is ester **10** with E stereochemistry.

Spectral data for ester **9** follow: ir (film) 1710 (C=O), 1640 (conjugated C=C), 3025, 910, 795 cm^{-1} (terminal–CH=CH_2); NMR (CCl_4, 60 MHz) δ 5.58 (s, 1 H, conjugated vinyl proton), 5.30–6.25 (m, 1 H, –C**H**=CH_2), 4.70–5.20 (m, 2 H, –CH=C**H**$_2$), 4.06 (q, 2 H, J = 7.0 Hz, ethoxy methylene, superimposed on a broad multiplet attributable to one α-methine proton), and 1.28 ppm (t, 3 H, J = 7.0 Hz, ethoxy methyl).

Spectral data for ester **10** follow: ir (film) 1710 (C=O), 1640 (conjugated C=C), 3050, 910, 795 cm^{-1} (terminal –CH=CH_2); NMR (CCl_4, 60 MHz) δ 5.55 (s, 1 H, conjugated vinyl proton), 5.30–6.25 (m, 1 H, –C**H**=CH_2), 4.70–5.20 (m, 2 H, –CH=C**H**$_2$), 4.06 (q, 2 H, J = 7.0 Hz, ethoxy methylene), and 1.28 ppm (t, 3 H, J = 7.0 Hz, ethoxy methyl).

Reaction with 2,4,4-Trimethylcyclohexanone (5). A solution of 182 mg (1.0 mmol) of trimethyl phosphonoacetate in 10 ml of dry dimethylformamide was added in a fast stream of drops to a stirred suspension of 48 mg (1.0 mmol) of 50% sodium hydride in 10 ml of dry dimethylformamide. The mixture was stirred for 30 min under nitrogen at 5°, and then a solution of 68 mg (0.49 mmol) of ketone **5** in 5 ml of dry dimethylformamide was added over a 5-

min period at 5°. The reaction mixture was stirred at room temperature for 48 hr. Then 100 ml of water was added to the mixture, and the reaction mixture was extracted with ether. The ethereal extracts were washed (water and brine), dried over anhydrous sodium sulfate, and concentrated. The residue was eluted through a column (silica gel) by using a mixture of hexane–ether (4:1) as the eluting solvent. The resulting material was evaporatively distilled (0.1 mm, 120°) to give 60 mg of colorless oil which was identified as the starting ketone **5**.

Reaction with 2-Methyl-4-*tert*-butylcyclohexanone (6). I. Reactions Using Trimethyl Phosphonoacetate. A. Reaction with Excess Phosphonate Anion (NaH). A solution of 3.5 g (19.2 mmol) of trimethyl phosphonoacetate in 25 ml of dry dimethylformamide was added in a fast stream of drops to a stirred suspension of 888 mg (18.5 mmol) of 50% sodium hydride in 25 ml of dry dimethylformamide. The mixture was stirred for 30 min under nitrogen at 5°; then a solution of 750 mg (4.5 mmol) of ketone **6** in 20 ml of dry dimethylformamide was added over a period of 15 min at 5°. The reaction mixture was stirred at room temperature for 48 hr. Then 300 ml of water was added to the mixture, and the reaction mixture was extracted with ether. The ethereal extracts were washed (water and brine), dried over anhydrous sodium sulfate, and concentrated. The ester product and unchanged ketone were eluted through a column (silica gel) using the mixture of hexane–ether (4:1) as the eluting solvent. The eluate was evaporatively distilled (0.15 mm, 110°) to give 804 mg (80% yield) of ester products. VPC analysis on a 20-ft 20% SE-30 column at 125° showed that the product contained 4% ketone 6 and had five peaks for the ester products with retention times of 2.4, 2.63, 2.75, 3.1, and 3.4 hr. The last fraction was the major isomer (72% relative to total peak area), and the second and third fractions were not completely separated.

The first fraction was isolated and identified as a β,γ-unsaturated ester. The ir spectrum of this ester shows the carbonyl absorption at 1735 cm^{-1} and the absence of conjugated double bond absorption; the NMR spectrum exhibited a vinyl proton absorption at δ 5.50 ppm (broad singlet), a sharp singlet for the methyl ester at δ 3.60 ppm, a singlet at δ 2.88 ppm for the α-methylene group, a doublet at δ 1.00 ppm with coupling constant J = 7.0 Hz for the C-2 methyl group, and a sharp singlet at δ 0.86 ppm for the *tert*-butyl group.

The ir spectrum of the last fraction shows carbonyl absorption at 1710 cm^{-1} and conjugated double bond absorption at 1640 cm^{-1}. The NMR spectrum exhibits a vinyl proton absorption at δ 5.48 ppm, a broad multiplet at δ 4.20–3.80 ppm for a C-2 methylene proton, a sharp singlet at δ 3.60 ppm for the methyl ester, a doublet at δ 1.05 ppm with coupling constant J = 7.0 Hz for the C-2 methyl group, and a singlet at δ 0.86 ppm for the *tert*-butyl group. The methyl doublet collapsed to a singlet upon decoupling irradiation at δ 2.32 ppm, which indicates that the downfield proton is not coupled to the C-2 methyl group. Ozonolysis of this fraction in a 50:50 mixture of ethyl acetate–acetic acid (see below) gave ketone **6a**, as indicated by the presence of a doublet at δ 0.93 ppm in the NMR spectrum. The above data proved that the last fraction is ester **15a**.

The ir spectrum of the fourth fraction shows carbonyl absorption at 1710 cm^{-1} and conjugated double bond absorption at 1640 cm^{-1}. The NMR spectrum exhibits a vinyl proton absorption at δ 5.58 ppm, a broad multiplet at δ 3.98–3.58 ppm for an equatorial methylene proton, a singlet at δ 3.60 ppm for the methyl ester, a doublet at δ 1.16 ppm with a coupling constant of J = 7.0 Hz for the C-2 methyl group, and a *tert*-butyl group absorption at δ 0.86 ppm. The methyl doublet collapses to a singlet upon decoupling irradiation at δ 2.40 ppm, which indicates that the downfield proton is not coupled to the C-2 methyl group. Ozonolysis of this fraction in a 50:50 mixture of ethyl acetate–acetic acid gave ketone **6b**, which shows a doublet at δ 1.10 ppm in the NMR spectrum. Thus, this fraction is proven to be ester **14a**.

The ir spectrum of the mixture of second and third fractions with the latter as the major component shows carbonyl absorption at 1710 cm^{-1} and conjugated double bond absorption at 1640 cm^{-1}. The NMR spectrum of the mixture shows absorptions attributable to both the major and the minor components. Absorptions assigned to the major component are a vinyl proton absorption at δ 5.48 ppm, a broad multiplet at δ 4.30–3.84 ppm for an α-methine proton, a sharp singlet at δ 3.60 ppm for the methyl ester, and a doublet at δ 1.12 ppm with coupling constant J = 7.0 Hz for the C-2 methyl group. The methyl doublet collapsed to a singlet upon decoupling irradiation at δ 4.00 ppm, indicating that the downfield proton was coupled to the C-2 methyl group. Ozonolysis of this mixture in a 50:50 mixture of ethyl acetate–acetic acid gave predominantly ketone **6b** with small amounts of ketone **6a** indicated by the NMR spectrum. Thus the third fraction was assigned structure **13a**.

The NMR spectrum of the minor component in this mixture of the second and third components exhibits a vinyl proton absorption at δ 5.56 ppm, a C-2 methine proton absorption at δ 2.92 ppm, a doublet at δ 1.08 ppm with coupling constant J = 7.0 Hz for the C-2 methyl group, and also a sharp singlet at δ 0.86 ppm for the *tert*-butyl group. The methyl doublet collapsed to a singlet upon decoupling irradiation at δ 2.92 ppm, indicating that the downfield proton was coupled to the C-2 methyl group. The structure of this ester cannot be ascertained with certainty from available data.

B. Use of Potassium *tert*-Butoxide as Base. A solution of 328 mg (1.8 mmol) of trimethyl phosphonoacetate in 5 ml of dry dimethylformamide was added in a fast stream of drops to 202 mg (1.8 mmol) of potassium *tert*-butoxide in 5 ml of dry dimethylformamide with stirring. The mixture was stirred for 30 min under nitrogen at 0°, and then a solution of 150 mg (0.9 mmol) of ketone **6** in 5 ml of dry dimethylformamide was added over a period of 5 min. The reaction mixture was stirred at room temperature for 30 hr. Then 100 ml of water was added to the mixture, and the reaction mixture was extracted with ether. The ethereal extracts were washed (acid, bicarbonate, and brine), dried over anhydrous magnesium sulfate and concentrated. The residue was distilled evaporatively (0.12 mm, 90°) to give 126 mg (63% yield) of ester products. VPC analysis on column A at 130° showed some starting ketone and five peaks for the isomeric ester products with the same retention times as described above. The last fraction was the major isomer.

C. Reaction with One-Half of the Theoretical Molar Quantity of Anion. A solution of 219 mg (1.2 mmol) of trimethyl phosphonoacetate in 5 ml of dry dimethylformamide was added in a fast stream of drops to a stirred suspension of 15 mg (0.3 mmol) of 50% sodium hydride in 5 ml of dry dimethylformamide. The mixture was stirred for 30 min under nitrogen at 5°, and then a solution of 101 mg (0.6 mmol) of ketone **6** in 5 ml of dry dimethylformamide was added over a period of 5 min at 5°. The reaction mixture was stirred at room temperature for 72 hr; then 100 ml of water was added to the mixture, and the reaction mixture was extracted with ether. The ethereal extracts were washed (water and brine), dried over anhydrous sodium sulfate, and concentrated. The ester product and unchanged ketone **6** were eluted through a column (silica gel) using the mixture of hexane–ether (4:1) as the eluting solvent. The eluate was evaporatively distilled (0.15 mm, 110°) to give 104 mg (77% yield) of products. VPC analysis on a 20-ft 20% SE-30 column at 140° showed starting ketone and five peaks for the ester products. The third and fourth fractions were the predominant isomeric products (~45 and ~46%, respectively, relative to total peak area of ester products), and the last fraction was a minor isomeric product (~7% relative to total peak area of ester products.)

D. Reaction with Approximately Equal Theoretical Molar Quantity of Anion. A solution of 219 mg (1.2 mmol) of trimethyl phosphonoacetate in 5 ml of dry dimethylformamide was added in a fast stream of drops to a stirred suspension of 30 mg (0.6 mmol) of 50% sodium hydride in 5 ml of dry dimethylformamide. The mixture was stirred for 30 min under nitrogen at 5°, and then a solution of 101 mg (0.6 mmol) of ketone **6** in 5 ml of dry dimethylformamide was added over a period of 5 min at 5°. The reaction mixture was stirred at room temperature for 48 hr. Then 100 ml of water was added to the mixture, and the reaction mixture was extracted with ether. The ethereal extracts were washed (water and brine), dried over anhydrous sodium sulfate, and concentrated. The ester product and unchanged ketone **6** were eluted through a column (silica gel) using the mixture of hexane–ether (4:1) as the eluting solvent. The eluate was evaporatively distilled (0.15 mm 110°) to give 114 mg (85% yield) of products. VPC analysis showed the same five peaks for ester products. The third and fourth fractions were the predominant isomeric products (~40 and ~39%, respectively, relative to total peak area of ester products), and the last fraction was a minor isomeric product (~19%).

E. Reaction with Excess Sodium Hydride. A solution of 728 mg (4.0 mmol) of trimethyl phosphonoacetate in 20 ml of dry dimethylformamide was added in a fast stream of drops to a stirred suspension of 288 mg (6.0 mmol) of 50% sodium hydride in 10 ml of dry dimethylformamide. The mixture was stirred for 30 min under nitrogen at 5°, and then a solution of 340 mg (2.0 mmol) of ketone 6 in 15 ml of dry dimethylformamide was added over a period of 10 min at 5°. The reaction mixture was stirred at room temperature for 48 hr. Then 300 ml of water was added to the mixture,

and the reaction mixture was extracted with ether. The ethereal extracts were washed (water and brine), dried over anhydrous sodium sulfate, and concentrated. The ester product and unchanged ketone 6 were eluted through a column (silica gel) using the mixture of hexane–ether (4:1) as the eluting solvent. The eluate was evaporatively distilled (0.15 mm, 95°) to give 343 mg (77% yield) of products. VPC analysis showed some starting ketone and five peaks for the ester products. The last fraction was the major one (70% relative to total peak area), but the first fraction (8% relative to total peak area) was increased over the amounts observed in run A.

II. Reaction Using Triethyl Phophonoacetate. A. Use of Sodium Hydride as Base. A solution of 291 mg (1.3 mmol) of triethyl phosphonoacetate in 5 ml of dry 1,2-dimethoxyethane (glyme) was added in a fast stream of drops to a stirred suspension of 58 mg (1.2 mmol) of 50% sodium hydride in 5 ml of dry 1,2-dimethoxyethane. The mixture was stirred for 30 min under nitrogen at room temperature, and then a solution of 101 mg (0.6 mmol) of ketone 6 in 4 ml of dry 1,2-dimethoxyethane was added over a period of 5 min at 25°. The reaction mixture was stirred at room temperature for 12 hr. Then 200 ml of water was added to the mixture, and the reaction mixture was extracted with ether. The ethereal extracts were washed (water and brine), dried over anhydrous sodium sulfate, and concentrated. The ester product and unchanged ketone were eluted through a column (silica gel) using the mixture of hexane–ether (4:1) as the eluting solvent. The eluate was evaporatively distilled (0.25 mm, 90°) to give 128 mg (90% yield) of product. VPC analysis on a 10% SE-30 column at 130° showed some starting ketone (24% of total peak area) and five peaks for the isomeric ester products with retention times of 30.5, 37.5, 45, 50, and 60 min. The last fraction was the major isomer (~75% relative to total peak area of ester products). Three of the components were isolated pure by preparative VPC. The second and fourth fractions were not isolated owing to the overlapping with the third and fifth fractions, respectively.

The ir spectrum of the first fraction shows carbonyl absorption at 1730 cm^{-1} and the absence of conjugated double bond absorption; the NMR spectrum shows one vinyl proton absorption as a multiplet at δ 5.33–5.69 ppm, ethoxy methylene absorption as a quartet at δ 4.06 ppm (J = 7.0 Hz), two α-methylene protons absorption as a singlet at δ 2.86 ppm, ethoxy methyl absorption as a triplet at δ 1.24 ppm (J = 7.0 Hz), α-methyl absorption as a doublet at δ 1.00 ppm (J = 7.0 Hz), and *tert*-butyl absorption as a singlet at δ 0.88 ppm. The above spectral data indicated that the isomer is a β,γ-unsaturated ester.

Anal. Calcd for $C_{15}H_{26}O_2$: 238.193270. Found: 238.192453.

The ir spectrum of the third fraction shows carbonyl absorption at 1710 cm^{-1} and conjugated double bond absorption at 1640 cm^{-1}; the NMR spectrum of this isomer shows one vinyl proton absorption as a singlet at δ 5.46 ppm, ethoxy methylene absorption as a quartet at δ 4.08 ppm (J = 7.0 Hz) superimposed on a broad multiplet attributable to one C-2 methine proton, ethoxy methyl absorption as a doublet at δ 1.16 ppm (J = 8.0 Hz), and *tert*-butyl absorption as a singlet at δ 0.88 ppm. Decoupling irradiation at δ 3.9 ppm caused collapse of the methyl doublet to a singlet. The above spectral data indicate that the isomer is α,β-unsaturated ester **13b.**

Anal. Calcd for $C_{15}H_{26}O_2$: 288.193270. Found: 238.193621.

The ir spectrum of the last fraction shows carbonyl absorption at 1710 cm^{-1} and conjugated double bond absorption at 1640 cm^{-1}; the NMR spectrum of this isomer shows a vinyl proton absorption as a singlet at δ 5.46 ppm, ethoxy methylene absorption as a quartet at δ 4.08 ppm (J = 7.0 Hz) superimposed on a broad multiplet attributable to one α-methylene proton (equatorial), ethoxy methyl absorption as a triplet at δ 1.16 ppm (J = 7.0 Hz), C-2 equatorial methyl absorption as a doublet at δ 1.06 ppm (J = 6.0 Hz), and *tert*-butyl absorption as a singlet at δ 0.88 ppm. The methyl doublet was collapsed to a singlet by decoupling irradiation at δ ~2.30 ppm. The above spectral data indicate that the isomer is the α,β-unsaturated ester **15b.**

Anal. Calcd for $C_{15}H_{26}O_2$: 238.193270. Found: 238.193387.

B. Use of Potassium *tert*-Butoxide as Base. A solution of 2.02 g (9.0 mmol) of triethyl phosphonoacetate in 15 ml of dry dimethylformamide was added in a fast stream of drops to 672 mg (6.0 mmol) of potassium *tert*-butoxide in 15 ml of dry dimethylformamide with stirring. The mixture was stirred for 30 min under nitrogen at 0°; and then a solution of 0.50 g (3.0 mmol) of ketone 6 in 20 ml of dry dimethylformamide was added over a period of 10 min. The reaction mixture was stirred at 0° for 30 min and at room temperature for 30 hr. Then 200 ml of water was added to the mixture, and the reaction mixture was extracted with ether. The ethereal extracts were washed (3*N* hydrochloric acid, bicarbonate, and brine), dried over anhydrous magnesium sulfate, and concentrated. The excess phosphonate was removed by passage through a column (silica gel) using the mixture of hexane–ether (4:1) as the eluting solvent. The eluate was evaporatively distilled (0.12 mm, 90°) to give 355 mg (50% yield) of ester products. VPC analysis on column A at 130° showed some starting ketone (~5% of total peak area) and five peaks for the isomeric ester products with same retention times as described above. The last fraction was the major isomer (~70% relative to total peak area of ester products). The spectral data were the same as described above.

Reaction with 2,6-Dimethyl-4-*tert*-butylcyclohexanone (7). A solution of 291 mg (1.3 mmol) of trimethyl phosphonoacetate in 10 ml of dry dimethylformamide was added in a fast stream of drops to a stirred suspension of 62 mg (1.3 mmol) of 50% sodium hydride in 5 ml of dry dimethylformamide. The mixture was stirred for 30 min under nitrogen at 5°, and then a solution of 85 mg (0.49 mmol) of a mixture of ketones **7a** and **7b** (about 2:1 ratio) in 10 ml of dry dimethylformamide was added over a period of 5 min at 5°. The reaction mixture was stirred at room temperature for 48 hr. Then 150 ml of water was added to the mixture, and the reaction mixture was extracted with ether. The ethereal extracts were washed (water and brine), dried over anhydrous sodium sulfate, concentrated, and evaporatively distilled (0.15 mm, 110°) to give 56 mg of product identified as the starting ketone 7.

Reaction with Bicyclo[3.2.1]octan-2-one (8). A solution of 405 mg (1.8 mmol) of triethyl phosphonoacetate in 10 ml of dry dimethylformamide was added in a fast stream of drops to a stirred suspension of 86 mg (1.8 mmol) of 50% sodium hydride in 10 ml of dry dimethylformamide. The mixture was stirred for 1.5 hr under nitrogen at room temperature, and then a solution of 200 mg (1.6 mmol) of bicyclo[3.2.1]octan-2-one (8) (Aldrich) in 5 ml of dimethylformamide was added. The reaction mixture was stirred at room temperature for 48 hr, diluted with 200 ml of water, and extracted with ether. The ethereal extracts were washed (water and brine), dried over anhydrous sodium sulfate, and concentrated. The ester product and unchanged ketone were eluted through a column (silica gel) by using the mixture of hexane–ether (4:1) as the eluting solvent. The eluate was evaporatively distilled (0.25 mm, 86°) to give 235 mg (76% yield) of α,β-unsaturated esters. VPC analysis on a 10% Apiezon L column at 160° showed two peaks in a ratio of 2:3 with the retention times of 15.2 and 17.2 min; the former fraction was shown to be ester **11** and the latter to be ester **12.**

Anal. Calcd for $C_{12}H_{18}O_2$: (ester **11**) 194.130670; (ester **12**) 194.130670. Found: (ester 11) 194.129943; (ester **12**) 194.129943.

Spectral data for ester **11** follow: ir (film) 1710 (C=O), 1640 cm^{-1} (conjugated double bond); nmr (CCl_4, 100 MHz) δ 5.34 (s, 1 H, vinyl proton), ethoxy methylene superimposed on a broad multiplet (4.10–4.50 ppm) attributable to a methine proton, and 1.22 ppm (t, 3 H, J = 7.0 Hz, ethoxy methyl).

Spectral data for ester **12** follow: ir (film) 1710 (C=O), 1640 cm^{-1} (conjugated double bond); nmr (CCl_4, 100 MHz) δ 5.46 (s, 1 H, vinyl proton), 4.1 (q, J = 3.5 Hz, ethoxy methylene), 3.55–3.88 (m, 1 H, equatorial methylene proton), and 1.22 ppm (t, 3 H, **J** = 7.0 Hz, ethoxy methyl).

When the above reaction was performed in 1,2-dimethoxyethane for 12 hr, a 68% yield of the same products was obtained.

Ozonolysis of Methyl 2-Methyl-4-*tert*-butylcyclohexylideneacetate (15a).[8,9] A solution of 10 mg of ester **15a** in 15 ml of ethyl acetate and 15 ml of acetic acid at ~20° was treated with an excess of ozone. This solution was allowed to stand cold for 20 min and was then stirred for 30 min with 0.4 g of powdered zinc at room temperature. Filtration and concentration of the filtrate under reduced pressure afforded an oily residue which was evaporatively distilled to give *cis*-2-methyl-4-*tert*-butylcyclohexanone (**6a**). The structure and stereochemistry of ketone **6** were confirmed by VPC and NMR spectroscopy in this and the following ozonolyses.

Ozonolysis of Ester 14a. Ester **14a** (~5 mg) was subjected to ozonolysis in a manner as described above to give *trans*-2-methyl-4-*tert*-butylcyclohexanone (**6b**).

Ozonolysis of the Mixture of Esters Containing Predominantly 13a. A mixture containing mainly **13a** and some of the second ester component (~7 mg) was subjected to ozonolysis in a manner as described above to give ketone **6** with the axial methyl doublet of *trans*-2-methyl-4-*tert*-butylcyclohexanone (**6b**) very distinct. A small amount of equatorial methyl doublet of *cis*-2-methyl-4-*tert*-butylcyclohexanone (**6a**) was also present.

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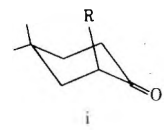
Registry No.—**4,** 16178-83-9; **5,** 2230-70-8; **6a,** 3211-27-6; **6b,** 3211-26-5; **7a,** 20826-63-5; **7b,** 20826-64-6; **8,** 5019-82-9; **9,** 53940-53-7; **10,** 53940-54-8; **11,** 53940-55-9; **12,** 53940-56-0; **13a,** 53940-57-1; **13b,** 53940-58-2; **14a,** 53940-59-3; **15a,** 53940-60-6; **15b,** 53940-61-7; 4,4-dimethylcyclohexanone, 4255-62-3; 4-*tert*-butylcyclohexanone, 98-53-3; pyrrolidine, 123-75-1; *N*-(2-methyl-4-*tert*-butylcyclohex-1-enyl)pyrrolidine, 53940-62-8; triethyl phosphonoacetate, 867-13-0; ethyl bromoacetate, 105-36-2; triethyl phosphate, 122-52-1; trimethyl phosphonoacetate, 5927-18-4; trimethyl phosphite, 121-45-9; methyl bromoacetate, 96-32-2; potassium *tert*-butoxide, 865-47-4.

References and Notes

(1) K. E. Harding, R. C. Ligon, T. Wu, and L. Rode, *J. Am. Chem. Soc.*, **94,** 6245 (1972).
(2) (a) M. Jorgenson and S. Patumtevapibal, *Tetrahedron Lett.*, 489 (1970); (b) H. Hauth, D. Stauffacher, P. Nicklaus, and A. Melera, *Helv. Chim. Acta*, **48,** 1087 (1967); (c) S. Tripett and D. M. Walker, *Chem. Ind. (London)*, 990 (1961).
(3) Although ketones **2** and **5** are conformationally mobile, a chair conformation with an axial C-2 substituent (i) would be highly disfavored by the 1,3-diaxial interactions of the C-2 and C-4 substituents.



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(4) Even under equilibrating conditions, only the 2,6-diequatorial and 2-axial-6-equatorial isomers of ketone **7** are expected to be present to any significant extent.[5]
(5) B. J. L. Huff, F. N. Tuller, and D. Caine, *J. Org. Chem.*, **34,** 3070 (1969).
(6) H. O. House, W. L. Respess, and G. M. Whitesides, *J. Org. Chem.*, **31,** 3128 (1966).
(7) Other examples of phosphonate carbanions giving β,γ-unsaturated esters have been reported: H. Kaneko and M. Okazaki, *Tetrahedron Lett.*, 219 (1966); R. C. Gupta, S. C. Srivastava, P. K. Grover, and N. Anand, *Indian J. Chem.*, **9,** 890 (1971).
(8) R. L. Clarke, S. J. Daum, P. E. Shaw, and R. H. Kullnig, *J. Am. Chem. Soc.*, **88,** 5865 (1966).
(9) R. B. Turner, O. Buchardt, E. Herzog, R. B. Morin, A. Riebel, and J. M. Sanders, *J. Am. Chem. Soc.*, **88,** 1766 (1966).
(10) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N.Y., 1965, p 113.
(11) N. L. Allinger and H. M. Blatter, *J. Amer. Chem. Soc.*, **83,** 994 (1961).
(12) W. S. Johnson and W. P. Schneider, *Org. Synth.*, **30,** 18 (1950).
(13) K. E. Harding, R. C. Ligon, C.-Y. Tseng, and T.-C. Wu, *J. Org. Chem.*, **38,** 3478 (1973).
(14) M. Yanagita and S. Inayama, *J. Org. Chem.*, **19,** 1725 (1954).
(15) B. J. L. Huff, F. N. Tuller, and D. Caine, *J. Org. Chem.*, **34,** 3070 (1969).
(16) J. M. Conia and P. Briet, *Bull. Soc. Chim. Fr.*, 3881, 3888 (1969).
(17) G. M. Kosolapoff, *J. Am. Chem. Soc.*, **67,** 1180 (1945).
(18) J. Wolinski and K. L. Erickson, *J. Org. Chem.*, **30,** 2208 (1965).
(19) The trimethyl phosphonacetate was kindly provided by Dr. A. F. Isbell, Texas A&M University.

Polyfluoroaryl Carbonyl Chemistry. Benzalacetophenones

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The polyfluorobenzalacetophenones **1, 2,** and **3** have been prepared and the effects of pentafluorophenyl groups on infrared and ultraviolet spectral properties evaluated. When the carbonyl is flanked by C_6F_5, haloform-type cleavage occurs readily in alkaline medium. The subject compounds undergo Michael addition of diethyl malonate with difficulty, but react with C_6H_5MgBr and C_6F_5MgBr to give 1,4-addition products, although in two cases the bimolecular compounds **8** and **9** are formed.

As part of studies on the effects of polyfluoroaryl substitution on the reactivity of neighboring functional groups, we have examined a variety of carbonyl compounds.[2] In this paper we report our observations on the chemistry of polyfluorobenzalacetophenones. The discussion is divided into three parts: preparation, spectral properties, and chemical reactions.

Preparation. Compounds **1, 2,** and **3** were all prepared by the Claisen–Schmidt reaction[3] (eq 1). Pentafluoro-

$$ArCHO + Ar'COCH_3 \xrightarrow{OH^-} ArCH{=}CHCAr' + H_2O \quad (1)$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad O$$

$$Ar = C_6H_5, C_6F_5$$
$$Ar' = C_6H_5, C_6F_5$$

$C_6F_5CH{=}CH{-}CC_6H_5$ (O) — **1**

$C_6H_5CH{=}CHCC_6F_5$ (O) — **2**

$C_6F_5CH{=}CHCC_6F_5$ (O) — **3**

benzaldehyde reacted with acetophenone in aqueous ethanolic alkali to give pentafluorobenzalacetophenone (**1**)[4] in 50% yield.

2,3,4,5,6-Pentafluoroacetophenone, required for the preparation of benzalpentafluoroacetophenone (**2**) and 2,3-dihydryl-*F*-benzalacetophenone[5] (**3**), was obtained in 56% yield by reaction of bis(pentafluorophenyl)cadmium with acetyl chloride (eq 2). In the subsequent condensation

$$2C_6F_5MgBr + CdCl_2 \longrightarrow [(C_6F_5)_2Cd] \xrightarrow{CH_3COCl} C_6F_5COCH_3 \quad (2)$$

reactions, the concentration of sodium hydroxide was reduced from the usual 6–7% to 1.5% and **2** and **3** were obtained in excellent yield (84–87%). At higher concentrations of alkali, a significant side reaction occurred, which will be discussed later. Compound **3** was prepared previously in 50% yield by a Wittig reaction.[6]

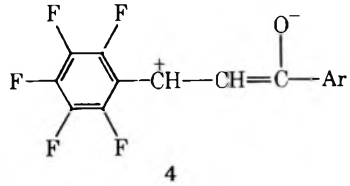
Spectral Properties. Infrared and ultraviolet spectral data for the benzalacetophenones are listed in Table I. The influence of neighboring fluorine atoms on carbonyl stretching frequencies has been reported previously.[7] The effect of the pentafluorophenyl group in shifting the ester carbonyl band to higher frequencies has been described.[2a] This trend is also evident in the present study.

Whereas benzalacetophenone exhibits $\nu_{C=O}$ 1667 cm^{-1}, the pentafluorophenyl group in **1** (ν 1674 cm^{-1}) causes an increase in double-bond character of the carbonyl group by minimizing charge delocalization, e.g., **4**. Although the para fluorine alone would enhance the contribution of **4**, the

Table I
Infrared and Ultraviolet Data for Fluorinated Benzalacetophenones[a]

	$\nu_{C=O}$, cm^{-1}	λ_{max}, nm	ϵ_{max}
$C_6H_5CH{=}CHC(=O)C_6H_5$	1667 (vs)	310	23,400
$C_6F_5CH{=}CHC(=O)C_6H_5$ (1)	1674 (s)	287	25,500
$C_6F_5CH{=}CHC(=O)C_6F_5$ (3)	1689 (s)	287	20,500
	1677 (m)		
$C_6H_5CH{=}CHC(=O)C_6F_5$ (2)	1678 (s)	307	21,600
	1666 (vs)		

[a] Carbon tetrachloride was the solvent for the infrared studies; 95% ethanol was used for the ultraviolet spectra.



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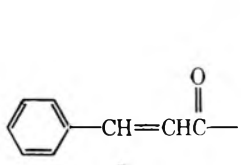
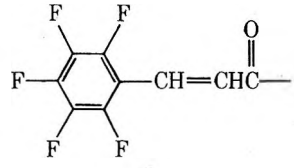
total effect of the C_6F_5 group is to destabilize the positive charge on the benzylic carbon.[8] 2,3-Dihydryl-*F*-benzalacetophenone (3) exhibits two carbonyl bands. The absorption at higher frequency (1689 cm^{-1}) is attributed to the additive effects of two pentafluorophenyl groups, the inductive influence of the C_6F_5 adjacent to >C=O, and destabilization of structure 4. The lower frequency band (1677 cm^{-1}) probably arises as a result of charge–dipole repulsion between carbonyl oxygen and the ortho fluorines of the neighboring fluoroaryl ring, which forces the ring out of the plane of the >C=O group. Similar considerations would also explain the dual absorption in 2.

It is evident from the ultraviolet data that the cinnamoyl systems 5 and 6 are the chromophores which absorb in the



5

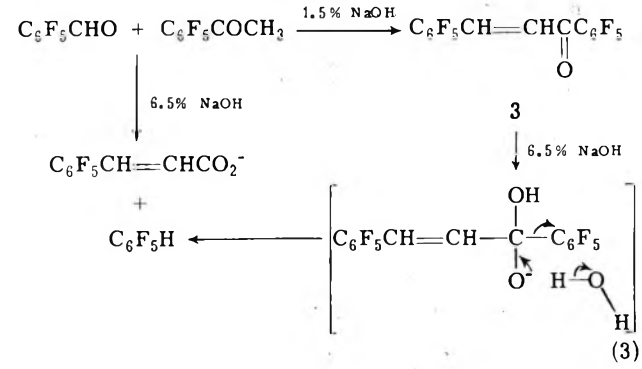


6

287–310-nm region. The nature of the aryl group attached to carbonyl is of little consequence, in agreement with previous reports[9,10] for benzalacetophenone, but contrary to the claim[11] that the entire molecule is responsible for these absorptions. In 5, π-electron delocalization makes an important contribution, while the C_6F_5 group, by destabilizing structures, such as 4, causes a hypsochromic shift. Thus, the ultraviolet and infrared spectra of these compounds are totally consistent.

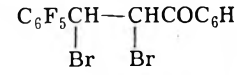
Benzalacetophenones usually exist as the trans isomers.[12] To obtain evidence of the configuration in the fluorinated compounds, proton magnetic resonance spectra were obtained for 2 and 3. Since all seven protons in 2 exhibit peaks in the same region, interpretation is difficult. However, the spectrum of 3 revealed two doublets located at δ 7.62 and 7.22, J_{HH} = 16 Hz, indicative of a trans configuration.[13] The doublet at δ 7.22 is further split into a triplet, indicating coupling of the benzylidene proton with the ortho fluorines of the adjacent pentafluorophenyl ring.

Reactions. With Alkali. As mentioned earlier, compounds 2 and 3 were prepared in excellent yield when the concentration of alkali was carefully controlled. In an attempt to prepare 3 by using a 6.5% solution of sodium hydroxide in aqueous ethanol, the sole products isolated were 2,3,4,5,6-pentafluoro-*trans*-cinnamic acid[14] and pentafluorobenzene (detected by GC). This observation provides another example of what is now well established,[14,15] that the C_6F_5 group adjacent to carbonyl behaves as a pseudo-halogen which undergoes haloform-type cleavage to pentafluorobenzene in alkaline medium (eq 3). Compound 2 behaves similarly to give cinnamic acid, while benzalacetophenone and 1, in which the carbonyl is flanked by phenyl, are unreactive under these conditions.



(3)

With Bromine. Addition of bromine to 1 gave the expected dibromide (7) in 93% yield, but the subsequent reac-



7

tion of 7 with sodium methoxide, followed by acidification, failed to yield the dibenzoylmethane, a reaction which proceeds readily with benzalacetophenone dibromide.[16] The material isolated in low yield was not characterized, other than to establish the presence of weak –C≡C– absorption in the infrared.

With Grignard Reagents. Since conjugate addition of phenylmagnesium bromide to benzalacetophenone to yield β,β-diphenylpropiophenone is a classic reaction,[17] we examined the behavior of the fluorinated chalcones 1–3 with phenylmagnesium bromide and all four chalcones with pentafluorophenylmagnesium bromide. The reactions were conducted by normal addition, with the Grignard reagent in 25% molar excess. The results are summarized in Table II. All of the reactions proceed by 1,4-addition to the α,β-unsaturated carbonyl systems to give saturated ketones. There was no evidence of the presence of tertiary alcohols due to 1,2-addition. However, in two cases, both involving the fluorine-containing Grignard, reaction proceeded beyond the initial 1,4-addition. On the basis of analytical data and infrared spectra, we believe that the products possess structures 8 and 9 (Table II), formed by reaction of 2 mol of the appropriate chalcone per mole of organometallic.

The formation of these bimolecular products from benzalacetophenone and 1 can be explained by the preferential attack on unreacted chalcone by the initially generated carbanion in successful competition with the weakly nucleophilic pentafluorophenylmagnesium bromide (Scheme I). Only when this carbanion is consumed after 1,4-addition to a second molecule of chalcone does the Grignard reagent again attack unreacted starting material to regenerate more of the carbanion. Bimolecular compounds are not observed in corresponding reactions with phenylmagnesium bromide because the phenyl anion is a better nucleophile than the intermediate carbanion. The failure to form biomolecular products by reaction of C_6F_5MgBr with 2 and 3 might be due to low nucleophilicities of the carbanions (vis-a-vis $C_6F_5\delta^-$ $(MgBr)\delta^+$) when flanked by the pentafluorobenzoyl group. In such cases, the anion probably exists primarily in the enolate form.[2b]

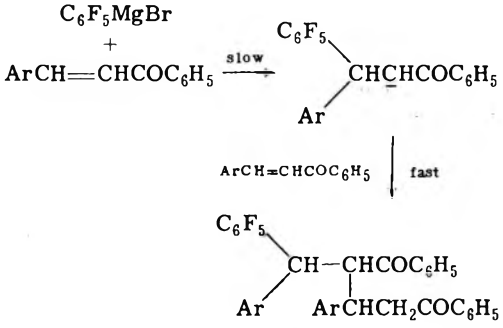
Michael Addition. All three polyfluorinated benzalace-

Table II
Reactions of Benzalacetophenones with Grignard Reagents

Reactants	Product	Yield, %	$\nu_{C=O}$, cm^{-1}
C_6H_5MgBr + $C_6H_5CH{=}CHCOC_6H_5$	$(C_6H_5)_2CHCH_2COC_6H_5$	81	1690
C_6H_5MgBr + $C_6F_5CH{=}CHCOC_6H_5$	see Experimental Section		1685
C_6H_5MgBr + $C_6H_5CH{=}CHCOC_6F_5$	$(C_6H_5)_2CHCH_2COC_6F_5$	83	1720
C_6H_5MgBr + $C_6F_5CH{=}CHCOC_6F_5$	$(C_6H_5)(C_6F_5)CHCH_2COC_6F_5$	60	1720
C_6F_5MgBr + $C_6H_5CH{=}CHCOC_6H_5$	$(C_6H_5)(C_6F_5)CHCHCOC_6H_5$ $C_6H_5CHCH_2COC_6H_5$ **8**[a]	36	1680, 1690
C_6F_5MgBr + $C_6F_5CH{=}CHCOC_6H_5$	$(C_6F_5)_2CHCHCOC_6H_5$ $C_6F_5CHCH_2COC_6H_5$ **9**[a]	42	1690
C_6F_5MgBr + $C_6H_5CH{=}CHCOC_6F_5$	$(C_6H_5)(C_6F_5)CHCH_2COC_6F_5$	45	1720
C_6F_5MgBr + $C_6F_5CH{=}CHCOC_6F_5$	$(C_6F_5)_2CHCH_2COC_6F_5$	40	1720

[a] Proposed structure.

Scheme I



8, Ar = C_6H_5
9, Ar = C_6F_5

tophenones failed to undergo the Michael reaction with diethyl malonate under the same experimental conditions in which benzalacetophenone gives the addition product in 90% yield.[18] Neither piperidine nor triethylamine were effective catalysts and the chalcones were recovered almost quantitatively. However, when 1 was mixed with 1 molar equiv of sodium diethyl malonate in ethanol at room temperature, reaction occurred. Although we were unsuccessful in isolating a solid product, we found that the infrared spectrum of the crude material was compatible with the Michael addition product, **10**, since both this material and

$C_6F_5CHCH_2COC_6H_5$
$CH(CO_2C_2H_5)_2$

10

the compound obtained from benzalacetophenone exhibited $\nu_{C=O}$ 1696 cm^{-1}.

Experimental Section

Except where noted, melting points are corrected and were obtained with a total immersion thermometer in an oil bath. Infrared spectra were obtained in carbon tetrachloride on a Perkin-Elmer Model 21 spectrophotometer. Ultraviolet spectra were measured in 95% ethanol using a Cary Model 11 PM spectrophotometer.

With carbon tetrachloride as the solvent, proton magnetic resonance spectra were obtained at 60 MHz on a well-calibrated Varian A-60 spectrometer. The precision of line frequencies was estimated to be ±0.5 Hz. The probe temperature was approximately 25°. The results are reported as δ values.

The elemental analyses were carried out by Micro-Tech Laboratories, Skokie, Ill.

Pentafluorobenzaldehyde was both synthesized[13] and purchased from Imperial Smelting Corp. Ltd., Bristol, England. Bromopentafluorobenzene and pentafluorobenzoyl chloride were obtained from Imperial Smelting Corp., and malonyl dichloride was purchased from Aldrich Chemical Co., Milwaukee, Wis.

Benzalacetophenone. Benzalacetophenone was prepared according to a previously described procedure.[19] After recrystallization from 95% ethanol, the product, mp 55.0–56.0°, was obtained in 58% yield.

Pentafluorobenzalacetophenone (1). A solution of 6.6 g (0.165 mol) of sodium hydroxide in 60 ml of water and 30 ml of 95% ethanol was placed in a 100-ml beaker equipped with a magnetic stirrer. Freshly distilled acetophenone (16.4 g, 0.135 mol) was added, the beaker was surrounded with crushed ice, and the stirrer was started. Pentafluorobenzaldehyde (26.4 g, 0.135 mol) was added at once (temperature rise) and a yellow solid immediately precipitated. The mixture was stirred at 20° for 1 hr, and the solid was filtered off, washed several times with water until all of the base had been removed, and finally washed with cold 95% ethanol. After air drying, the product, mp 144–146°, weighed 20.0 g (50%). It was recrystallized three times from an absolute ethanol–benzene solution (55% alcohol, 45% benzene v/v). After drying in vacuo, the light yellow powder melted at 144.6–145.8° (lit.[4] mp 142–143°); 2,4-dinitrophenylhydrazone, mp 217.8–218.4° (lit.[4] mp 187–189°). Anal. Calcd for $C_{15}H_7F_5O$: C, 60.42; H, 2.37. Found: C, 60.74; H, 2.52. λ_{max} (EtOH) 287 nm (ϵ 25,500); ir 1674 cm^{-1} (s).

2,3,4,5,6-Pentafluoroacetophenone. In a 250-ml, three-necked, round-bottomed flask fitted with an efficient stirrer, a reflux condenser, and a dropping funnel with a nitrogen inlet tube were placed 3.0 g (0.12 mol) of magnesium turnings and 30 ml of anhydrous ether (dried over sodium). Bromopentafluorobenzene (30 g, 0.12 mol) in 45 ml of dry ether was added over a 60-min period. After addition was complete, the mixture was stirred at room temperature for 1 hr. The flask was cooled in ice, the dropping funnel was removed, and 11.7 g (0.064 mol) of anhydrous cadmium chloride (dried at 100°) was added over a 5-min period. The funnel was replaced, the ice bath was removed, and the mixture was heated under reflux for 75 min. At this point the Gilman test for the presence of Grignard reagent was negative. The flask and condenser were arranged for distillation and ether was removed by distilla-

tion as stirring was continued until the residue became very viscous. Anhydrous, thiophene-free benzene (45 ml) was added, and 15 ml of liquid was removed by distillation. An additional 45 ml of benzene was added and the reflux condenser replaced. The mixture was refluxed with vigorous stirring for a few minutes, then cooled to 5° and a solution of 8.3 g (0.11 mol) of freshly distilled acetyl chloride in 25 ml of dry benzene was added during 2–3 min. After addition was complete, the mixture was stirred at room temperature for 18 hr, poured into 150 g of crushed ice containing 75 ml of 25% sulfuric acid, and the resulting two-phase mixture stirred for 5 min. The dark brown benzene layer was separated, and the water layer extracted with two 30-ml portions of benzene. The combined benzene layers were washed successively with 45 ml of saturated sodium chloride solution, 45 ml of saturated sodium bicarbonate solution, 45 ml of water, and 25 ml of saturated sodium chloride solution. The benzene layer was dried over anhydrous sodium sulfate and the benzene removed on a flash evaporator at room temperature. The dark residue was distilled in vacuo to give 14.0 g (56%) of 2,3,4,5,6-pentafluoroacetophenone, bp 65–66° (5 Torr), ^{1}H NMR δ 2.67 (q_5).

2,3,4,5,6-Pentafluorocinnamic Acid. A solution of 0.60 g (0.015 mol) of sodium hydroxide in 5.2 g of water and 4.0 ml of 95% ethanol was placed in a 30-ml beaker equipped with a magnetic stirrer. The solution was stirred and cooled with ice; then 2.5 g (0.012 mol) of 2,3,4,5,6-pentafluoroacetophenone was added at once. This was followed by the immediate addition of 2.36 g (0.012 mol) of pentafluorobenzaldehyde. The mixture quickly turned yellow, then red-brown. In a few minutes, two liquid phases were evident. After an additional 1.5 hr of stirring at 25°, the mixture was left in a refrigerator for 15 hr. No precipitate formed. On acidification of the mixture with dilute hydrochloric acid, the white 2,3,4,5,6-pentafluorocinnamic acid precipitated, mp 146–148°, λ_{max} (EtOH) 260 nm.[13] This material rapidly decomposed on exposure to air.

2,3-Dihydryl-*F*-benzalacetophenone (3). A solution of 0.10 g (0.0025 mol) of sodium hydroxide in 4.2 g of water and 3.2 ml of 95% ethanol was placed in a 30-ml beaker equipped with a magnetic stirrer. The solution was stirred and cooled with ice; then 2.0 g (0.0095 mol) of 2,3,4,5,6-pentafluoroacetophenone was added at once. This was followed by the immediate addition of 1.89 g (0.0096 mol) of pentafluorobenzaldehyde. The mixture rapidly turned yellow, and after a few minutes of stirring, two yellow liquid phases were evident. After nearly 2 hr of stirring at room temperature, a yellow solid formed which was filtered off, washed with water to remove alkali, and air dried. The yellow powder weighed 3.1 g (84%). After a double sublimation the product was in the form of white leaflets, mp 58.4–59.0° (lit.[5] mp 56–57.5°); 2,4-dinitrophenylhydrazone, mp 208.4–209.0°. Anal. Calcd for $C_{15}H_2F_{10}O$: C, 46.41; H, 0.52. Found: C, 46.85; H, 0.73. λ_{max} (EtOH) 287 nm (ϵ 20,500); ir 1689 (s), 1677 cm^{-1} (m); ^{1}H NMR δ 7.62 (d), 7.22 (d), further split into a triplet.

Benzalpentafluoroacetophenone (2). A solution of 0.10 g (0.0025 mol) of sodium hydroxide in 4.2 g of water and 3.2 ml of 95% ethanol was placed in a 30-ml beaker equipped with a magnetic stirrer. The solution was stirred and cooled with ice; then 2.1 g (0.01 mol) of 2,3,4,5,6-pentafluoroacetophenone was added at once. This was followed by the immediate addition of 1.06 g (0.011 mol) of benzaldehyde. A two-phase yellow mixture quickly formed. After a few minutes a solid precipitated, and after 1 hr of stirring at room temperature, the yellow solid was removed by filtration. The solid was washed with water to remove alkali and air dried. The product weighed 2.6 g (87%). Three recrystallizations from 95% ethanol gave white needles, mp 102.2–102.9°; 2,4-dinitrophenylhydrazone, mp 246.8–248.0°. Anal. Calcd for $C_{15}H_7F_5O$: C, 60.42; H, 2.37. Found: C, 60.43; H, 2.51. λ_{max} (EtOH) 307 nm (ϵ 21,600); ir 1678 (m), 1666 cm^{-1} (s).

Pentafluorophenylmagnesium Bromide and Benzalacetophenone. To 1.43 g (0.0585 g-atom) of magnesium turnings just covered with a layer of ether was added at once an approximately 10-ml portion of the solution containing 12 g (0.0488 mol) of bromopentafluorobenzene and 60 ml of ether, while the reaction mixture was being stirred magnetically under a nitrogen atmosphere. After reaction had started and spontaneous refluxing ensued, the remainder of the solution of bromopentafluorobenzene was added dropwise to maintain a gentle reflux. An ice bath was employed to cool the flask whenever the reaction became too vigorous. After addition was complete, the mixture was stirred at room temperature for 2–3 hr, until most of the magnesium had reacted. At this point, the Grignard solution, which was virtually black, was cooled in an ice bath, and a solution containing 8.1 g (0.039 mol) of benzalacetophenone and 81 ml of ether was added dropwise to the solution of Grignard reagent. After addition, the mixture was stirred at room temperature under a nitrogen atmosphere for approximately 18 hr, then decomposed with ice and a saturated solution of ammonium chloride to obtain a clear aqueous phase under the dark organic layer. After the ether layer was separated, the aqueous phase was extracted with ether (3 × 50 ml), and the combined ether layers dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The dark oily residue was kept in a vacuum desiccator overnight. The ir spectrum of this oily residue revealed a strong band at 1685 cm^{-1}, but no band in the hydroxyl region. When the residue was treated with a small amount of alcohol, a solid appeared after a few days. After two recrystallizations from alcohol–benzene, 4.1 g (36%) of white needles, mp 183–184°, was obtained. Anal. Calcd for $C_{36}H_{25}F_5O_2$: C, 73.97; H, 4.31; mol wt, 584. Found: C, 73.86; H, 4.35; mol wt (Rast), 570.

The ir spectrum displayed a partially resolved doublet at 1680 and 1690 cm^{-1}. The above data indicate that this compound is probably 3,5-diphenyl-5-pentafluorophenyl-4-benzoylvalerophenone (8).

Pentafluorophenylmagnesium Bromide and Pentafluorobenzalacetophenone (1). The reaction was carried out according to the procedure described for the reaction between pentafluorophenylmagnesium bromide and benzalacetophenone.

Pentafluorobenzalacetophenone (5.96 g, 0.02 mol) in 40 ml of ether was treated with pentafluorophenylmagnesium bromide, prepared from bromopentafluorobenzene (6.18 g, 0.025 mol) in ether (31 ml) with 0.73 g (0.03 g-atom) of magnesium. The ir spectrum of this crude product did not show any hydroxyl band. The viscous, dark residue, after treatment with decolorizing carbon and alcohol, gave a light-colored solid, mp 152–155°. Recrystallization from alcohol–benzene (4:1) yielded approximately 3 g (42%) of needles, mp 158–159°. Anal. Calcd for $C_{36}H_{15}F_{15}O_2$: C, 56.56; H, 1.97; mol wt, 764. Found: C, 56.25, 56.69; H, 1.87, 2.20; mol wt (Rast), 710. The ir spectrum displayed bands at 1690 (C=O), 1525 and 1505 cm^{-1} (aromatic ring). The data indicated that this compound is probably 3,5,5-tris(pentafluorophenyl)-4-benzoylvalerophenone (9).

Pentafluorophenylmagnesium bromide with Benzalpentafluoroacetophenone (2). This reaction was carried out according to the method described above. The Grignard reagent, prepared from 1.02 g (0.00413 mol) of bromopentafluorobenzene and 0.12 g (0.005 g-atom) of magnesium, was treated with 1 g (0.0033 mol) of benzalpentafluoroacetophenone. The ir spectrum of the crude solid product did not exhibit hydroxyl absorption. After two crystallizations from alcohol, 0.7 g (45%) of product was obtained, mp 63–64.5°. Anal. Calcd for $C_{21}H_8F_{10}O$: C, 54.09; H, 1.73. Found: C, 53.94; H, 1.70. Ir 1720 (C=O), 1525 and 1500 cm^{-1} (aromatic ring), in accord with the structure of 2,2,3 trihydryl-3-phenyl-1,3-*F*-diphenyl-1-propanone.

Pentafluorophenylmagnesium Bromide with 2,3-Dihydryl-*F*-benzalacetophenone (3). The procedure employed for the reaction between pentafluorophenylmagnesium bromide and benzalacetophenone was used. Bromopentafluorobenzene (3.09 g, 0.0125 mol) in 15 ml of ether, 0.364 g (0.015 g-atom) of magnesium, and 3.88 g (0.01 mol) of 2,3-dihydryl-*F*-benzalacetophenone in 20 ml of ether were used. The dark oily product gave no evidence of hydroxyl absorption in the ir spectrum. This material was dissolved in hot absolute ethanol, treated with Norite, and filtered. On cooling, white plates precipitated which were crystallized from absolute ethanol. In this manner, 2.2 g (40% yield) of 2,2,3-trihydryl-1,3,3-*F*-triphenyl-1-propanone was obtained, mp 63.5–64.5°. Anal. Calcd for $C_{21}H_3F_{15}O$: C, 45.34; H, 0.54. Found: C, 45.37; H, 0.77. Ir 1720 (C=O), 1525 and 1500 cm^{-1} (aromatic ring).

Phenylmagnesium Bromide with Benzalacetophenone. This reaction was carried out using 0.365 g (0.015 g-atom) of magnesium, 1.98 g (0.0125 mol) of bromobenzene in 6 ml of ether, and 2.08 g (0.01 mol) of benzalacetophenone in 20 ml of ether, according to the procedure described previously for reaction of pentafluorophenylmagnesium bromide and benzalacetophenone. The oily residue, upon treatment with a small amount of alcohol, gave a white solid. The ir spectrum of this crude product in carbon tetrachloride showed no evidence of a hydroxyl group. After recrystallization from ethanol, 2.3 g (81%) of 1,3,3-triphenyl-1-propanone was obtained, mp 95–96° (lit.[17] mp 96°), ir 1690 cm^{-1} (C=O).

Phenylmagnesium Bromide and Pentafluorobenzalacetophenone (1). Pentafluorobenzalacetophenone (5.96 g, 0.02 mol) was treated with phenylmagnesium bromide, prepared from 0.73 g (0.03 g-atom) of magnesium and 3.93 g (0.025 mol) of bromobenzene, following the usual procedure. From this mixture was ob-

tained a light brown, oily material which after thorough drying in a vacuum desiccator did not reveal the presence of a hydroxyl band in the infrared spectrum. All attempts to isolate a solid product from this oily material were unsuccessful. The ir spectrum of this oil showed strong carbonyl absorption at 1685 cm^{-1}.

Phenylmagnesium Bromide and Benzalpentafluoroacetophenone (2). Benzalpentafluoroacetophenone (2 g, 0.0067 mol) was treated with phenylmagnesium bromide prepared from 0.24 g (0.01 g-atom) of magnesium and 1.31 g (0.0084 mol) of bromobenzene, following the usual procedure. About 2.3 g of crude product, which melted around 110°, was obtained readily. This solid gave no evidence of a hydroxyl group in the ir spectrum. Colorless needles (2.1 g, 83%) were obtained after crystallization from absolute ethanol, mp 116.5–118°. Anal. Calcd for $C_{21}H_{13}F_5O$: C, 67.02; H, 3.48. Found: C, 67.59; H, 3.46. The ir spectrum of this compound, 1-pentafluorophenyl-3,3-diphenyl-1-propanone: 1720 (C=O), 1530 and 1502 cm^{-1} (aromatic ring).

Phenylmagnesium Bromide and 2,3-Dihydryl-*F*-benzalacetophenone (3). 2,3-Dihydryl-*F*-benzalacetophenone (1.25 g, 0.00323 mol) was treated with phenylmagnesium bromide prepared from 1.14 g (0.00403 mol) of bromobenzene and 0.12 g (0.00485 g-atom) of magnesium, following the usual procedure. The ir spectrum of the crude product did not show any hydroxyl band. Colorless needles (0.9 g, 60%) were obtained after two crystallizations from absolute ethanol, mp 63–64.5°. The infrared spectrum and melting point were identical with those of 2,2,3-trihydryl-3-phenyl-1,3-*F*-diphenyl-1-propanone, prepared by reaction of pentafluorophenylmagnesium bromide with benzalpentafluoroacetophenone. There was no depression in mixture melting point of the two products.

Reactions of Benzalacetophenones with Diethyl Malonate and Piperidine. A previously described procedure[17] was followed. An alcoholic solution of ketone, diethyl malonate, and piperidine was refluxed in an oil bath for 3 days. The reaction mixture was cooled and enough water was added to precipitate solid material. The solid was collected by filtration and washed with water, then with cold 95% ethanol, and crystallized from ethanol.

All of the materials used were thoroughly purified before use. Diethyl malonate was distilled under reduced pressure, piperidine was distilled from potassium hydroxide, and alcohol was distilled from magnesium ethoxide.

All compounds isolated were identified by mixture melting points and infrared spectra.

With Benzalacetophenone. Ethyl α-carbethoxy-β-phenyl-γ-benzoylbutyrate (0.94 g, 85%), mp 70–71° (lit.[17] mp 70–71°), was isolated from the reaction of 0.625 g (0.003 mol) of benzalacetophenone, 0.48 g (0.003 mol) of diethyl malonate, and 0.0255 g (0.003 mol) of piperidine in 3 ml of alcohol.

With Pentafluorobenzalacetophenone (1). Pentafluorobenzalacetophenone 0.894 g (0.003 mol), 0.48 g (0.003 mol) of diethyl malonate, 0.0255 g (0.0003 mol) of piperidine, and 3 ml of alcohol were used. About 0.8 g of pentafluorobenzalacetophenone was recovered.

With 2,3-Dihydryl-*F*-benzalacetophenone (3). This ketone (**3**, 0.388 g, 0.001 mol), 0.16 g (0.001 mol) of diethyl malonate, 0.0282 g (0.0003 mol) of piperidine, and 3 ml of alcohol were used. About 0.25 g of purified **3** was recovered.

With Benzalpentafluoroacetophenone (2). Benzalpentafluoroacetophenone (0.894 g, 0.003 mol), 0.48 g (0.003 mol) of diethyl malonate, 0.0255 g (0.0003 mol) of piperidine, and 3 ml of alcohol was used. About 0.7 g of the starting ketone was recovered.

Pentafluorobenzalacetophenone (1) with Sodium Diethyl Malonate. Sodium diethyl malonate was prepared from sodium ethoxide (0.01 mol in 10 ml of alcohol) and diethyl malonate (0.60 g, 0.01 mol) by refluxing the mixture for 3 hr. Then pentafluorobenzalacetophenone (2.98 g, 0.01 mol) was mixed with the sodium diethyl malonate in ethyl alcohol (40 ml) and stirred at room temperature for approximately 24 hr. The orange-colored reaction mixture was acidified with a sufficient amount of acetic acid, and most of ethyl alcohol was removed under vacuum. The resulting syrup was mixed with 150 ml of carbon tetrachloride and 50 ml of *n*-hexane, and filtered to remove insoluble material. A viscous residue was obtained from the filtrate when solvent was removed. All attempts to obtain a solid product from the residue were unsuccessful. The infrared spectrum of this crude product (residue) in carbon tetrachloride showed a band at 1696 cm^{-1}.

Pentafluorobenzalacetophenone (1) with Diethyl Malonate and Triethylamine. Pentafluorobenzalacetophenone (2.98 g, 0.01 mol) was dissolved in a minimum amount of ethyl alcohol (40 ml) and mixed with diethyl malonate (0.01 mol, 1.6 g), triethylamine (0.28 ml, 0.02 mol), and 1 drop of acetic acid. After 24 hr of heating under reflux, 2.5 g of starting material was recovered.

Pentafluorobenzalacetophenone Dibromide (7). Pentafluorobenzalacetophenone (5.0 g, 0.017 mol) was dissolved in 50 ml of carbon tetrachloride and 100 ml of chloroform and the mixture was cooled to 0°. Bromine (2.7 g, 0.017 mol) was added with stirring and, after addition was complete, stirring at 0° was continued for 1 hr. The mixture was then allowed to warm to room temperature over a 1-hr period and the solvent stripped off on a flash evaporator. The white pentafluorobenzalacetophenone dibromide remained, 7.13 g (93%), mp 115–118°.

Reaction of 7 with Sodium Methoxide. Pentafluorobenzalacetophenone dibromide (3.5 g, 0.0074 mol) in 5.0 ml of absolute methanol was heated to reflux with stirring in a three-necked flask fitted with a condenser, a dropping funnel, and a magnetic stirrer. A solution of 0.825 g (0.0153 mol) of sodium methoxide in 6.0 ml of absolute methanol was added over 50 min,[13] a yellow solution being formed. Refluxing was continued for an additional 10 min. The mixture was acidified with 0.2 ml of concentrated hydrochloric acid and refluxed for 5 min. Cold water (5.0 ml) was then added and the mixture was rapidly cooled in ice, forming a yellow solid. This was removed by filtration, washed with water, and recrystallized from methanol to give 0.6 g of a white solid, mp 95–110° after three recrystallizations, ir 2200 cm^{-1} (w, $-C{\equiv}C-$). The material was not examined further.

Registry No.—**1**, 54081-32-2; **1** 2,4-DNP, 54053-74-6; **2**, 54081-33-3; **2** 2,4-DNP, 54019-70-4; **3**, 32782-50-6; **3** 2,4-DNP, 54003-52-0; **7**, 54003-53-1; **8**, 54003-54-2; **9**, 54003-55-3; benzalacetophenone, 614-47-1; acetophenone, 98-86-2; pentafluorobenzaldehyde, 653-37-2; 2,3,4,5,6-pentafluoroacetophenone, 652-29-9; bromopentafluorobenzene, 344-04-7; 2,3,4,5,6-pentofluorocinnamic acid, 34234-46-3; benzaldehyde, 100-52-7; phenyl bromide, 108-86-1; 2,2,3-trihydryl-3-phenyl-1,3-*F*-diphenyl-1-propanone, 54036-73-6; 2,2,3-trihydryl-1,3,3-*F*-triphenyl-1-propanone, 54003-56-4; 1-pentafluorophenyl-3,3-diphenyl-1-propanone, 54003-57-5; 1,3,3-triphenyl-1-propanone, 606-86-0; diethyl malonate, 105-53-3; piperidine, 110-89-4; sodium diethyl malonate, 996-82-7; triethylamine, 121-44-8; sodium methoxide, 124-41-4.

References and Notes

(1) Abstracted, in part, from the M.S. thesis of V.D.B., Jan 1966, and the Ph.D. thesis of H.H.K., June 1967.
(2) (a) R. Filler, J. F. White, A. J. Kacmarek, and I. J. Solomon, *Can. J. Chem.*, **44**, 2346 (1966); (b) R. Filler, Y. S. Rao, A. Biezais, F. N. Miller, and V. D. Beaucaire, *J. Org. Chem.*, **35**, 930 (1970).
(3) "Organic Syntheses", Collect. Vol. I, Wiley, New York, N.Y., 1941, p 78.
(4) N. G. Ivanova, V. A. Barkhash, and N. N. Vorozhtsov, Jr., *Zh. Obshch. Khim.*, **39**, 1347 (1969); *Chem. Abstr.*, **71**, 80878w (1969).
(5) This nomenclature conforms to the rules recently approved by the American Chemical Society for naming highly fluorinated organic compounds. To fully conform to the nomenclature recommended by the Division of Organic Chemistry (*Adv. Chem. Ser.*, No. 126), this compound should be named *trans*-2,3-dihydryl-1,3-*F*-diphenyl-2-propen-1-one.
(6) V. M. Vlasov, *Zh. Vses. Khim. Ova.*, **15**, 476 (1970); *Chem. Abstr.*, **75**, 35600w (1971).
(7) (a) R. Filler, *J. Am. Chem. Soc.*, **76**, 1376 (1954); (b) D. R. Husted and A. H. Ahlbrecht, ibid., **75**, 1605 (1953); (c) G. Rappaport, M. Hauptschein, J. F. O'Brien, and R. Filler, ibid., **75**, 2695 (1953); (d) E. T. McBee and D. L. Christman, ibid., **77**, 755 (1955); (e) R. Filler and S. M. Naqvi, *Tetrahedron*, **19**, 879 (1963).
(8) (a) R. Filler, C. S. Wang, M. A. McKinney, and F. N. Miller, *J. Am. Chem. Soc.*, **89**, 1026 (1967); (b) G. A. Olah and M. B. Comisarow, ibid., **89**, 1027 (1967); (c) S. V. Kulkarni, R. Schure, and R. Filler, ibid., **95**, 1859 (1973).
(9) W. B. Black and R. E. Lutz, *J. Am. Chem. Soc.*, **77**, 5134 (1955).
(10) L. N. Ferguson and R. P. Barnes, *J. Am. Chem. Soc.*, **70**, 3907 (1948).
(11) H. H. Szmant and A. J. Basso, *J. Am. Chem. Soc.*, **74**, 4397 (1952).
(12) R. E. Lutz and R. H. Jordan, *J. Am. Chem. Soc.*, **72**, 4090 (1950).
(13) N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, "NMR Spectra Catalog", No. 1, Varian Associates, Palo Alto, Calif., 1962.
(14) A. K. Barbour, M. W. Buxton, P. L. Coe, R. Stephens, and J. C. Tatlow, *J. Chem. Soc.*, 808 (1961).
(15) P. L. Coe, R. G. Plevey, and J. C. Tatlow, *J. Chem. Soc. C*, 597 (1966).
(16) Reference 3, p 205.
(17) (a) E. P. Kohler, *Am. Chem. J.*, **31**, 642 (1904); (b) M. S. Kharasch and D. C. Sayles, *J. Am. Chem. Soc.*, **64**, 2972 (1942).
(18) R. Connor and D. B. Andrews, *J. Am. Chem. Soc.*, **56**, 2713 (1934).
(19) Reference 3, p 78.

On the Use of Geminal Coupling Constants of Methylene Protons Adjacent to Carbonyl Groups for Structural and Conformational Assignments

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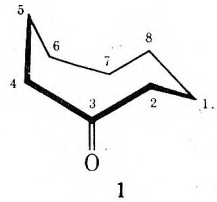
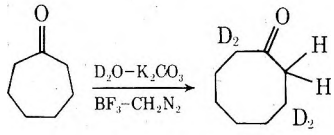
The analysis of the pmr spectrum of cyclooctanone-2,2,7,7-d_4 at −160° provides two values of geminal coupling constants: ^2J = −11.0 and −16.0 Hz. The least negative value is associated with the methylene protons on C(2) of the BC conformation (1) and demonstrates unambiguously that the prediction of the Barfield–Grant relationship is wrong in the vicinity of θ = 120° and, further, provides an order of magnitude for the positive contribution to ^2J from a carbonyl group predicted by molecular orbital calculations. The angular dependence of ^2J is discussed in light of these results.

In connection with another conformational study[1,2] we became interested in the precise relationship of the angular dependence of the geminal coupling constant characteristic of the methylene protons in the $-CH_2C(=O)-$ fragment. A brief review of the literature[3-10] has revealed that the graphical relationships obtained from semiempirical calculations[4,5] were generally valid but that uncertainties still persisted in the vicinity of θ = 120° [11] for which the two methods of calculations predict opposite effects—negative by the valence-bond approach[4] and positive by the molecular orbital approach.[5]

It appears that experimental verification of theory has been hampered by the fact that relatively few compounds of known rigid conformation have the particular geometry of interest. This situation led us to investigate cyclooctanone, whose stable conformation is known to be a boat-chair (BC, 1)[12] for which molecular models suggest pertinent geometrical dispositions between the carbonyl group and the adjacent methylene groups at positions 2 and 4.



1



2

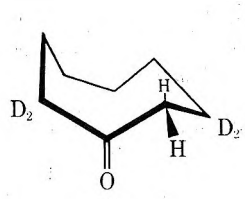
Consequently the partially deuterated cyclooctanone-2,2,7,7-d_4 (**2**), having a simplified ^{1}H NMR spectrum, was prepared from cycloheptanone as shown above through α-deuteration followed by ring expansion with diazomethane.[13]

Results and Discussion

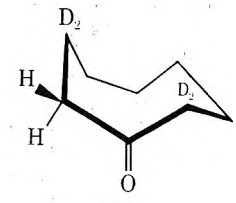
The 100-MHz deuterium-decoupled ^{1}H NMR spectrum of **2** at 25° shows a singlet at δ 2.36 (α-CH_2), a band centered at δ 1.9 (2 H), and a broad band centered at δ 1.5 (6 H). Figure 1 illustrates the spectral changes occurring as the temperature is lowered. At −135°, the AB quartet ($\Delta\nu \approx$ 48 Hz and $^2J \approx$ −14 Hz) observed at low field is easily recognized as arising from the α-CH_2 protons; the apparent asymmetric intensities observed are caused partly by greater exchange broadening of the downfield doublet and partly by the superposition of the upfield doublet on a very broad band arising from a change in the signal originally at δ 1.9. The left half of the quartet is seen to broaden significantly at −145°, whereas the lines of the right half remain much narrower. Eventually at −160°, two AB are easily recognized as characteristic of the α-CH_2 protons of **2** (the line diagrams under the spectrum identify each quartet). Overlapping with the broad signal again accounts for the observed departure from symmetric intensities.

The spectral lines of the AB patterns are naturally broad at this low temperature[14] but it is nevertheless possible to determine precise values for the ^{1}H NMR parameters. Analysis provides $\Delta\nu$ = 73.0 ± 0.5 Hz and ^2J = −11.0 ± 0.3 Hz for one quartet and $\Delta\nu$ = 29.5 ± 0.5 Hz and ^2J = −16.0 ± 0.2 Hz for the other quartet.

The spectral changes observed are characteristic of the slowing down of both pseudo-rotation ($\Delta G^\ddagger$ = 6.3 kcal/mol) and ring inversion ($\Delta G^\ddagger$ = 7.5 kcal/mol) for cyclooctanone[12] such that at −160° the spectrum contains signals characteristic of the two different methylene groups in the two possible diastereomeric BC forms of **2**, namely **2a** and **2b**. Consequently each of the two ^2J values measured must



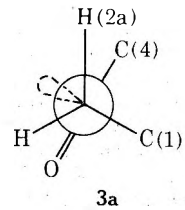
2a



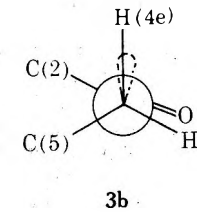
2b

be assigned to one of these diastereomers [*i.e.*, to the methylene protons on either C(2) or C(4) of the BC conformation].

Molecular models reveal that the relationships between the α-CH_2 protons and the carbonyl group in **2a** and **2b** are as shown by structures **3a** and **3b**, respectively. The first



3a



3b

one represents the projection about the C(2)–C(3) bond of BC and shows that the π-orbital lobe and methylene protons are essentially staggered; thus the expected ^2J value is equal to that predicted for a dihedral angle (θ) near 120°. On the other hand, **3b** illustrates the projection about the C(4)–C(3) bond and shows that the π-orbital lobe and H(4e) are essentially eclipsed; the expected ^2J value is then predicted for θ near 0°.[4] It is therefore clear[3-10] that the

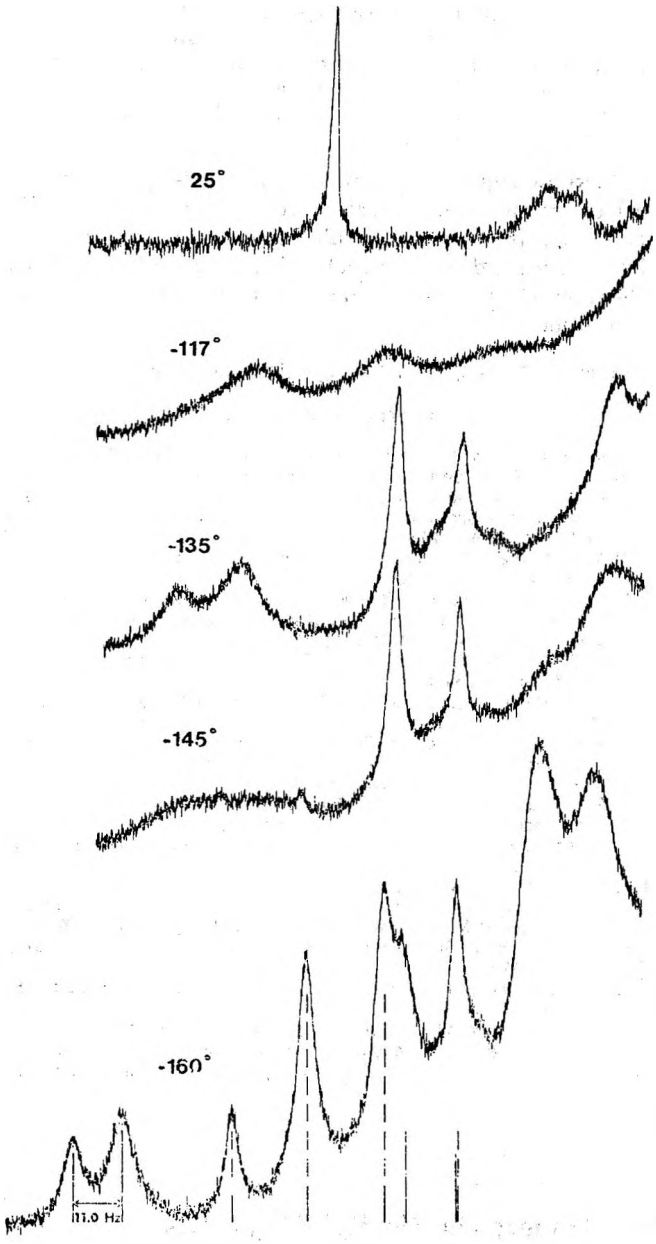


Figure 1. The 100-MHz deuterium-decoupled ^1H NMR spectrum of the two lower field signals of **2** at 25° and the spectral change observed at lower temperatures.

less negative coupling constant (−11.0 Hz) must be associated with the C(2) methylene protons while the more negative coupling (−16.0 Hz) must be associated with the C(4) protons.

There exists ample evidence[6,7] illustrating that ^2J is also dependent on the magnitude of the C–CH_2–C angle. Accordingly it must be noted that this angle is undoubtedly larger in cyclooctanone than in either methane or cyclohexane. Estimates of 115–117° are realistic[15] and consequently the reference value to which contributions (ΔJ) from the π-bond orientation are to be referred should be more negative than −12.4 (methane) or −13.0 Hz (cyclohexane).[3,4] The value of −14.3 Hz determined for cyclooctane-d_{14}[16] is probably the most appropriate reference on which a semiquantitative rationalization of our results can be based. Consequently the empirical value of ΔJ = −1.7 Hz for the protons on C(4) shows excellent agreement with an estimate for $\theta \simeq 0°$ predicted theoretically from the Barfield–Grant relationship.[4] On the other hand, the value of ΔJ = +3.3 Hz for the protons on C(2) definitely contradicts the prediction for $\theta \simeq 120°$. This positive contribution to ^2J, in fact, agrees with the qualitative prediction of the molecular

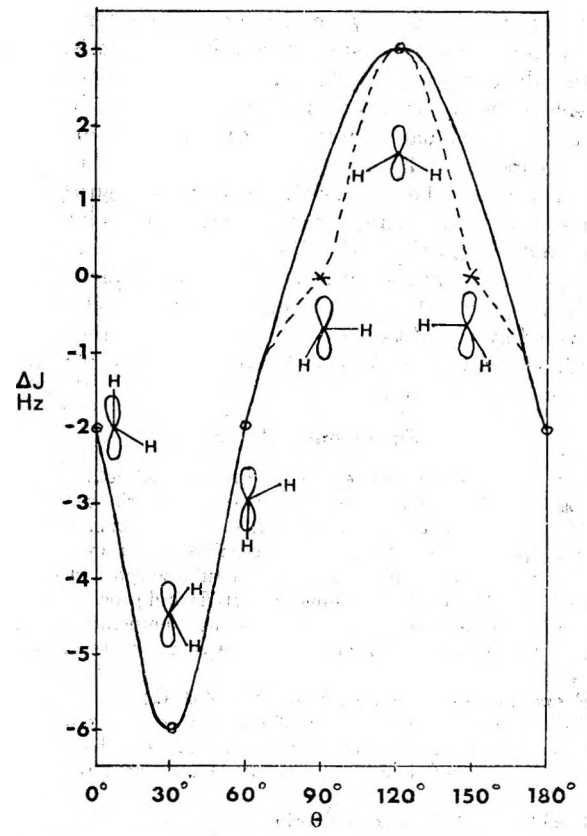


Figure 2. Graphical representation of the effect of the dihedral angle (θ) between a methylene group and the π lobes of an adjacent carbonyl group on ^2J. The small drawings illustrate the projection of the methylene protons on the π bond for several values of θ.

orbital theory[5] and essentially fixes the order of magnitude for such a positive contribution by a carbonyl group.

Because of the uncertainty in depicting the absolute disposition of the carbonyl group in **1** from molecular models, the above ΔJ values must not be interpreted in the most quantitative sense. The important significance is that, in the range of 0 to 180° for θ, $\Delta J \cong -2$ Hz is a good estimate of the carbonyl contribution for θ in the vicinity of 0, 60, and 180°, while $\Delta J \cong +3$ Hz is a good estimate of the carbonyl contribution for θ in the vicinity of 120°.

Molecular orbital calculations[5] have shown that the negative contribution (θ = 0 to ~90°) is caused by hyperconjugative electron withdrawal from the antisymmetric orbitals of the CH_2 group, whereas the positive contribution ($\theta \sim 90$ to ~150°) is caused by electron withdrawal from the symmetric orbitals. The theory also predicts that both effects should be essentially null at 90°.

Although the absolute values of ΔJ for θ = 30 and 90° are not known with great precision, the value of −6 Hz has been proposed as an estimate for θ = 30° from a consideration of experimental data.[4,6,7] Experimental evaluation of ΔJ near 90° has involved the analysis of cyclohexanone derivatives for which $\theta \approx 86°$ [7] and it has been found that ΔJ is indeed close to zero.

The ambiguity in the vicinity of 120° having been removed convincingly by our results, it is therefore tempting to draw a curve as in Figure 2 to illustrate graphically the angular dependence of ΔJ with θ. Two possibilities are shown near 90° (solid and dotted lines) and it is difficult to choose between them at the present. It is, however, reassuring that the difference between both lines is within 1 Hz. Since experience[6,7] has shown that such a curve should in practice be visualized as a narrow band to reflect uncertainties arising from factors not related to the presence of the carbonyl group, the difference between the two lines is

not very significant for practical applications. On the other hand, analytical expressions describing the precise behavior are dependent on the ΔJ value at 90° and it appears desirable to wait for more experimental results before attempting to evaluate empirically the constants involved in such expressions.[4,10b]

Accordingly, the relationship shown in Figure 2 illustrates clearly that many structural alternatives involving a carbonyl group can be identified confidently in a practical way and the great insight into the local environment of the carbonyl group of the BC conformation of cyclooctanone provided by the ^2J values of 2 further stresses the power of geminal couplings as a sensitive probe for specific conformational relationships.

Experimental Section

The VPC analyses and separation were carried out on a Varian Aerograph A90-P3 instrument using helium as carrier gas.

The ^{1}H NMR spectra were obtained at 100 MHz on a 5% solution of cyclooctanone-2,2,7,7-d_4 (2) in chlorodifluoromethane containing a small quantity of Me_4Si in a tube which had been degassed and sealed. The instrumental details and procedures are as described earlier[17] with the exception that temperatures are reported to ±1° since greater precision was not necessary in this work.

Preparation of Cyclooctanone-2,2,7,7-d_4 (2). Cycloheptanone (1.5 g), 60 ml of D_2O, and 6.0 g of K_2CO_3 were refluxed for 5 hr. After cooling, the ketone was extracted with ether. The ether solution was then dried with $MgSO_4$ and its volume was adjusted to 30 ml.

Freshly distilled boron trifluoride etherate (1 ml) was added to the solution followed by portions of a diazomethane solution in ether[13] while stirring adequately. Aliquots of the reaction mixture were taken periodically and analyzed by VPC using a Carbowax 20M column at 175° in order to monitor the extent of ring expansion. The reaction was stopped when the chromatogram suggested that about 60% of the mixture was cyclooctanone. Water (20 ml) was added and the ether layer was then separated and washed with a saturated solution of $NaHCO_3$ and with water and then dried over $MgSO_4$. The solution was concentrated and the cyclooctanone present was isolated by preparative VPC using a UC-W-98 column (15 ft × 0.375 in., 165°).

Reinjection of the isolated product on a Carbowax column showed it to be free of other ketones and to have the same retention time as an authentic commercial (Aldrich) sample of cyclooctanone. The ^{1}H NMR spectrum (Figure 1) shows that the isotopic purity of the cyclooctanone-2,2,7,7-d_4 (2) thus prepared is sufficient for the planned study.

Acknowledgment. We wish to acknowledge the technical contribution of Robert Mayer, who recorded the ^{1}H NMR spectra, several stimulating discussions with Cambyse Vaziri, and the financial assistance from the National Research Council of Canada and the Quebec Ministry of Education.

Registry No.—**2**, 53927-13-2; cycloheptanone, 502-42-1.

References and Notes

(1) M. St-Jacques and C. Vaziri, *Tetrahedron Lett.*, **42**, 4331 (1972).
(2) C. Vaziri, Ph.D. Thesis, Université de Montréal, 1974.
(3) L. M. Jackman and S. Sternhell, "Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N.Y., 1969, p 273.
(4) M. Barfield and D. M. Grant, *J. Am. Chem. Soc.*, **85**, 1899 (1963); *Adv. Magn. Reson.*, **1**, 149 (1965).
(5) (a) J. A. Pople and A. A. Bothner-By, *J. Chem. Phys.*, **42**, 1339 (1965); (b) G. E. Maciel, J. W. McIver, Jr., N. S. Ostlund, and J. A. Pople, *J. Am. Chem. Soc.*, **92**, 4151 (1970).
(6) R. C. Cookson, T. A. Crabb, J. J. Frankel, and J. Hudec, *Tetrahedron, Suppl.*, **No. 7**, 335 (1966).
(7) R. Cahill, R. C. Cookson, and T. A. Crabb, *Tetrahedron*, **25**, 4711 (1969).
(8) V. F. Bystrov, *Russ. Chem. Rev.*, **41**, 281 (1972).
(9) F. I. Carroll and J. T. Blackwell, *Tetrahedron Lett.*, 4173 (1970).
(10) (a) R. R. Fraser and B. F. Raby, *J. Am. Chem. Soc.*, **94**, 3458 (1972); (b) R. R. Fraser and R. N. Renaud, *Can. J. Chem.*, **49**, 755 (1971).
(11) The dihedral angle θ is defined as in ref 4. It is the dihedral angle between the π orbital and a C–H bond. The definition of the dihedral angle ϕ in ref. 5 and 10 is such that $\phi = \theta - 30°$.
(12) (a) F. A. L. Anet, M. St-Jacques, P. M. Henrichs, A. K. Cheng, J. Krane, and L. Wong, *Tetrahedron*, **30**, 1629 (1974); (b) F. A. L. Anet, M. St-Jacques, and P. M. Henrichs, *Intra-Sci. Chem. Rep.*, **4**, 251 (1970).
(13) F. A. L. Anet, M. St-Jacques, and G. N. Chmurny, *J. Am. Chem. Soc.*, **90**, 5243 (1968).
(14) F. A. L. Anet, G. N. Chmurny, and J. Krane, *J. Am. Chem. Soc.*, **95**, 4423 (1973).
(15) References cited in F. A. L. Anet, *Top. Curr. Chem.*, **45**, 169 (1974).
(16) F. A. L. Anet and M. St-Jacques, *J. Am. Chem. Soc.*, **88**, 2585 (1966).
(17) M. Bernard, L. Canuel, and M. St-Jacques, *J. Am. Chem. Soc.*, **96**, 2929 (1974).

Formation and Interconversion of Allene Dimers via Bisallyl Diradicals. Possibilities on and Documentation of the Supergraph

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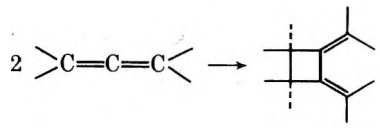
A coding system is developed to handle interconversions among 1,2-dimethylenecyclobutanes (D) and associated planar (P) and orthogonal (O) bisallyl diradicals. In the most general case, a graph of 320 edges links the 64 D's, 32 P's, and 32 O's. Compact labels for the species and algorithms for interconversion steps DO, OP, etc., have been devised. Relationships among those D's, P's, and O's which formally originate in the allene KHC=C=CHK are summarized in several graphs.

Graph theory or systems analysis[1] has recently been applied to isomerizations. That is, given species ML_n, e.g., a trigonal bipyramid or octahedral complex, one can describe all of the permutational isomers and their isomerization paths either by a graph or in a topological representation.[2] For example, the graph of the 1,2 rearrangements of the carbocation $R_1R_2R_3C-CR_4R_5^+$ involves 30 distinct interconversions (edges) among the 20 isomers (points).[2a] Here we wish to focus on an example of complex genealogy in allene dimer chemistry in which three different structural types, each with its set of permutational isomers, are variously connected by bond-making, bond-breaking, and conformational interconversions. A graph derived for this system may be regarded as a projection of the energy hypersurface on which these species lie, through which reactant coordinates pass, and with which mechanisms must be consistent. The important feature that deserves emphasis is that the present approach can be generalized to even more complex systems in which groups of species of different symmetries are interconvertible.

A common entry into the 1,2-dimethylenecyclobutanes is via allene dimerization.[3]



(1)

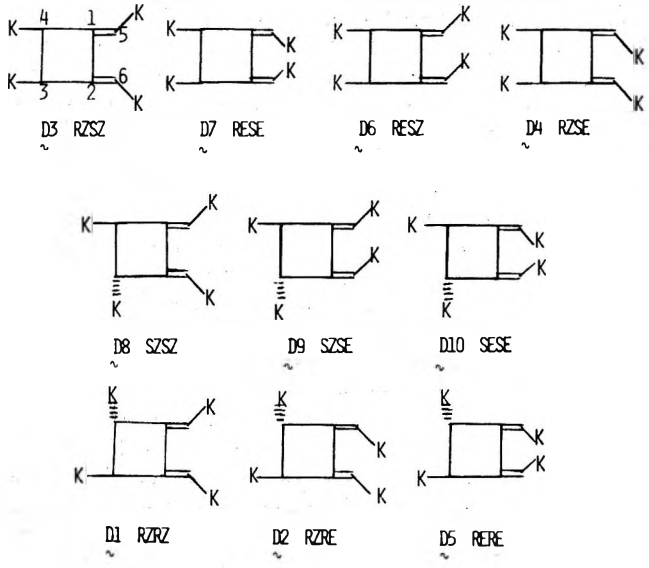
D

There are, of course, other C_6 species which are isomeric with D, e.g., 1,3-dimethylenecyclobutane, biscyclopropylidene, 3,4-dimethylene-1-hexene, methylenespiropentane, etc., and other paths to D, e.g., from $\Delta^{1,4}$-bicyclo[2.2.0]hexene.[4] These possibilities are all interesting and often chemically significant but will be excluded to keep the problem at hand manageable. As it is, numerous isomeric dimers can be derived from various allenes in process 1: $K_2C{=}C{=}CH_2$ (3); $HKC{=}C{=}CH_2$ (10); $KLC{=}C{=}CH_2$ (10); KHC=C=CKH (10); KHC=C=CLH (36); JHC=C=CKL (36); abC=C=Ccd + efC=C=Cgh (64). This diversity is by no means hypothetical, since there are numerous examples of D mixtures resulting from the dimerization of allenes.[3]

Evolution of a Typical Graph. The allene, HKC=C=CKH, leads to a dimer set of intermediate complexity, which will be used as the focus of this section. The isomers are set out in detail in Chart I. It is generally agreed that

Chart I

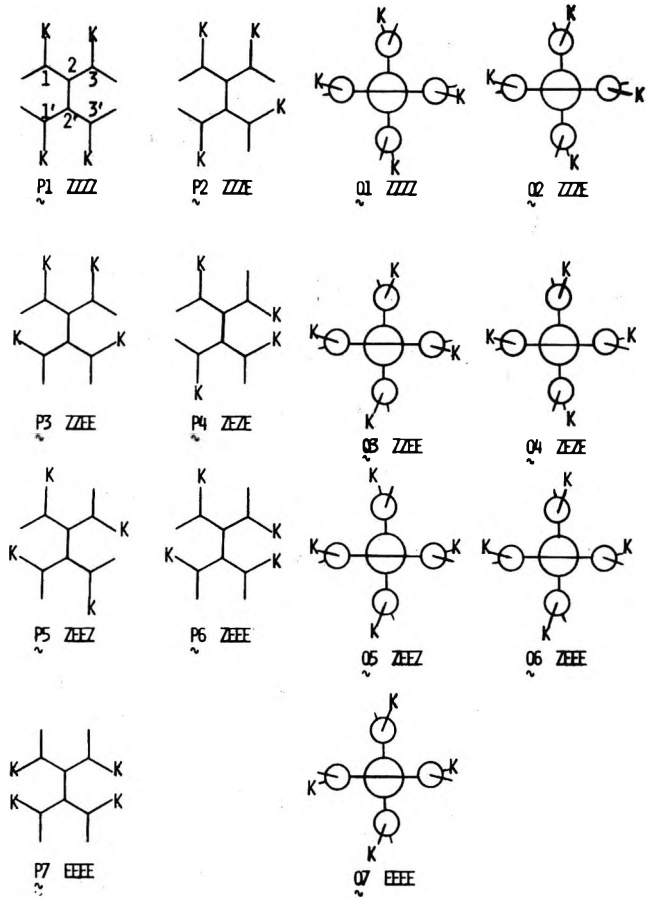
1,2-Dimethylenecyclobutanes, D, Derived from the Dimerization of KCH=C=CHK. Labels are *R*, Rectus; *S*, Sinister; *E*, Sequential Trans; *Z*, Sequential Cis



process 1 as well as the interconversions among D probably occur via 2,2′-bisallyl diradicals.[4-7] These radicals may take up an infinite number of conformations but we arbitrarily designate the wholly planar (P) and orthogonal (O) forms of bisallyl as the primarily interesting or pertinent ones for the problem at hand. To facilitate visualizing and manipulating O, we use a hybrid Fischer–Newman projection: the 2 and 2′ carbon atoms are represented in projection at the center of the large circle, the 1 and 3 carbon atoms are at the centers of the top and bottom circles, respectively, and the 1′ and 3′ carbon atoms are at the centers of the left and right circles, respectively; as is customary, a circle defines a projection plane and lines (bonds) which cross the circle are projected from the front and those which do not cross are projected from behind onto the plane.[5] All of the P and O isomers are given in Chart II. With the aid of these projection formulas it is easily seen that, except for the enantiomeric pair O4 and O5, the O's have a plane of symmetry perpendicular to the projection plane: no optical isomers are possible.

Chart II

Planar (P) and Orthogonal (O) Bisallyl Diradicals Derived from KCH=C=CHK



We proceed now to "connect" the isomers. That is, interconversions among them result from rotations about the middle (2,2′) or end (1,2 or 2,3, etc.) bonds of the bisallyl diradical. Specifically, rotation around the middle bond interconverts P's and O's, while rotations around end bonds interconvert P's to P's or O's to O's. Either by inspection or the use of models one can find all of the rotation between the pairs of isomers. These are summarized in a PO graph (Figure 1). Note that the 14 species are linked by 25 edges.

Among the numerous processes open to the bisallyl diradical, e.g., dissociation, rearrangement, etc., we confine our attention to its collapse to 1,2-dimethylenecyclobutane (D). There are, however, several stereoelectronic restraints on the accessible modes of ring closure. The molecular orbitals of the P and O forms have been characterized[8] and ring closure to or ring opening from D have been specified as disrotatory for P and conrotatory for O.[8a,9] Four conrotatory *least motion* conversions of an O species, which involve ca. $\pi/4$ changes of the bonds, are given in Figure 2. (Non-least-motion closure involving ca. $3\pi/4$ bond changes were rejected.)

In Figure 1 we give the three PD graphs for the allowed disrotatory cyclizations from all P's to D's and two OD graphs for O to D openings. There are 16 PD and 18 OD edges or reaction steps represented in Figure 1.

The reaction steps in Figure 1 are, of course, energy limited. Because of electron delocalization in the allylic halves of P and O, barriers to end rotations (B_e) are somewhat higher than the usual single-bond barriers in hydrocarbons:

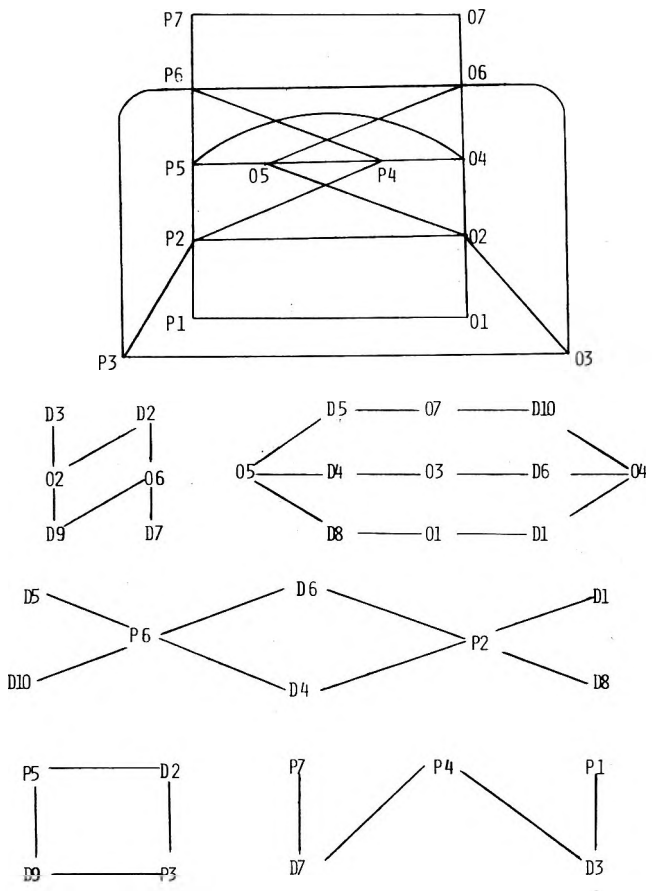


Figure 1. Graphs of the interconversions of dimeric species formed from the allene, HKC=C=CHK: 1,2-dimethylenecyclobutanes (D); planar (P) and orthogonal (O) bisallyl diradicals.

12 to 13 ± 2 kcal/mol has been suggested.[10] Secondly, it is probable that the O's are at, or close to, local energy minimums. Molecular orbital calculations indicate an energy difference (B_m) which places unsubstituted P ca. 4 or 10 kcal/mol above O.[8] Depending on the method of calculation, one may have to adjust B_m for the interaction of the 1,1′ and 3,3′ inward-facing hydrogen atoms. For unsubstituted bisallyl, crude limits on this steric energy can probably be set at <3.75 and >1 kcal/mol by the rotational barriers of 2,3-dimethylbutane and biphenyl.[11] (These considerations only permit one to assume a skew structure—we use the orthogonal geometry because of its simplicity and symmetry.) Thirdly, ring formation from diradicals, e.g., to cyclobutane, appears to have an energy barrier (E_c) of ca. 8 kcal/mol.[12] If such a barrier also holds for bisallyl, then it appears that $B_e > E_c > B_m$. All of these barriers become important when one confronts the complete graph of a given system and must make decisions relevant to specific reaction paths.[3-5]

Documentation of the Supergraph. In this section we consider P, O, and D and their interconversions as a topological problem. In the background is also the notion of storing in and retrieving from a computer sets of related species and reactions.[2h,13] The supergraph, which includes graphs of conformational (PP, PO) as well as chemical changes (PD, OD) and also contains this information, is too complex to picture, but one can obtain it or portions of it by means of a computer. Previous analyses of this type have often dealt with a single set of permutational isomers, but systems involving several kinds of isomerism and conversion processes are also on record.[2h,i]

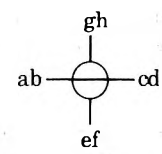
Each species consists of a basic carbon framework and eight peripheral groups. There are a variety of representations of such structures.[14] However, by labeling the gross framework D, P, and O, and by adopting certain IUPAC stereochemical conventions, we can code each species concisely. The following rules are used:[15] a has priority over b, c has priority over d, etc.; ab has priority over cd, which has priority over ef, etc; all of these substituents have priority over carbons; ab, cd, ef, and gh are associated with R, R′, r, and r′ or Z, Z′, z, and z′ configurations, respectively, depending on whether they are bonded to the ring or the methylene groups, ba, dc, fe, and hg are associated with S, S′, s, and s′ or E, E′, e, and e′ configurations, respectively, depending on whether they are bonded to the ring or the methylene groups. For a *normal* or *standard* label, ab and cd precede ef and gh; labels for the ring substituents of each pair precede those for the methylene substituents. Together with the letter D a four-letter label is adequate to characterize all of the isomers (Octal numbers could also have been used.[16]) Since it is sometimes useful to index D, we also use D(I) as a label, but this is simply a guide for listing rather than an indicator of structure.

Table I
1,2-Dimethylenecyclobutane (D) Structures and Descriptive Labels

D(I)	Configuration	Code	D(J)	Configuration	Code
1	abcdefgh	RZ′rz′	1	abcdabcd	RZ′RZ′
2	abcdefhg	RZ′re′	2	abcdabdc	RZ′RE′
3	abcdfegh	RZ′sz′			
4	abcdfehg	RZ′se′	8	abcddcba	RZ′S′E
5	abcdghef	RZ′r′z	9	abdcabdc	RE′RE′
8	abcdhgfe	RZ′s′e	15	abdcdcba	RE′S′E
9	abdcefgh	RE′rz′	16	bacdbacd	SZ′SZ′
16	abdchgfe	RE′s′e	21	bacddcba	SZ′S′E
17	bacdefgh	SZ′rz′	22	badcbadc	SE′SE′
64	dcbahgfe	S′Es′e	26	badcdcba	SE′S′E
			27	cdbacdba	R′ZR′E
			36	dcbadcba	S′ES′E

In some of the interconversions, species may turn up with a nonstandard D label, e.g., Z′Ser′; this is equivalent to the standard label, SZ′r′e. Since the rules for interconversion were formulated for the standard format, normalization should be performed as soon as a nonstandard label appears. Captions in Figure 2 illustrate three labeling systems. In Table I we give the coding for the general case as well as for a simpler dimer set.

A related priority system holds for P(I) and O(I). Groups of higher priority which face outward are labeled Z or z, otherwise E or e. Primes on these letters distinguish cd from ab and gh from ef. One can always arrange to have the ab pair in the upper left quadrant and label from *left* to *right* across the top and then *left* to *right* across the bottom. The coding for Q(I) is identical with that of P(I), except that the potential chirality of the structure must be taken into account. We follow the IUPAC rules for a species with a chiral axis, that is, we use the Fischer convention, for an *R* structure.[15]



The four-letter label then follows the priority rules with the appropriate *unprimed* letter in the third position for *R*- and in the fourth position for *S*-bisallyl. O22 EZ′z′e and O19 EZ′ez′, for example, are enantiomers. A typical structure is illustrated in Figure 2. Detailed coding is given in Table II. Incidentally, if a nonstandard label turns up for

Table II
Planar (P) or Orthogonal (O) Bisallyl Structures and Descriptive Labels

(I)[a]	Configuration	Code	(J)[b]	Configuration	Code
1	abcdefgh	ZZ′zz′	1	abcdabcd	ZZ′ZZ′
2	abcdefhg	ZZ′ze′	2	abcdabdc	ZZ′ZE′
3	abcdfegh	ZZ′ez′	3	abcdbacd	ZZ′EZ′
4	abcdfehg	ZZ′ee′	4	abcdbadc	ZZ′EE′
5	abcdghef	ZZ′z′z	5	abcdcdab	ZZ′Z′Z
8	abcdhgfe	ZZ′e′e	8	abcddcba	ZZ′E′E
9	abdcefgh	ZE′zz′	9	abdcabdc	ZE′ZE′
16	abdchgfe	ZE′e′e	12	abdccdba	ZE′Z′E
17	bacdefgh	EZ′zz′			
			15	bacdbacd	EZ′EZ′
24	bacdhgfe	EZ′e′e			
25	badcefgh	EE′zz′	18	bacddcba	EZ′E′E
			19	badcbadc	EE′EE′
32	badchgfe	EE′e′e	20	badcdcba	EE′E′E

[a] P(I) or O(I). [b] P(J) or O(J).

O, e.g., Z′Eez′, this indicates that the *normal* projection formula can be recovered by an inplane rotation of π: effectively this operation interchanges the order of the letters in each pair and yields the normal label for O22. Finally, by identifying the species deriving from KHC=C=CKH discussed earlier with those from abC=C=Cab and by using the conventions of Tables I and II, one can obtain the codes for D(K), P(K), and O(K) of Charts I and II.

We denote interconversions between species by two-letter terms, e.g., DO (0601) indicates D6 → O1. It will also be convenient to use the following definitions for specific label pairs.

a (RS), (R′S′), (rs), (r′s′), (ZE), (Z′E′) (ze), (z′e′)
b (RZ), (R′Z′), (rz), (r′z′), (SE), (S′E′), (se), (s′e′)
c (RE), (R′E′), (re), (r′e′), (SZ), (S′Z′), (sz), (s′z′)

[a] Conjugates. [b] Relates. [c] Inverts.

The main problem here is to formulate the interconversion rules in a manner consistent with the way the species have been coded. These are given first in words and then more compactly in symbolic form.

PP or OO. These involve a rotation of an outside bond in bisallyl: each O or P has access to four such steps. This isomerization, e.g., eq 2, is described by interchanging a and b *or* c and d, etc., i.e., change one of the four-letter labels to its conjugate.

$$\begin{matrix} \text{ZZ′z′e} \leftarrow \\ \text{EE′z′e} \leftarrow \end{matrix} \text{EZ′z′e} \begin{matrix} \rightarrow \text{EZ′e′e} \\ \rightarrow \text{EZ′z′z} \end{matrix} \qquad (2)$$

OP or PO. Each bisallyl has two such steps, e.g., eq 3: either retain the label or interchange the last two letters.

$$\begin{matrix} \text{O} \\ \text{EZ′z′e} \end{matrix} \leftarrow \begin{matrix} \text{P22} \\ \text{EZ′z′e} \end{matrix} \rightarrow \begin{matrix} \text{O} \\ \text{EZ′ez′} \end{matrix} \qquad (3)$$

PD. There are two *disrotatory* interconversions, PD, e.g., eq 4. Keeping either the first and third or second and fourth letters the same, substitute one relate and one invert for the other two letters.

$$\begin{matrix} \text{D RZ′r′e} \leftarrow \\ \text{D SZ′s′e} \leftarrow \end{matrix} \begin{matrix} \text{P22} \\ \text{EZ′z′e} \end{matrix} \begin{matrix} \rightarrow \text{D ER′z′r or R′Erz′} \\ \rightarrow \text{D ES′z′s or S′Esz′} \end{matrix} \qquad (4)$$

OD. The four conrotatory closures (OD) of Figure 2 are given in eq 5 as follows. Retain either the first and fourth or second and third letter labels and interchange the other two with relates; or retain the first and third or second and fourth letter labels and interchange the other two with inverts.

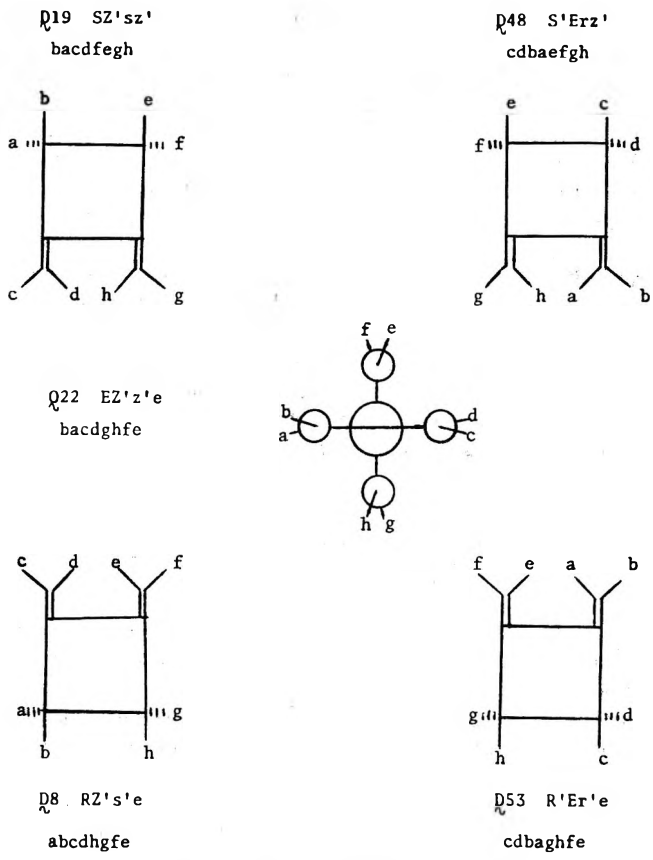


Figure 2. Least Motion (π/4) conrotatory closures of an orthogonal bisallyl diradical to give four dimers. The labeling code is explained in the text.

$$\begin{matrix} \text{D ER′r′e or R′Er′e} \leftarrow \\ \text{D SZ′z′s or SZ′sz′} \leftarrow \end{matrix} \begin{matrix} \text{O22} \\ \text{EZ′z′e} \end{matrix} \begin{matrix} \rightarrow \text{D ES′z′r or S′Erz′} \\ \rightarrow \text{D RZ′se} \end{matrix} \qquad (5)$$

DP. The disrotatory ring openings, DP, are illustrated in eq 6. Retain letters 2 and 4 of the label; invert one of the remaining letters and replace the other by the relate.

$$\text{P} \begin{matrix} \text{E′Ez′e} \\ \text{or EE′ez′} \end{matrix} \leftarrow \begin{matrix} \text{D} \\ \text{S′Es′e} \end{matrix} \rightarrow \text{P} \begin{matrix} \text{Z′Ee′e} \\ \text{or EZ′ee′} \end{matrix} \qquad (6)$$

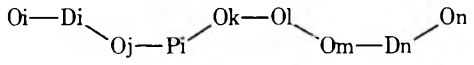
DO. For the two conrotatory ring openings DO, retain letters 2 and 4 and either invert letters 1 and 3 or insert their relates; finally interchange the last two letters, e.g.

$$\text{O} \begin{matrix} \text{E′Ee′e} \\ \text{or EE′ee′} \end{matrix} \leftarrow \begin{matrix} \text{D} \\ \text{S′Es′e} \end{matrix} \rightarrow \text{O} \begin{matrix} \text{Z′Ez′e} \\ \text{or EZ′ez′} \end{matrix} \qquad (7)$$

The preceding statements may be expressed concisely, providing it is understood that 1234 is the four-letter label which is to be changed, that the slant (/) means "or", and that cnj, rel, and inv are read as "replace with the conjugate, relate, and invert", respectively, the letters that follow.

PP or OO cnj (1/2/3/4)
PO or OP 1234/1243
PD [13(rel 2 inv 4)/(rel 4 inv 2)]/
[24(rel 1 inv 3)/(rel 3 inv 1)]
OD (14 rel 23)/(23 rel 14)/(13 inv 24)/(24 inv 13)
DP 24[(rel 1 inv 3)/(inv 1 rel 3)]
DO [24(inv 13)]/[(rel 1) 2 4 rel 3]

Some comments on the graph of our general case are of interest. The *degree* or *valency*[1b] of each vertex (species) is 4 for D and 10 for each of P and O. The total number of edges is 32 × 4 (OD) + 32 × 2 (OP) + 32 × ½ (OO) + 32 × 2 (PD) or 320. A minimum *path*[1b] (edge sequence) between Di and Dj can be evolved as follows. Open each D up along its OD's and compare the configurations of the O's deriving from each dimer. The maximum difference could be one in which each letter in the four-letter label as well as the order (chirality) for a pair, say Oi and On, are different. Of necessity, any other pairing of O's will have fewer differences and would be chosen. Suppose then that Oj and Om are to be linked. If their chirality is identical, three more edges, or less, will be needed; if their chirality is different, one P will have to be interposed in the sequence. Thus, *a minimum path* could consist of as few as two and as many as six edges.



The reader is now in a position to compare the pictorial with the formal approach to this system of three type of species and their interconversions. Certainly, the pictorial approach is worth retaining in those systems with the simpler substitution patterns. At the level of the graphs which include D(I) or D(J), we believe that the formal approach has become a necessity. In any case, chemical information and/or judgments can now be introduced to analyze the problem further.

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Registry No.—1,2-Dimethylenecyclobutane, 14296-80-1.

References and Notes

(1) (a) D. H. Rouvray, *Chem. Br.*, **10,** 11 (1974); (b) M. Behzad and G. Chartrand, "Introduction to the Theory of Graphs", Allyn and Bacon, Boston, Mass., 1971.
(2) (a) A. T. Balaban, D. Farcasiu, and R. Banica, *Rev. Roum. Chim.*, **11,** 1205 (1966); (b) M. Gielen and C. Depasse-Delit, *Theor. Chim. Acta*, **14,** 212 (1969); (c) S. Leibowitz, I. R. Epstein, and D. J. Kleitman, *J. Am. Chem. Soc.*, **96,** 2704 (1974); (d) C. K. Johnson and C. J. Collins, ibid., **96,** 2514 (1974); (e) W. G. Klemperer, ibid., **95,** 380, 2105 (1973); (f) P. Gillespie, P. Hoffmann, H. Klusacek, D. Marquarding, S. Pfohl, F. Ramirez, E. A. Tsolis, and I. Ugi, *Angew. Chem., Int. Ed. Engl.*, **10,** 687 (1971); (g) D. Hellwinkel, M. Melan, and C. R. Degel, *Tetrahedron*, **29,** 1895 (1973); (h) J. G. Gordon II and R. H. Holm, *J. Am. Chem. Soc.*, **92,** 5319 (1970); (i) E. M. Engler, M. Farcasiu, A. Sevin, J. M. Cense, and P. v. R. Schleyer, ibid., **95,** 5769 (1973).
(3) J. E. Baldwin and R. H. Fleming, *Fortschr. Chem. Forsch.*, **15,** 281 (1970).
(4) J. J. Gajewski and C. N. Shih, *J. Am. Chem. Soc.*, **94,** 1675 (1972).
(5) K. G. Migliorese and S. I. Miller, *Tetrahedron*, **30,** 385 (1974).
(6) (a) W. R. Roth and G. Erker, *Angew. Chem., Int. Ed. Engl.*, **12,** 503 (1973); W. R. Roth, M. Heiber, and G. Erker, ibid., **12,** 504 (1973); (b) W. Grimme and H.-J. Rother, *Angew. Chem., Int. Ed. Engl.*, **12,** 505 (1973); (c) C.-S. Chang and N. C. Bauld, *J. Am. Chem. Soc.*, **94,** 7593 (1972).
(7) T. Beetz and R. M. Kellogg, *J. Am. Chem. Soc.*, **95,** 7925 (1973).
(8) (a) B. G. Odell, R. Hoffmann, and A. Imamura, *J. Chem. Soc., B*, 1675 (1970); (b) W. W. Schoeller, *Tetrahedron Lett.*, 2043 (1973).
(9) Unequivocal demonstrations of conrotatory closure of O have yet to be found, although the indications in several examples are strongly persuasive[5] and, in one case at least, compelling.[4] Apparent violations of conrotatory closure are numerous, although many of these may be ascribed to multistep processes and/or equilibrium rather than kinetic control of the product. There is the interesting example of 2,3-dimethylenebicyclo[2.2.0]hexane, which appears to be constrained to open in disrotatory fashion to give what must be a near coplanar bisallyl, 2,3-dimethylenecyclohexa-1,3-diene.[6]
(10) W. v. E. Doering and G. H. Beasley, *Tetrahedron*, **29,** 2231 (1973).
(11) (a) J. P. Lowe, *Prog. Phys. Org. Chem.*, **6,** 1 (1968); (b) A. d'Annibale, L. Lunazzi, A. C. Boicelli, and D. Macciantelli, *J. Chem. Soc., Perkin Trans. 2*, 1396 (1973); K. E. Howlett, *J. Chem. Soc.*, 1055 (1960); J. R. Pedersen, *Acta Chem. Scand.*, **26,** 3181 (1972).
(12) L. M. Stephenson and J. I. Brauman, *J. Am. Chem. Soc.*, **93,** 1988 (1971).
(13) (a) M. F. Lynch, J. M. Harrison, W. G. Town, and J. E. Ash, "Computer Handling of Chemical Structure Information", Macdonald, London, and American Elsevier, New York, N.Y., 1971, Chapters 1 and 2; (b) W. S. Woodward and T. L. Isenhour, *Anal. Chem.*, **46,** 422 (1974); (c) H. A. Clark, J. C. Marshall, and T. L. Isenhour, *J. Chem. Educ.*, **50,** 645 (1973).
(14) Y. Kudo, T. Yamasaki, and S. Sasaki, *J. Chem. Doc.*, **13,** 225 (1973).
(15) (a) "IUPAC Tentative Rules for the Nomenclature of Organic Chemistry. Section E. Fundamental Stereochemistry", *J. Org. Chem.*, **35,** 2847 (1970); (b) P. F. Hudrlik, *J. Chem. Doc.*, **13,** 203 (1973).
(16) A. Feldman, *J. Org. Chem.*, **24,** 1556 (1959).

Notes

Olefin Synthesis. Rate Enhancement of the Elimination of Alkyl Aryl Selenoxides by Electron-Withdrawing Substituents

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The synthetic utility of the gentle olefin-forming syn elimination of alkyl phenyl selenoxides has recently been demonstrated by us[1] and others.[2] However, attempts at forming terminal olefins via the decomposition of primary alkyl phenyl selenoxides have been less successful.[3] We now report a modification that provides for facile elimination of primary alkyl aryl selenoxides to olefins.

In a study[4] on the pyrolysis of a series of para-substituted aryl alkyl sulfoxides, Emerson observed that electron-withdrawing substituents increased the rate of olefin formation, whereas electron-donating substituents decreased the rate. These rates were correlated by a Hammett plot giving $\rho = +0.51$. In light of this, we prepared several substituted aryl lauryl selenoxides. Each selenoxide decomposed to olefin at room temperature, and the effect of different substituents on the rate of elimination is shown in Table I. We observed the same pattern as Emerson, in that electron-withdrawing substituents facilitated the selenoxide elimination.[5]

Table I reveals that electron-withdrawing substituents on the aromatic ring increased both the rate of elimination and the final yield of olefin. Since the aryl-substituted selenium reagents are generally more difficult to prepare on a large scale than diphenyl diselenide, use of the former reagents is probably not necessary for simple cases such as lauryl phenyl selenide.[6] However, we and others[3] have found that when there are substituents on the β and/or γ carbons in the alkyl chain, the yield of olefin can be low with the unsubstituted aryl reagent even after several days.

Table I
Selenoxide Decomposition[a]

Selenide[b]	Temp, °C	Time,[c] hr	Yield, %
2-$NO_2C_6H_4$-SeR (1)	0	0.5	91
2-CF_3-4-$NO_2C_6H_3$SeR (2)	25	0.5	88
4-NO_2-C_6H_4-SeR (3)	25	1.5	93
3-CF_3-C_6H_4-SeR (4)	25	2	70
4-Cl-C_6H_4-SeR (5)	25	6	77
C_6H_5-SeR (6)	25	20	77[d]
4-CH_3O-C_6H_4-SeR (7)	25	7	60

[a] The selenide was dissolved in THF and excess (10 equiv) 30% H_2O_2 was added. Yields of 1-dodecene were determined by GLC relative to an internal standard. [b] The selenides [R = $(CH_2)_{11}CH_3$] were prepared by treating 1-bromododecane with the corresponding ArSeNa species, prepared in situ by reduction of the diselenide[6] (2, 4, 5, 6, 7) or selenocyanate[7] (1, 3) with sodium borohydride in ethanol. [c] These are the approximate times after which further production of olefin was negligible, measured from completion of oxidation as determined by TLC. [d] It should be noted that there is a difference between this yield (77%) and that (6%) previously reported[1a] for this same substrate. We have not been able to reproduce the earlier low yield and at present have no explanation for this discrepancy.

Table II
Selenoxide Decomposition[a]

Selenide[b]	Temp, °C	Time, hr	Yield, %	Registry no.
C_6H_5-Se-CH_2-cyclohexyl	25	9.5 48	47 46	53973-68-5
4-Cl-C_6H_4Se-CH_2-cyclohexyl	25	9.5	85	53973-69-6
2-NO_2-C_6H_4-Se-CH_2-cyclohexyl	25	9.5	92	53973-70-9

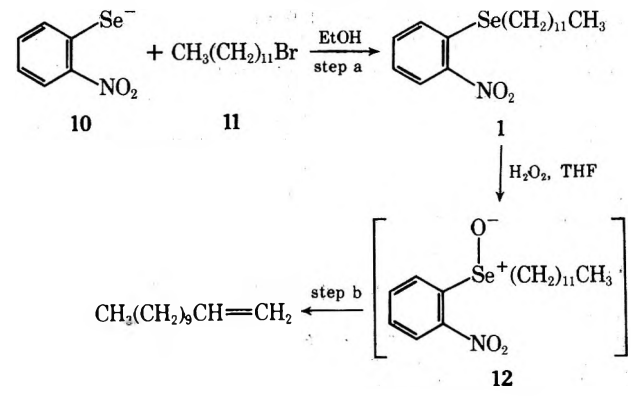
[a] Reactions were run as given in Table I, footnote *a*. Time was measured from the addition of H_2O_2. Yields of methylenecyclohexane were determined by GLC. [b] The selenides were prepared by treating the tosylate of cyclohexanemethanol with the corresponding selenide anion.

In such cases, use of the aryl substituted reagent is essential for a high yield. For example, Table II shows that the *o*-nitro substituted reagent afforded twice the yield of methylenecyclohexane as the unsubstituted reagent.

The selection of the best substituted reagent is a compromise between ease of preparation, yield in the alkylation step, and yield in the elimination step. In view of this, *o*-nitrophenyl selenocyanate (13)[8] and 4,4′-dichlorodiphenyl diselenide (14)[9] are among the better reagents. The dichloro diselenide 14 is particularly attractive since it is as easy to prepare as diphenyl diselenide. Although there will undoubtedly be cases where the potent effect of the *o*-nitro substituent will be needed to facilitate elimination, in most instances the of the *p*-chloro substituent should suffice.

A typical procedure is illustrated in Scheme I for the *o*-nitro case. The selenide anion 10 was treated with bromide

Scheme I



10 11 1 12

11 to afford selenide 1. The selenide was not isolated, but was oxidized by excess hydrogen peroxide to the unstable selenoxide 12, which decomposed readily to 1-dodecene. Results of this one-pot sequence are presented in Table III. Although *o*-nitrophenyl lauryl selenoxide (12) decomposes in higher yield (91%, Table I), the overall yield of olefin is not much higher than that obtained from the other systems. This is due to the lower yield in the alkylation step (step a, Scheme I).

The effect of electron-withdrawing substituents on those synthetic transformations that employ electrophilic seleni-

Table III
Conversion of 1-Bromododecane to 1-Dodecene[a]

Anion precursor	Step a	Step b	Yield, %
2-NO_2-C_6H_4SeCN (13)	8 hr	10 hr, 25°	76 (62)
(4-Cl-$C_6H_5Se)_2$ (14)	8 hr	10 hr, 25°	70 (62)
$(C_6H_5Se)_2$ (15)	8 hr	10 hr, 25°	59

[a] Reactions were run on a 5-mmol scale, analogous to the procedure given in the Experimental Section. Yields of 1-dodecene were determined by GLC, except for those in parentheses, which were determined by isolation.

um reagents[1c,d,2a–c,f,g] is currently being investigated in our laboratory.

Experimental Section

Preparation of 1-Dodecene. To a cooled (ice bath) suspension of *o*-nitrophenyl selenocyanate (**13**, 10.26 g, 0.045 mol) in absolute ethanol (200 ml) in a 500-ml, three-necked, round-bottom flask under nitrogen, sodium borohydride (1.9 g, 0.05 mol) was added in small batches while stirring magnetically. A dark red solution resulted. (Caution! Reduction of the selenocyanate is exothermic and vigorous hydrogen evolution occurs.) 1-Bromododecane (11.15 g, 0.045 mmol) was added and the solution was stirred at room temperature for 8 hr. Tetrahydrofuran (100 ml) was added; and after cooling again in an ice bath, 30% hydrogen peroxide (39 ml, 0.45 mol) was added dropwise over a period of 1 hr. The ice bath was removed and the solution stirred for an additional 8 hr. The mixture was diluted with water and extracted with hexane. The hexane layer was washed with aqueous sodium carbonate and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a dark orange oil. Filtration through alumina (hexane) gave upon removal of the solvent a colorless oil, which upon vacuum distillation (83–85°, 7 mm) gave 1-dodecene (4.65 g, 62%).

Preparation of o-Nitrophenyl Selenocyanate (13). According to the procedure of Bauer,[8] *o*-nitroaniline (20.7 g, 0.15 mol) was added to 6 *M* HCl (90 ml) contained in a 1-l., three-necked, round-bottom flask fitted with a mechanical stirrer and addition funnel. After stirring for 5 min, the suspension was cooled to 0° and a solution of sodium nitrite (12.4 g, 0.18 mol) in water (60 ml) was slowly added. Urea (3.5 g) was added after 20 min and the reaction was checked with starch–iodide paper. Sodium acetate (25 g) was added to give pH ~ 6 on pH paper. A solution of potassium selenocyanate[10] in water (100 ml) was added slowly, giving a mushy, dark brown solid. The solid was collected, washed with water, recrystallized from 95% ethanol (700 ml), and dried in vacuo to give light brown crystals (22.4 g, 66%), mp 139–141° (lit. mp 142°).

Preparation of Diphenyl Diselenide 15. (All operations should be carried out in a well-ventilated hood.)

In a 3-l., three-necked, round-bottom flask, equipped with a reflux condenser, mechanical stirrer, 2-l. addition funnel, and nitrogen inlet, were placed 58 g (2.43 mol) of magnesium turnings and a crystal of iodine. The apparatus was flamed out under a stream of dry nitrogen and allowed to cool to room temperature.

A solution of bromobenzene (380 g, 2.43 mol) in 1280 ml of anhydrous ether (two 1-lb cans) was placed in the addition funnel. The magnesium was covered with a layer of anhydrous ether and several milliliters of neat bromobenzene were added to initiate the reaction. Once initiated, the reaction was stirred vigorously and the halide added at such a rate as to maintain a gentle reflux (2–2.5 hr). Stirring of the brown solution was continued for 0.5 hr, and the dropping funnel was replaced with a glass stopper.

Powdered black selenium [192 g, 2.43 mol (B & A)] was added in 1–2-g portions (exothermic) to the vigorously stirred solution, over a 2.5-hr period; the resulting gray-green suspension was stirred for 0.5 hr.

The mixture was poured into a 6-l. erlenmeyer flask containing 4 l. of crushed ice; concentrated hydrochloric acid (375 ml) was then slowly added with swirling until all of the ice had melted. The contents of the flask were poured into a 6-l. separatory funnel, the aqueous layer was removed and extracted once with 400 ml of ether, and the combined organic layers were filtered through a Celite pad into a 4-l. filtration flask. To the dark orange solution, in the same flask, 1600 ml of 95% ethanol, five pellets of potassium hydroxide, and a 3-in. magnetic stirring bar were added. The flask was stoppered with a one-hole cork, and a glass tube inserted, until it just reached the surface of the liquid. Air was drawn rapidly over the vigorously stirred solution until a thick yellow precipitate was formed and the odor of selenophenol had disappeared. For convenience, the oxidation was allowed to proceed overnight, permitting most of the ether to evaporate.

The yellow slurry was filtered on a 160-mm Büchner funnel, washed several times with cold 95% ethanol, sucked as dry as possible, then dried overnight under a high vacuum at 40° to afford 286 g (75%) of the bright yellow diselenide (mp 63–65°).

The ethanol filtrate may be concentrated on a rotary evaporator to yield a second crop of diselenide; the total yield is then raised to 77–80%. The residual red oil may be vacuum distilled to afford diphenyl selenide (167°, 16 mm), a by-product of this preparation.

Diphenyl diselenide prepared in this manner is a bright yellow, crystalline, air-stable compound, with a faint odor. It is sufficiently pure for all subsequent reactions; purer material may be obtained by recrystallization from hexanes.

The above procedure is a modification of a procedure[11] for the preparation of selenophenol.

Preparation of 4,4′-Dichlorodiphenyl Diselenide (14). This light-orange solid was prepared in 75% yield from *p*-bromochlorobenzene following exactly the same procedure as given above for the preparation of diphenyl diselenide.

Acknowledgments. We are grateful to the National Science Foundation (GP-30485X), Chevron Research Co., the Mobil Foundation, the Camille and Henry Dreyfus Foundation, and the Sloan Foundation for support of this research. We are indebted to Dr. R. F. Lauer for developing the diphenyl diselenide preparation and to Stephen P. Singer for preparing bis(2-trifluoromethyl-4-nitrophenyl) diselenide.

Registry No.—**1**, 53973-63-0; **2**, 53973-64-1; **3**, 53973-65-2; **4**, 54019-82-8; **5**, 53973-66-3; **6**, 42066-69-3; **7**, 53973-67-4; **10**, 54019-83-9; **11**, 112-29-8; **13**, 51694-22-5; **14**, 20541-49-5; **15**, 1666-13-3; 1-dodecene, 112-41-4; sodium borohydride, 16940-66-2; bromobenzene, 108-86-1; selenium, 7782-49-2; *p*-bromochlorobenzene, 106-39-8; sodium o-nitrobenzenoselenol, 53973-71-0; sodium 2-(trifluoromethyl)-4-nitrobenzeneselenol, 53973-72-1; sodium *p*-nitrobenzeneselenol, 53973-73-2; sodium *m*-(trifluoromethyl)benzeneselenol, 37773-11-8; sodium *p*-chlorobenzeneselenol, 41491-33-2; sodium benzeneselenol, 23974-72-3; sodium *p*-methoxybenzeneselenol, 41422-62-2; bis[4-nitro-2-(trifluoromethyl)phenyl] diselenide, 53973-74-3; bis[*m*-(trifluoromethyl)phenyl] diselenide, 53973-75-4; bis(*p*-methoxyphenyl) diselenide, 38762-70-8; *p*-nitrophenylselenocyanate, 19188-18-2; methylenecyclohexane, 1192-37-6; tosylate of cyclohexanemethanol, 3725-11-9; phenylselenide anion, 14971-39-2; *p*-chlorophenylselenide anion, 54019-84-0; KSeCN, 3425-46-5; 2-chloro-5-nitrobenzotrifluoride, 777-37-7.

References and Notes

(1) (a) K. B. Sharpless, M. W. Young, and R. F. Lauer, *Tetrahedron Lett.*, 1979 (1973); (b) K. B. Sharpless and R. F. Lauer, *J. Am. Chem. Soc.*, **95**, 2697 (1973); (c) K. B. Sharpless, R. F. Lauer, and A. Y. Teranishi, *ibid.*, **95**, 6137 (1973); (d) K. B. Sharpless and R. F. Lauer, *J. Org. Chem.*, **39**, 429 (1974).

(2) (a) H. J. Reich, I. L. Reich, and J. M. Renga, *J. Am. Chem. Soc.*, **95**, 5813 (1973); (b) D. L. J. Clive, *J. Chem. Soc., Chem. Commun.*, 695 (1973); (c) P. A. Grieco and M. Miyashita, *J. Org. Chem.*, **39**, 120 (1974); (d) *Tetrahedron Lett.*, 1869 (1974); (e) D. N. Jones, D. Mundy, and R. D. Whitehouse, *Chem. Commun.*, **86** (1970); (f) H. J. Reich, J. M. Renga, and I. L. Reich, *J. Org. Chem.*, **39**, 2133 (1974); (g) H. J. Reich, *ibid.*, **39**, 428 (1974).

(3) Private communications from Professor Dieter Seebach (Justus Liebig Universität), Professor Paul Grieco (University of Pittsburgh), and Professor Paul Dowd (University of Pittsburgh).

(4) D. W. Emerson and T. J. Korniski, *J. Org. Chem.*, **34**, 4115 (1969).

(5) We were recently informed that three other research groups have independently discovered that electron-withdrawing substituents accelerate these selenoxide eliminations: private communications from Professor H. J. Reich (University of Wisconsin), Professor D. Seebach (Justus Liebig Universität), and Professor R. H. Schlessinger (University of Rochester).

(6) 4,4′-Dimethoxydiphenyl diselenide (ref 7, p 1095) and bis(2-trifluoromethylphenyl) diselenide were prepared on a 25-mmol scale (based on the corresponding aryl bromide) analogous to the procedure for diphenyl diselenide. Bis(2-trifluoromethyl-4-nitrophenyl) diselenide was prepared by refluxing a solution of KSeCN (prepared in situ by heating potassium cyanide and gray selenium powder in DMAC) and 2-chloro-5-nitrobenzotrifluoride in DMAC for 4 hr. The mixture was poured into water and the solid collected by filtration. The dark brown solid was extracted into hot CH_2Cl_2 and filtered. After the solvent was removed, the resulting green

solid was recrystallized from absolute ethanol to give yellow-green needles (67%), mp 136–137°.
(7) Houben-Weyl, "Methoden der Organischen Chemie", Band IX, Georg Thieme Verlag, Stuttgart, 1955, p 944.
(8) H. Bauer, *Ber.*, **46**, 92 (1913).
(9) Reference 7, p 1096.
(10) The potassium selenocyanate used in this preparation was made according to G. R. Waitkins and R. Shutt, *Inorg. Synth.*, **2**, 186 (1946).
(11) D. G. Taster, "Organic Syntheses", Collect. Vol. III, Wiley, New York, N.Y., 1955, p 771.

Acid-Catalyzed Hydrolysis of Amidosulfites

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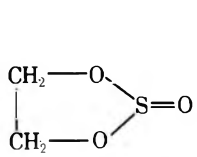
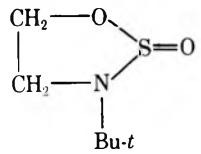
The mechanisms of the acid-catalyzed hydrolysis of cyclic sulfites, e.g., ethylene sulfite (**1**), have been studied in some detail.[1] Only recently have successful syntheses been described of the analogous cyclic amidosulfites.[2,3] They hydrolyze in strong acid to the corresponding amino alcohol.[3] We now report the first kinetic study of the acid-catalyzed ring opening of this class of compound on 3-*tert*-butyl-1,2,3-oxathiazolidine 2-oxide (**2**).



1



2

The rate of hydrolysis of **2** in acid solution at room temperature is much higher than that of **1** and its kinetic behavior had to be studied using stopped-flow spectrophotometry. The first-order rate constants, k_ψ, for the hydrolysis of **2** in aqueous solutions of mineral acids at fairly low acidity (<2 *M*) are shown in Table I. All of the acids studied showed similar catalytic effects at the same molar concentration. This is in marked contrast to the effect of acids on the hydrolyses of **1**. In this latter case the catalytic effect of the acids falls in the order HBr > HCl > $HClO_4$ because ethylene sulfite hydrolyzes by both a bimolecular (A2) and a nucleophilic catalysis mechanism.

Table I
Hydrolysis Rate, k_ψ (sec^{-1}), of 2 in Aqueous Mineral Acids

$HClO_4$ Concn, *M*, at 22°						
0.10	0.20	0.52	0.72	1.04	1.56	2.06
0.59	1.09	2.85	4.36	6.84	11.0	15.4
HCl Concn, *M*, at 22°						
0.10	0.20	0.50	0.70	1.00	1.50	2.00
0.49	1.17	2.92	4.18	6.29	10.7	15.1
HBr Concn, *M*, at 22°						
0.16	0.40	0.56	0.80	0.96	1.20	1.60
0.91	2.37	3.36	5.21	6.40	8.21	12.0
$HClO_4$ (0.52 *M*) at Various Temp, °C						
14.2	21.0	25.0	28.9	33.9	39.7	
1.99	2.85	3.96	4.93	6.39	9.85	

Analysis of the kinetic data for the hydrolysis of **2** shown in Table I in terms of the Bunnett approach[4] leads to a w value of 6.8, suggesting that water is acting both as a nucleophile and a proton transfer agent. The entropy of activation, $\Delta S^\ddagger$ (−19.1 ± 1.4 eu), calculated from the data in Table I also falls in the range associated with a bimolecular rate-determining step.[5]

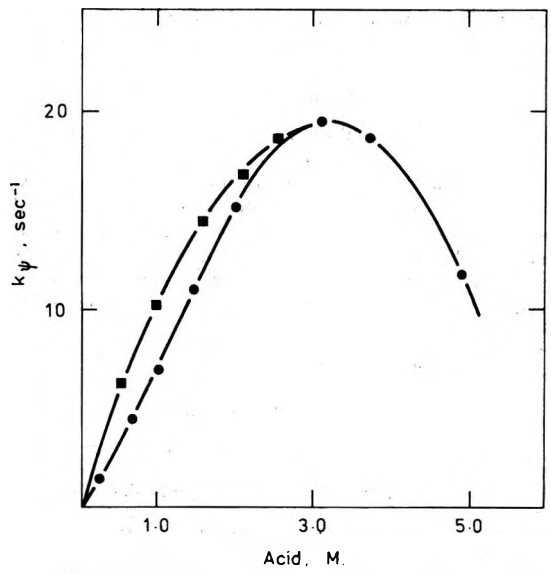
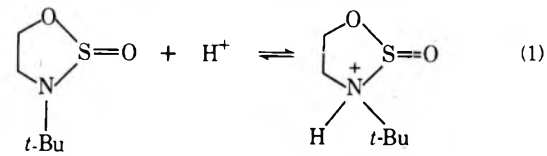


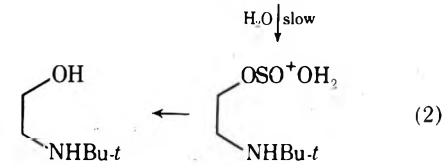
Figure 1. Hydrolysis of **2** in water at 22°: ●, $HClO_4$; ■, $HClO_4$ + $NaClO_4$ (3.0 *M*).

At higher concentrations of perchloric acid (>2 *M*) the rate of hydrolysis of **2** goes through a maximum, as shown in Figure 1. Such rate maxima can arise in two common ways, either as a result of extensive protonation of a basic substrate as in the hydrolysis of amides[6] or the superposition of a specific salt effect on an acid-catalyzed reaction such as observed in the hydrolysis of some sulfites,[7] phosphates,[8] and phosphinates.[9] In mixtures of perchloric acid and sodium perchlorate at constant ionic strength (Figure 1) the rate at first increases linearly with increase in acid concentration and then curves over. Similar behavior has been observed in the hydrolysis of amides and related compounds, e.g., hydroxamic acids, and has been attributed to extensive protonation of the substrate.[10] Such a view is supported by the values of the kinetic solvent isotope effect, $k_1^{D_2O}/k_1^{H_2O}$ (KSIE), which are 1.16, 0.67, and 0.58 at 0.516, 4.26, and 4.61 *M* perchloric acid, respectively (compargd at the same molar concentration of acid). A similar fall of the KSIE with increasing acidity observed for the hydrolysis of amides has been discussed by Bell[11] and Wiberg[12] in terms of the increasing extent of protonation of the substrate and the weaker nucleophilic reactivity of D_2O compared to H_2O.

The kinetic behavior of **2**, in particular the absence of nucleophilic catalysis, the occurrence of a rate maximum, and the high reactivity of **2** in acid solution, contrasts markedly with that of ethylene sulfite and suggests a different mechanism. One possible mechanism consistent with such behavior assumes a rapid preequilibrium protonation of **2** in which protonation is assumed to occur on nitrogen followed by slow rate-determining attack of a water molecule at sulfur (eq 1 and 2). The high reactivity of **2** and the



(1)



(2)

nature of the product are consistent with such a mechanism.

Experimental Section

The *tert*-butyl amidosulfite **2** prepared by the method of Deyrup and Moyer[2] had bp 60–62° (0.4 mm) [lit.[2] bp 70–75° (0.3 mm)]. Kinetics were followed at 276 nm using a Durham-Gibson stopped-flow spectrophotometer. Optical densities were measured on the photograph of the oscilloscope trace and rate constants determined graphically. The values of k_ψ in Table I are the average of several runs at each acid concentration. Average deviation from the mean is less than 5%. Initial concentration of amidosulfite in kinetic runs was ca. 10^{-3} *M*.

Registry No.—**2**, 18366-45-5.

References and Notes

(1) C. A. Bunton, P. B. D. de la Mare, and J. G. Tillett, *J. Chem. Soc.*, 4754 (1958).
(2) H. Takei, H. Shimizu, M. Higo, and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, **41**, 1925 (1968).
(3) J. A. Deyrup and C. L. Moyer, *J. Org. Chem.*, **34**, 175 (1969).
(4) J. F. Bunnett, *J. Am. Chem. Soc.*, **83**, 4956, 4968, 4973, 4978 (1961).
(5) F. A. Long, J. G. Pritchard, and F. E. Stafford, *J. Am. Chem. Soc.*, **79**, 2362 (1957).
(6) J. T. Edward and S. C. R. Meacock, *J. Chem. Soc.*, 2000 (1957).
(7) J. G. Tillett, *J. Chem. Soc.*, 5138 (1960).
(8) C. A. Bunton and S. J. Farber, *J. Org. Chem.*, **34**, 767 (1969).
(9) P. Haake and G. Hurst, *J. Am. Chem. Soc.*, **88**, 2544 (1966).
(10) A. J. Buglass, K. Hudson, and J. G. Tillett, *J. Chem. Soc. B*, 123 (1971).
(11) R. P. Bell, "Acid Base Catalysis," Oxford University Press, London, 1941.
(12) K. R. Wiberg, *Chem. Rev.*, **55**, 713 (1955).

Sulfur-Containing Polypeptides XVII. The *S*-Carbomethoxysulfenyl Derivative as a Protective Group for Cysteine[1,2]

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The synthesis of unsymmetrical disulfides via sulfenylthiocarbonates has been reported by Brois et al.[4] In comparison to sulfenyl thiocyanates or sulfenyl iodides, these derivatives of thiols offer the advantage of often being crystalline, stable molecules that yield carbonyl sulfide, methanol, and the disulfide when treated with thiols. Recently,

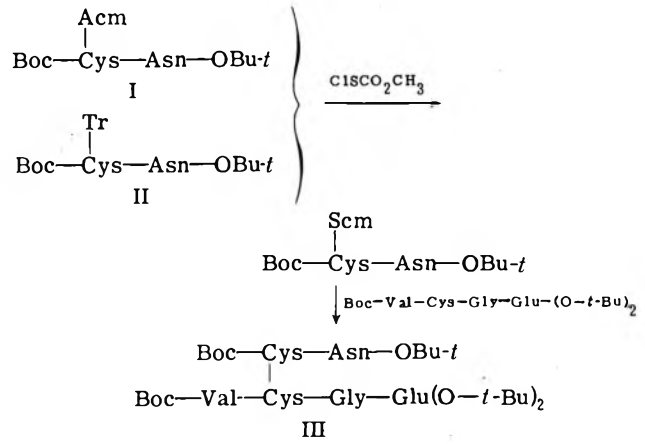
$$R'\text{—S—X} \xrightarrow{\text{ClSCO}_2\text{CH}_3} R'\text{—S—S—CO}_2\text{CH}_3 \xrightarrow{\text{RSH}} R'\text{—S—S—R} + \text{COS} + \text{CH}_3\text{OH}$$

X = H, Tr, Bzh, Bzl, Acm

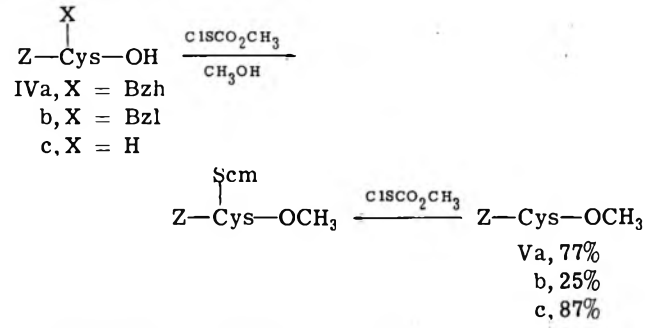
Kamber[5] has shown not only that carbomethoxysulfenyl chloride can be utilized to convert cysteine to the intermediate *S*-carbomethoxysulfenyl derivative[6] but also that the *S*-trityl and *S*-acetamidomethyl derivatives are cleaved by the sulfenyl chloride. Kamber also utilized the method to prepare fully protected open-chain cystine derivatives as illustrated by the conversion of I or II to III.

The present report concerns our studies with the *S*-carbomethoxysulfenyl (Scm) group; these experiments establish that the group is stable to many of the conditions employed for deblocking and coupling operations used in peptide synthesis. Thus, the Scm group can serve as an S-protective group as well as a labile intermediate useful for the selective conversion of a cysteine residue to cystine in the late stage of a synthesis.

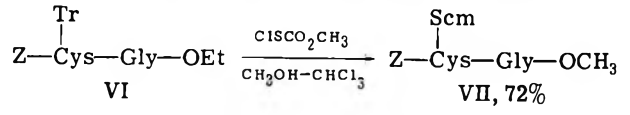
Our preliminary experiments established that the *S*-benzhydryl, *S*-trityl, and (in low yield) the *S*-benzyl



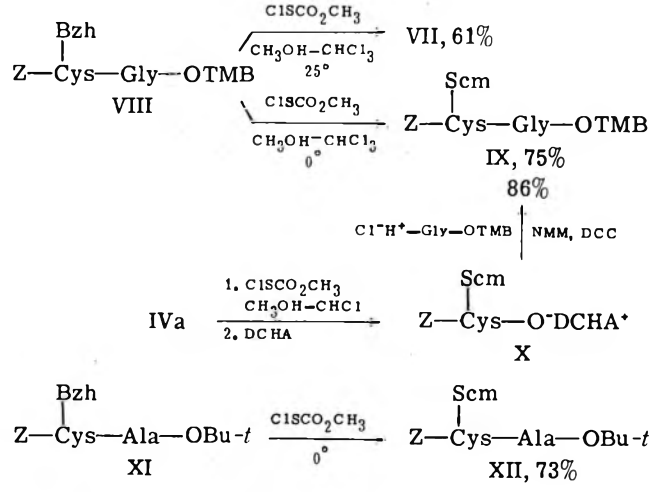
thioethers of cysteine could be converted to the corresponding Scm derivative. However, these experiments also



indicated that esterification of free carboxyl groups or transesterification were potential problems. A study of conditions designed to circumvent this problem indicated that esterification or ester interchange could be avoided by conducting the reaction at 0° or by the addition of calcium carbonate to the reaction mixture.[7] The preparation of the di-

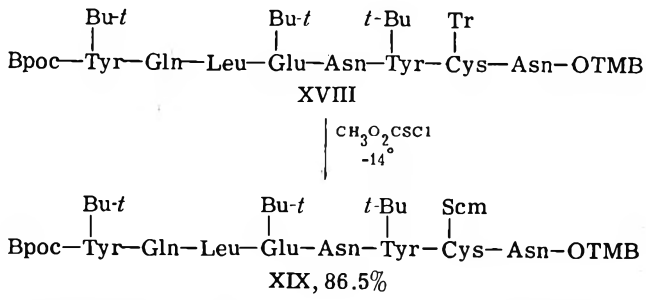


peptides IX and XII (both containing acid-labile ester groups) as well as the salt of the carboxylic acid, X, indicated that the undesirable reactions could be suppressed. The

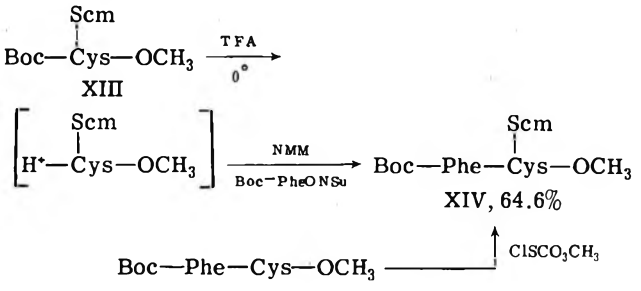


stability of other acid-labile protective groups, used to block certain side-chain functionalities in peptides, toward carbomethoxysulfenyl chloride was indicated by the conversion of the octapeptide derivative (XVIII) to the corresponding Scm peptide (XIX).

The fact that coupling reactions could be successfully conducted in the presence of the Scm group without cleav-

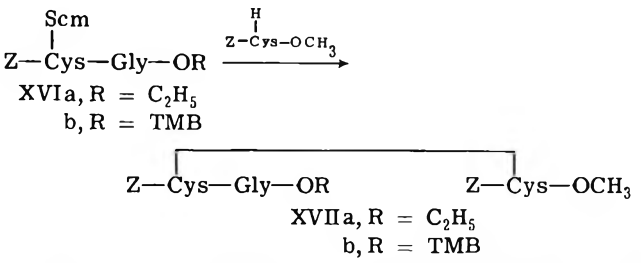


age of the sulfur–sulfur bond was established by the preparation of IX from X and 2,4,6-trimethylbenzyl glycinate. The conversion of XIII to XIV by coupling with *N*-*tert*-butyloxycarbonyl-L-phenylalanine *N*-hydroxysuccinimide ester indicated that the amino group of *S*-carbomethoxysulfenyl-L-cysteine could also be acylated without loss of the Scm group.



Although intermediate sulfenyl iodides[8] or sulfenyl thiocyanates[9] generated from cysteine derivatives react readily with various thioether, hemithioacetal, and *S*-acetamidomethyl derivatives of cysteine, as well as with cysteine itself, the *S*-carbomethoxysulfenyl derivatives are converted to unsymmetrical disulfides only when treated with thiols. Thus the Scm derivatives are considerably more selective in their reactivity with sulfur nucleophiles than sulfenyl thiocyanates or sulfenyl iodides.

The preparation of the unsymmetrical cystine derivative, XVII, from XVI and methyl *N*-carbobenzoxy-L-cysteinate was also studied in various solvents. In chloroform–methanol (1:1) solvent a 79% yield of XVIIb was obtained in 4 hr; using pyridine 50% of XVIIa resulted in 24 hr together with some *N*-carbobenzoxy-L-cystine methyl ester. Similar results were obtained in trifluoroacetic acid–acetic acid (1:1). When the reaction was conducted in *N*,*N*-dimethylacetamide for 30 hr a 50% yield of XVIIb was obtained together with a 40% recovery of unreacted XVIb; in DMF only a small amount of XVIIb was produced with substantial amounts of symmetrical disulfide.



Experimental Section

Melting points are uncorrected. Combustion analyses were performed by Atlantic Microlab, Inc., Atlanta, Ga. Optical rotations were measured using a Perkin-Elmer Model 141 polarimeter. Column chromatography was performed on 0.05–0.20 mm silica gel. Thin layer chromatography was conducted on silica gel GF 254 using the following solvent systems: (A) chloroform–methanol, 9:1; (B) 9.5:0.5; (C) 9.8:0.2; (D) 9.9:0.1. Unless otherwise stated products were dried in vacuo over phosphorus pentoxide.

Methyl *N*-Benzyloxycarbonyl-*S*-carbomethoxysulfenyl-L-cysteinate (V). A. From Methyl *N*-Benzyloxycarbonyl-L-cysteinate. A solution of 2.69 g (0.01 mol) of IVc[10] in 50 ml of absolute methanol was treated with 1.38 g (0.011 mol) of carbomethoxysulfenyl chloride[11] in one portion at room temperature and the reaction mixture was stirred for 2 hr. The solvent was removed in vacuo and the residue was triturated with hexane. The hexane was decanted and the resulting gum recrystallized from ethyl acetate–hexane to provide 2.98 g (83%) of V: mp 61°; homogeneous system A, R_f 0.66; $[\alpha]^{25}D$ + 17.6° (c 1, $CHCl_3$).

Anal. Calcd for $C_{14}H_{17}NO_6S_2$: C, 46.78; H, 4.70; N, 17.84. Found: C, 46.90; H, 4.80; N, 17.70.

B. From *N*-Benzyloxycarbonyl-L-cysteine. To a solution of 2.55 g (0.01 mol) of *N*-benzyloxycarbonyl-L-cysteine[12] in 50 ml of absolute methanol was added 1.38 g (0.011 mol) of carbomethoxysulfenyl chloride in one portion at room temperature. The reaction mixture was stirred for 3 hr and worked up as described above to yield 3.12 g (87%) of V, identical in all respects with the material produced in A.

C. **From *N*-Benzyloxycarbonyl-*S*-benzhydryl-L-cysteine (IVa).** A suspension of 3.01 g (5.0 mmol) of *N*-benzyloxycarbonyl-*S*-benzhydryl-L-cysteine dicyclohexylamine salt[13] in 100 ml of ethyl acetate was converted to the free acid by washing with 100 ml of 10% citric acid. The oily acid was dissolved in 50 ml of absolute methanol and treated with 0.69 g (5.5 mmol) of carbomethoxysulfenyl chloride in one portion. After 3 hr the reaction mixture was worked up in the manner described above to yield 2.76 g (77%) of V, identical with the material obtained in A.

D. From *N*-Benzyloxycarbonyl-*S*-benzyl-L-cysteine (IVb). To a solution of 1.7 g (5.0 mmol) of IVb[14] in 100 ml of 2,2,2-trifluoroethanol–methanol (25:5) solvent was added 0.69 g (5.5 mmol) of carbomethoxysulfenyl chloride in one portion. The reaction mixture was stirred at 25° for 4 days; work-up in the usual manner provided 0.43 g (25%) of product identical with that obtained in A.

Methyl *N*-*tert*-Butyloxycarbonyl-*S*-carbomethoxysulfenyl-L-cysteinate. A suspension of *N*-*tert*-butyloxycarbonyl-*S*-trityl-L-cysteine dicyclohexylammonium salt[15] in 200 ml of ethyl acetate was converted to the free acid with 100 ml of 10% citric acid solution. The resulting gum was dissolved in 50 ml of chloroform–methanol (1:1) and treated with 1.38 g (0.011 mol) of carbomethoxysulfenyl chloride in one portion at 0°. The reaction mixture was stirred for 6 hr and worked up in the usual manner and the solid recrystallized from hexane to yield 2.1 g (66%) of the ester: mp 78°; $[\alpha]^{25}D$ +27.7° (*c* 1, $CHCl_3$); homogeneous system D.

Anal. Calcd for $C_{11}H_{19}NO_6S_2$: C, 46.60; H, 5.89; N, 4.30; S, 19.70. Found: C, 46.70; H, 5.89; N, 4.20; S, 19.50.

2,4,6-Trimethylbenzyl *N*-Benzyloxycarbonyl-*S*-benzhydryl-L-cysteinylglycinate (VIII). A suspension of 6.02 g (0.01 mol) of *N*-benzyloxycarbonyl-*S*-benzhydryl-L-cysteine dicyclohexylamine salt and 2.44 g (0.01 mol) of 2,4,6-trimethylbenzyl glycinate hydrochloride[16] in 100 ml of a chloroform–1,2-dimethoxyethane (1:1) solvent was cooled to −10° and treated with 1.15 g (0.01 mol) of *N*-hydroxysuccinimide and 2.1 g (0.01 mol) of DCC. The stirred suspension was allowed to warm to room temperature and stirred for 2 hr. The suspension was filtered, the filtrate evaporated in vacuo, and the residue dissolved in ethyl acetate and washed with cold solutions of 10% citric acid, 1 *M* sodium bicarbonate, and saturated sodium chloride solution. The dried organic layer was evaporated; chromatography of the crude product (4.5 g) on silica gel using chloroform as the eluent provided 4.0 g of solid. Recrystallization from chloroform–hexane provided 3.9 g (64%) of the dipeptide derivative: mp 126°; homogeneous, system B, R_f 0.5; $[\alpha]^{25}D$ −22.4° (c 1, DMF).

Anal. Calcd for $C_{36}H_{38}N_2O_5S$: C, 70.78; H, 6.22; N, 4.58; S, 5.25. Found: C, 70.88; H, 6.22; N, 4.64; S, 5.11.

Methyl *N*-Benzyloxycarbonyl-*S*-carbomethoxysulfenyl-L-cysteinylglycinate (VII). A. From 2,4,6-Trimethylbenzyl *N*-Benzyloxycarbonyl-*S*-benzhydryl-L-cysteinylglycinate. To a solution of 1.5 g (2.5 mmol) of VIII in 50 ml of chloroform–methanol (1:1) was added 0.37 g (2.75 mmol) of carbomethoxysulfenyl chloride. The reaction mixture was stirred at 25° for 48 hr; the solvent was removed in vacuo and the residue triturated with hot hexane. The residue was chromatographed on silica gel using chloroform as the eluent. The solid was recrystallized from a chloroform–hexane mixture to yield 0.8 g (61%) of the dipeptide derivative: mp 109°; homogeneous, system A, R_f 0.8; $[\alpha]^{25}D$ −92.6° (c 1, $CHCl_3$).

Anal. Calcd for $C_{16}H_{20}N_2O_7S_2$: C, 46.14; H, 4.84; N, 6.72; S, 15.40. Found: C, 46.11; H, 4.87; N, 6.63; S, 15.50.

B. From Ethyl *N*-Benzyloxycarbonyl-*S*-trityl-L-cysteinyl-

glycinate (VI). A solution of 2.9 g (5 mmol) of VI was treated with 0.69 g (0.011 mol) of carbomethoxysulfenyl chloride under the conditions described above. After 6 hr removal of the solvent and chromatography of the residue provided 1.5 g (72%) of VII identical with the material obtained in A.

2,4,6-Trimethylbenzyl *N*-Benzyloxycarbonyl-*S*-carbomethoxysulfenyl-L-cysteinylglycinate (IX). A. From 2,4,6-Trimethylbenzyl *N*-Benzyloxycarbonyl-*S*-benzhydryl-L-cysteinylglycinate. To a solution of 1.5 g (2.5 mmol) of VIII in 50 ml of chloroform–methanol (1:1) at 0° was added 0.37 g (2.75 mmol) of the sulfenyl chloride. The reaction mixture was stirred at 0° for 6 hr. The solvent was removed and the residue worked up in the manner previously described. Recrystallization of the solid from petroleum ether (bp 30–60°) provided 0.98 (75%) of IX: mp 144–146°; homogeneous, system B; $[\alpha]^{25}D$ −69.9° (*c* 1, $CHCl_3$).

Anal. Calcd for $C_{25}H_{30}N_2O_7S_2$: C, 56.15; H, 5.66; N, 5.24; S, 11.99. Found: C, 55.88; H, 5.71; N, 5.13; S, 12.14.

B. From *N*-Benzyloxycarbonyl-*S*-carbomethoxysulfenyl-L-cysteine (IVa). *N*-Benzyloxycarbonyl-*S*-carbomethoxysulfenyl-L-cysteine Dicyclohexylamine Salt (X). A suspension of 5.9 g (0.01 mol) of the dicyclohexylamine salt of IVa in 100 ml of ethyl acetate was washed with 100 ml of 10% citric acid solution. The dried oily acid was dissolved in 50 ml of chloroform–methanol (1:1) solution containing 1.1 g (0.011 mol) of calcium carbonate and treated with 1.38 g (0.011 ml) of the sulfenyl chloride at 0°. The reaction mixture was stirred for 3 hr and worked up in the usual manner to provide a gum which was treated with 1.83 g (0.01 mol) of dicyclohexylamine. Recrystallization of the precipitated solid from chloroform–petroleum ether provided 4.29 g (77.7%) of X as a white solid: mp 139–140; $[\alpha]^{22}D$ −30.1° (*c* 1, $CHCl_3$).

Anal. Calcd for $C_{25}H_{38}N_2O_6S_2$: C, 57.00; H, 7.27;N, 5.32; S, 12.81. Found: C, 56.73; H, 7.23; N, 5.34; S, 12.20.

Coupling of X with 2,4,6-Trimethylbenzyl Glycinate. A suspension of 2.9 g (5.5 mmol) of X was converted to the free acid as previously described. The acid was suspended in 50 ml of chloroform–methylene chloride (1:1) solution, cooled to 0°, and treated with 1.22 g (5.0 mmol) of 2,4,6-trimethylbenzyl glycinate hydrochloride, 0.51 g (5.0 mmol) of *N*-methylmorpholine, and 1.11 g (5.5 mmol) of DCC. The solution was stirred at 0° for 12 hr and for 6 hr at room temperature. The reaction mixture was filtered and the filtrate evaporated. A solution of the residue in ethyl acetate was washed with 10% citric acid solution and water. Evaporation of the organic layer and recrystallization of the residue from ethyl acetate provided 2.29 g (86%) of IX: mp 142°; $[\alpha]^{22}D$ −71.4° (*c*, 1, $CHCl_3$).

Anal. Found: C, 56.39; H, 5.79; N, 5.34; S, 11.89.

***tert*-Butyl *N*-Benzyloxycarbonyl-*S*-benzhydryl-L-cysteinyl-L-alaninate (XI).** A suspension of 6.02 g (0.01 mol) of the dicyclohexylamine salt of IVa and 1.8 g (0.01 mol) of *tert*-butyl L-alaninate hydrochloride in 50 ml of methylene chloride was cooled to −10° and treated with 1.15 g (0.01 mol) of *N*-hydroxysuccinimide and 2.1 g (0.01 mol) of DCC. The stirred suspension was allowed to warm to 25° and stirred for 2 hr. Work-up in the manner previously described provided a gum which was recrystallized from chloroform–hexane to yield the desired ester: mp 73°; homogeneous, system B; $[\alpha]^{25}D$ +9.0° (*c* 1, $CHCl_3$).

Anal. Calcd for $C_{31}H_{36}N_2O_5S$: C, 67.86; H, 6.70; N, 5.10; S, 5.84. Found: C, 67.93; H, 6.76; N, 5.08; S, 5.93.

***tert*-Butyl *N*-Benzyloxycarbonyl-*S*-carbomethoxysulfenyl-L-cysteinyl-L-alaninate (XII).** To a solution of 1.36 g (2.5 mmol) of XI in 50 ml of chloroform–methanol at 0° was added 0.37 g (2.7 mmol) of the sulfenyl chloride. The reaction mixture was stirred at 0° for 6 hr and worked up in the usual manner to provide a gum. The gum was chromatographed on silica gel using chloroform as eluent. Recrystallization of the resulting solid from chloroform–petroleum ether yielded 0.86 g (73%) of XII: mp 70°; homogeneous, system C, R_f 0.6; $[\alpha]^{25}D$ −75.2° (*c* 1, $CHCl_3$).

Anal. Calcd for $C_{20}H_{28}N_2O_7S_2$: C, 50.83; H, 5.97; N, 5.92; S, 13.51. Found: C, 50.80; H, 5.97; N, 5.81; S, 13.42.

Methyl *N*-*tert*-Butyloxycarbonyl-L-phenylalaninyl-*S*-carbomethoxysulfenyl-L-cysteinate (XIV). A. From Methyl *S*-Carbomethoxysulfenyl-L-cysteinate. A solution of 0.715 g (2.2 mmol) of XIII in 2 ml of cold methylene chloride was treated with 1 ml of cold trifluoroacetic acid. After 30 min the reaction mixture was evaporated to dryness; the last traces of acid were removed by the addition of toluene and evaporation. The resulting gum was dried, dissolved in 5 ml of methylene chloride, cooled to 0°, and treated with 0.242 g of *N*-methylmorpholine and 0.724 g (2.0 mmol) of the *N*-hydroxysuccinimide ester of *N*-*tert*-butyloxycarbonyl-L-phenylalanine. The reaction mixture was stirred for 24 hr at 0° and 2 hr at 25° and filtered and the filtrate was evaporated in vacuo. The product was extracted from the resulting gum with hot hexane and obtained as 0.61 g (64.6%) of white solid: mp 112–113°; homogeneous, system C; $[\alpha]^{26}D$ +5.0° (*c* 1, $CHCl_3$).

Anal. Calcd for $C_{20}H_{28}N_2O_7S_2$: C, 50.82; H, 5.97; N, 5.93; S, 13.57. Found: C, 50.96; H, 5.98; N, 6.03; S, 13.58.

B. From Methyl *N*-*tert*-Butyoxycarbonyl-L-phenylalaninyl-*S*-benzhydryl-L-cysteinate (XV). To 0.549 g (1.0 mmol) of XV in 2.5 ml of chloroform–methanol (1:1) was added 0.14 g (1.1 mmol) of the sulfenyl chloride. The reaction was conducted at 0°. Work-up in the usual manner provided 0.354 g (75%) of XIV: mp 113°; $[\alpha]^{26}D$ +4.6° (*c* 1, $CHCl_3$).

Anal. Found: C, 50.83; H, 6.03; N, 5.96; S, 13.64.

***N*-*tert*-Butyloxycarbonyl-*S*-carbomethoxysulfenyl-L-cysteinyl-L-asparagine 2,4,6-Trimethylbenzyl Ester.** To a solution of 0.710 g (1 mmol) of *N*-*tert*-butyloxycarbonyl-*S*-trityl-L-cysteinyl-L-asparagine 2,4,6-trimethylbenzyl ester (17) in 4 ml of chloroform–methanol (2:1) at 0° was added 0.176 (2 mmol) of the sulfenyl chloride. The reaction mixture was stirred at 0° for 50 min and then treated with 2.2 ml of 1 *N* aqueous diethylamine followed by 100 ml of chloroform. The chloroform solution was washed with 10% citric acid and twice with water. After drying over sodium sulfate, the solvent was concentrated to 3 ml, and the product was precipitated with petroleum ether. Recrystallization from chloroform–petroleum ether (30–60°) provided 0.46 g (82.5%) of product: homogeneous, system A, R_f 0.56; mp 125–127°; $[\alpha]^{25}D$ −50.0° (*c* 0.5, methanol).

Anal. Calcd for $C_{24}H_{35}O_8N_3S_2$: C, 51.68; H, 6.32; N, 7.53; S, 11.49. Found: C, 51.60; H, 6.33; N, 7.47; S, 11.42.

***N*-2-(p-Diphenylyl)isopropyloxycarbonyl-*O*-tert-butyl-L-tyrosyl-L-glutaminyl-L-leucyl-γ-*tert*-butyl-L-glutamyl-L-asparaginyl-*O*-*tert*-butyl-L-tyrosyl-*S*-carbomethoxysulfenylcysteinyl-L-asparaginyl 2,4,6-Trimethylbenzyl Ester (XIX).** To a solution of 0.183 g (0.1 mmol) of the protected octapeptide XVIII[17] in 4 ml of chloroform–methanol (2:1) at −14° was added 17.6 μl of the sulfenyl chloride and the reaction mixture was stirred at −10° for 28 min. The reaction mixture was then stirred with 0.22 ml of 1 *N* aqueous diethylamine for 5 min below 0°. The solvent was evaporated and the residue was triturated with cold 10% citric acid. The solid was filtered, washed with water, and dried. Recrystallization of the solid from chloroform containing a few drops of methanol–petroleum ether provided 145 mg (86.5%) of product: mp 235–238°; homogeneous system A, R_f 0.4; $[\alpha]^{23}D$ −44.4° (*c* 0.5, chloroform–methanol, 9:1).

Anal. Calcd for $C_{85}H_{116}O_{20}N_{11}S_2$: C, 60.85; H, 6.97; N, 9.18; S, 3.82. Found: C, 60.62; H, 6.93; N, 9.19; S, 3.95.

Registry No.—IVa, 53957-20-3; IVa dicyclohexylamine salt, 54062-81-6; IVb, 3257-18-9; IVc, 53907-29-2; V, 53907-34-9; VI, 3695-78-1; VII, 53907-35-0; VIII, 53907-17-8; IX, 53907-18-9; X, 53907-20-3; XI, 53907-21-4; XII, 53907-22-5; XIII, 53907-23-6; XIV, 53907-24-7; XV, 53907-25-8; XVIII, 53907-26-9; XIX, 53907-27-0; methyl *N*-benzyloxycarbonyl-L-cysteinate, 53907-28-1; carbomethoxysulfenyl chloride, 26555-40-8; *N*-benzyloxycarbonyl-L-cysteine, 53907-29-2; *N*-*tert*-butyloxycarbonyl-*S*-trityl-L-cysteine dicyclohexylammonium salt, 26988-59-0; 2,4,6-trimethylbenzyl glycinate hydrochloride, 6645-08-5; *tert*-butyl-L-alaninate hydrochloride, 13404-22-3; *N*-*tert*-butyloxycarbonyl-L-phenylalanine, 13734-34-4; *N*-*tert*-butyloxycarbonyl-*S*-carbomethoxysulfenyl-L-cysteinyl-L-asparagine 2,4,6-trimethylbenzyl ester, 53907-30-5; *N*-*tert*-butyloxycarbonyl-*S*-trityl-L-cysteinyl-L-asparagine 2,4,6-trimethylbenzyl ester, 30806-18-9.

References and Notes

(1) Supported by Grants GM-07966 and AM-03416, National Institutes of Health, U.S. Public Health Service.

(2) The following abbreviations have been utilized in the text: Bu-t = *tert*-butyl; Tr = trityl; Bzh = benzhydryl; Bzl = benzyl; Acm = acetamidomethyl; Z = benzyloxycarbonyl; Boc = *tert*-butylcarbonyl; TMB = 2,4,6-trimethylbenzyl; Scm = carbomethoxysulfenyl; DCHA = *N,N*-dicyclohexylamine; NSu = hydroxysuccinimide; DCC = *N,N*-dicyclohexylcarbodiimide.

(3) On leave from Presidency College, Madras, India.

(4) S. J. Brois, J. F. Pilot, and H. W. Barnum, *J. Am. Chem. Soc.*, **92**, 7629 (1970).

(5) B. Kamber, *Helv. Chim. Acta*, **56**, 1370 (1973).

(6) Following Kamer's suggestion we have utilized the abbreviation Scm to designate the $-SCO_2CH_3$ group.

(7) Kamber[5] apparently prevented this problem by performing the reaction in the presence of *N,N*-diethylamine; magnesium oxide could probably also be utilized.

(8) B. Kamber, *Helv. Chim. Acta*, **54**, 927 (1971).

(9) R. G. Hiskey and B. F. Ward, Jr., *J. Org. Chem.*, **35**, 1118 (1970).

(10) R. G. Hiskey and D. N. Harpp, *J. Am. Chem. Soc.*, **87**, 3695 (1965).
(11) G. Zumach and Kuhle, *Angew. Chem., Int. Ed. Engl.*, **9**, 54 (1970).
(12) L. Zervas, I. Photaki, and N. Ghelis, *J. Am. Chem. Soc.*, **85**, 1337 (1963).
(13) L. Zervas and I. Photaki, *J. Am. Chem. Soc.*, **84**, 3893 (1962).
(14) H. C. Beyerman, C. A. M. Boers-Boonekamp, and H. Maasen van dam Brink-Zimmermannova, *Recl. Trav. Chim. Pays-Bas*, **87**, 257 (1968).
(15) R. G. Hiskey, L. M. Beacham, and V. G. Matl, *J. Org. Chem.*, **37**, 2472 (1972).
(16) J. A. MacLaren, *Aust. J. Chem.*, **25**, 1293 (1972).
(17) R. G. Hiskey, E. T. Wolters, G. Ulku, and V. Ranga Rao, *J. Org. Chem.*, **37**, 2478 (1972).

Studies with α-Methyl Amino Acids. Resolution and Amino Protection[1a]

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We have prepared derivatives of α-methyl amino acids that are suitable for use in peptide synthesis because it appears that peptide hormone analogs containing them might be of special interest. Marshall and Bosshard[2a] and Marshall et al.[2b] have shown by theoretical studies on the allowed dihedral angles of model peptides that the replacement of the α proton of an amino acid residue with a methyl group results in a dramatic reduction of the conformational space available to the backbone of the peptide chain at the position where that residue occurs. These calculations have subsequently been confirmed by others.[3,4] Peptide hormone analogs containing α-methyl amino acid residues should therefore have a sterically rigid backbone conformation at those positions and would correspond closely to "conformational analogs" of the hormone, i.e., analogs which have a primary structure essentially identical with that of the native hormone but which are capable of adopting conformations that would comprise only a small subset of the total set available to the parent molecule.

Should such an analog be biologically active, important constraints might thereby be placed on evolving models of the conformation assumed by the hormone as it interacts with its receptor. In addition, if side-chain interactions were essential for binding, such analogs, which retain all of the native hormone's side chains, might offer a route to inhibitors which bind to the receptor but which are not capable of inducing subsequent events necessary to activity owing to their conformational inflexibility. This sort of inhibitor might be missed by schemes of analog generation which involve varying only the character or position of side chains.

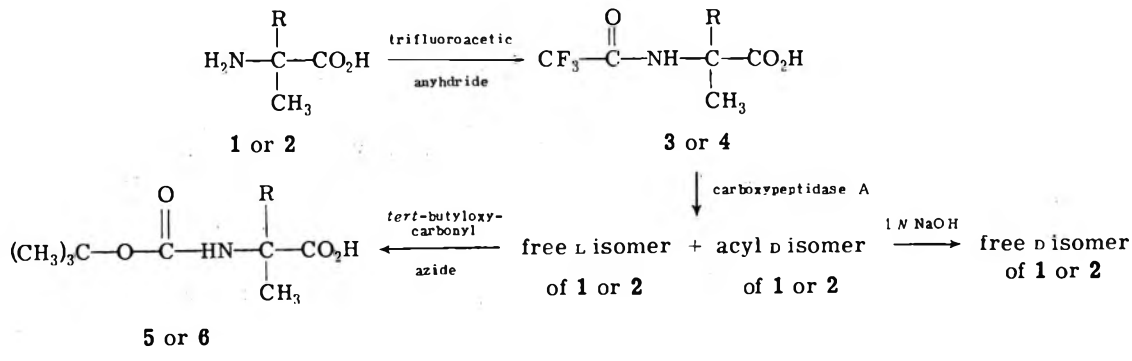
Analogs bearing α-methyl groups would also be expected to be metabolized slowly, since model compounds containing α-methyl amino acids are known to be resistant to chemical hydrolysis[5,6] and to enzymatic attack by both endopeptidases[7] and exopeptidases.[8,9] The synthesis of such analogs might therefore result in the generation of either long-acting agonists or antagonists or of peptides which lack either property but which nonetheless potentiate the effect of endogenous hormone by interfering with its degradation.

We chose to resolve and protect α-methylphenylalanine (2-amino-2-methyl-3-phenylpropionic acid) and α-methylvaline (2-amino-2,3-dimethylbutyric acid) because both phenylalanine and valine occur in angiotensin II, a molecule of current interest. In achieving optical resolution of amino acids, enzymatic digestion of their acylated derivatives is often the method of choice, since it is less tedious and more rapid than many chemical resolution procedures. Since it is known that one enzyme commonly used for such purposes, hog renal acylase I, is unable to catalyze the hydrolysis of *N*-acetyl-α-methylphenylalanine,[7] we decided to use commercially available bovine carboxypeptidase A (CPA). We prepared the *N*-trifluoroacetyl derivatives of the amino acids because they are generally far superior substrates for CPA when compared to the *N*-acetyl derivatives[10] and because such a procedure had proven convenient for the resolution of other amino acids in our laboratory.[11]

We followed described procedures in synthesizing α-methylphenylalanine (**1**) and α-methylvaline (**2**) (Scheme I) from the corresponding ketones, phenylacetone and 2-methyl-3-butanone, respectively.[12,13] These amino acids can be trifluoroacetylated readily with trifluoroacetic anhydride in trifluoroacetic acid by the method of Weygand and Geiger,[14] though not by the milder method of Schallenberg and Calvin[15] which employs *S*-ethylthiol trifluoroacetate in aqueous solution and is an excellent procedure for many amino acids.

Both *N*-trifluoroacetyl-α-methylphenylalanine (**3**) and *N*-trifluoroacetyl-α-methylvaline (**4**) are digested stereospecifically by CPA, releasing the L isomers of **1** and **2** and leaving the D isomers of **3** and **4** intact. The protected derivatives can easily be separated from the amino acids by a simple extraction procedure and the D isomers of **1** and **2** can be generated from D isomers of **3** and **4** by mild saponification. The absolute configuration of α-methylphenylalanine has been determined previously,[16,17] and the direction and magnitude of the optical rotation of the free amino

Scheme



1, **3**, **5**, R = $CH_2C_6H_5$

2, **4**, **6**, R = $CH(CH_3)_2$

acid appearing in solution after the treatment of racemic **3** or **4** with CPA confirm the expectation that the enzyme selectively digests the L isomers and not the D isomers of these compounds. In this regard, we are grateful to Dr. F. W. Bollinger of Merck Laboratories for supplying us with a sample of chemically resolved L-α-Me-Phe · HCl with which to compare our material. To our knowledge, α-Me-Phe has not been resolved enzymatically before, and neither chemical nor enzymatic resolution of α-Me-Val has been achieved previously.

The susceptibility of these derivatives to degradation by CPA is consistent with the side-chain specificity of the enzyme and with its ability to slowly degrade acyl derivatives of D-alanine. This suggests that this resolution procedure is generally applicable to α-methyl amino acids whose side chains are compatible with the specificity of CPA. In this regard, preliminary studies on the resolution of α-methylleucine by polymer-bound CPA indicate the utility of the enzyme in that form and the general applicability of the procedure. To date, however, the procedure has been applied only to the three α-methyl amino acids mentioned.

Protecting the amino groups of **1** and **2** with a function suitable for use in solid-phase peptide synthesis, such as the *tert*-butyloxycarbonyl function (*t*-Boc),[18] is a more difficult problem. Other investigators have encountered difficulty in preparing *t*-Boc-α-methylalanine (*t*-Boc-2-amino-2-methylpropionic acid), citing optimum yields of from 8.7[19] to 12%[20] under conditions which result in over 80% yields for amino acids routinely used in peptide synthesis. Apparently the problem of steric hindrance due to the extra α-alkyl substituent which complicates the synthesis of *t*-Boc-α-methylalanine is magnified when the amino acid side chain is bulkier than a methyl group. Our yields of *t*-Boc-L-α-methylphenylalanine (**5**) and *t*-Boc-L-α-methylvaline (**6**) were less than 2% and essentially 0%, respectively, under a variety of standard conditions. Procedures which proved to be ineffective in our hands in generating **5** and **6** include that of Schnabel,[21] which employs *t*-Boc azide in aqueous solution, that of Ragnarsson et al.,[22] which employs *t*-Boc phenylcarbonate in dimethyl sulfoxide (DMSO), and a variation on the latter procedure which employs *t*-Boc *p*-nitrophenylcarbonate and hydroxybenzotriazole in dimethylformamide.[23]

Compounds **5** and **6** can be synthesized from **1** and **2** in DMSO at an elevated temperature with an excess of organic base and periodic additions of *t*-Boc azide (to counteract the decomposition of that reagent) over a prolonged period. The yield of **5** so obtained was excellent (70%), and although the yield of **6** was five times lower owing to the added steric problem of the β-branched structure of **2**, this procedure is our current method of choice for preparing *t*-Boc-α-methyl amino acids. The use of compounds **5** and **6** in the solid-phase synthesis of peptide hormone analogs is currently in progress, and their chemical and biological properties will be described in a subsequent report.

Experimental Section

All melting points were determined in open capillaries and are uncorrected. Thin layer chromatography on silica gel G plates (Brinkman) was performed on each compound in two systems, 1-butanol–pyridine–acetic acid–H_2O (15:10:3:12) and 1-butanol–acetic acid–H_2O (4:1:1). The R_f values will be designated BP R_f and BAW R_f. Elemental analyses were performed by PCR Inc., Gainesville, Fla., or by Galbraith Laboratories, Knoxville, Tenn.

Preparations of *N*-Trifluoroacetyl-α-methylphenylalanine (3) and *N*-Trifluoracetyl-α-methylvaline (4). Either 17.1 g (0.1 mol) of α-methylphenylalanine (**1**) or 13.1 g (0.1 mol) of α-methylvaline (**2**) was dissolved in 60 ml of trifluoroacetic acid and chilled to 0°. A total of 17.6 ml (0.12 mol) of trifluoroacetic anhydride was then added over a period of 5 min and the resulting solution was stirred at 0° for 1 hr. The solvent and excess anhydride were then evaporated under reduced pressure and the resulting oil was diluted with 100 ml of H_2O. Aliquots of 2 *N* NaOH were added to the aqueous slurry with vigorous stirring until a pH of 7 was achieved, at which point a clear solution was obtained that was treated with charcoal, filtered, and adjusted to pH 3. The precipitated **3** or **4** was collected by filtration, and the mother liquor was extracted three times with ethyl acetate. The extracts were combined, dried with Na_2SO_4, concentrated under reduced pressure, and seeded with crystals of **3** or **4**. The resulting solid was washed with hexane, combined with the first crop, and recrystallized from benzene–hexane (for **3**) or from ethyl acetate–toluene (for **4**). The yield of **3** was 75% (20.6 g) and its physical characteristics follow: mp 162–163°; BAW R_f 0.68, BP R_f 0.65. Anal. Calcd for $C_{12}H_{12}NO_3F_3$: C, 52.37; H, 4.36; N, 5.09. Found: C, 52.08; H, 4.61; N, 4.80. The yield of **4** was 72% (16.4 g) and its physical characteristics follow: mp 112–113°; BAW R_f 0.70, BP R_f 0.60. Anal. Calcd for $C_8H_{12}NO_3F_3$: C, 42.29; H, 5.28; N, 6.15. Found: C, 42.11; H, 5.33; N, 6.12.

Enzymatic Digestion. Either 13.8 g (0.05 mol) of **3** or 10.4 g (0.05 mol) of **4** was added to 400 ml of H_2O and stirred vigorously while 2 *N* NaOH was added until a clear solution of pH 7.2 was obtained. A total of 20 mg of DFP-treated carboxypeptidase A (Sigma Chemical Co., St. Louis, Mo.) was then added, and the solution was maintained at 37° by a thermostated water bath and at pH 7.2 by a Radiometer pH-Stat. After 16 hr of gentle stirring, the solution was adjusted to pH 5, treated with charcoal, and filtered to remove the enzyme. It was then adjusted to pH 3 with 1 *N* HCl and extracted three times with ethyl acetate. The treatment from this point on depended on whether **3** or **4** had been the starting material.

For **3** the aqueous solution was neutralized and concentrated by boiling until the L isomer of **1** began to crystallize, and then it was allowed to cool to room temperature. The crystals were collected by filtration, and a second crop was harvested from the mother liquor. The two crops were combined and dried overnight at 70° under reduced pressure. The yield was 78% (3.32 g). The material is pure enough for most synthetic purposes at this point but does contain some NaCl, which can be removed by recrystallization from H_2O. The physical characteristics follow: mp 279–280° dec (compare 275–276° for racemate); BAW R_f 0.45, BP R_f 0.62; $[\alpha]^{25}_{300}$ −47.8° (H_2O, *c* 0.716). Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.04; H, 7.32; N, 7.82. Found: C, 67.32; H, 7.40; N, 7.69.

The ethyl acetate extracts containing the D isomer of **3** ($[\alpha]^{25}D$ −30.0 (ethyl acetate, *c* 10.3)) were combined, dried with Na_2SO_4, and concentrated under reduced pressure. The residual syrup was dissolved in 60 ml of ethanol to which 60 ml of 1 *N* NaOH was added, and the solution was allowed to stand for 72 hr. It was then neutralized with HCl and evaporated to dryness. The salty residue was dissolved in H_2O and the free D isomer of **1** was obtained in the manner described above for the L isomer. The yield was 74% (2.96 g), and the physical characteristics follow: mp 279–280° dec; BAW R_f 0.46, BP R_f 0.62; $[\alpha]^{25}_{300}$ +47.8° (H_2O, *c* 0.716).

For **4** the aqueous solution was neutralized and evaporated to dryness. The salty residue was purified by 100 transfers in a 1-butanol–H_2O–trifluoroacetic acid (50:50:1) countercurrent distribution system. The amino acid was located by performing thin layer chromatography on the contents of each tube, and the contents of tubes 40–60 were pooled and evaporated to dryness. The white residue was dissolved in H_2O, and the solution was neutralized with NH_4OH and boiled until crystallization began. It was then allowed to cool to room temperature and the crystals were collected by filtration. A second crop was collected, combined with the first, lyophilized twice from H_2O, and dried overnight at 70° under reduced pressure. The yield was 70% (2.30 g) and the physical characteristics follow: mp 281–282° (sublimes without melting, compare 273–274° for the racemate); BAW R_f 0.29, BP R_f 0.54; $[\alpha]^{25}D$ −3.92° (H_2O, *c* 1.31). Anal. Calcd for $C_6H_{13}NO_2$: C, 54.96; H, 9.93; N, 10.69. Found: C, 55.18; H, 9.89; N, 10.68.

The ethyl acetate extracts containing the D isomer of **4** ($[\alpha]^{25}_{400}$ −18.6 (ethanol, *c* 1.5)) were treated in the same manner as for compound **3** except that after saponification and neutralization, the solution was evaporated to dryness, and the salty residue containing the D isomer of **2** was purified in the manner described above for the L isomer. The yield was 69% (2.28 g) and the physical characteristics follow: mp 281–282° (sublimes without melting); BAW R_f 0.28, BP R_f 0.54; $[\alpha]^{25}D$ = +3.90° (H_2O, c 1.31).

Preparation of the Dicyclohexylamine Salts of *N*-*tert*-Butyloxycarbonyl-L-α-methylphenylalanine (5) and *N*-*tert*-Butyloxycarbonyl-L-α-methylvaline (6). Either 1.71 g (0.01 mol) of **1** or 1.31 g (0.01 mol) of **2** was dissolved in 50 ml of dimeth-

yl sulfoxide with 3.5 g (0.03 mol) of tetramethylguanidine. A total of 1.5 ml (0.01 mol) of *t*-Boc azide was added immediately, and the solution was stirred at 40° for 3 weeks with the addition of 0.4 ml of *t*-Boc azide every 3 days. The solution was then diluted with 150 ml of H_2O, brought to pH 2.5 with the addition of solid $NaHSO_4$, and extracted five times with ethyl acetate. The extracts were combined, dried with Na_2SO_4, and evaporated under reduced pressure. The viscosity of the residual oil was reduced by the addition of a small amount of ethyl acetate, and an excess of dicyclohexylamine was added. The resultant crystalline salts were collected by filtration and recrystallized from ethyl acetate. The yield of **5** was 70% (3.22 g), and its physical characteristics follow: mp 230–231°; BAW R_f 0.81, BP R_f 0.70; $[\alpha]^{25}D$ +16.8° (2% acetic acid in ethanol, *c* 0.46). Anal. Calcd for $C_{27}H_4N_2O_4$: C, 70.43; H, 9.57; N, 6.09. Found: C, 70.41; H, 9.68; N, 6.04. The yield of **6** was 13% (0.533 g), and its physical characteristics follow: mp 181–182°; BAW R_f 0.74, BP R_f 0.72; $[\alpha]^{25}_{300}$ +32.6° (ethanol, c 2.06). Anal. Calcd for $C_{23}H_{44}N_2O_4$: C, 66.97; H, 10.79; N, 6.74. Found: C, 66.91; H, 10.68; N, 6.78.

Registry No.—DL-**1**, 1132-26-9; D-**1**, 17350-84-4; L-**1**, 23239-35-2; DL-**2**, 26287-62-7; D-**2**, 53940-82-2; L-**2**, 53940-83-3; DL-**3**, 53940-84-4; D-**3**, 53940-85-5; DL-**4**, 53940-86-6; D-**4**, 53940-87-7; **5**, 53940-89-9; **6**, 53940-91-3; *t*-Boc azide, 1070-19-5.

References and Notes

(1) (a) Supported by a grant-in-aid (AHA-73-754) from the American Heart Association and a grant from the National Institutes of Health (HE-14509). A preliminary report of this work was presented at the 8th Midwest Regional Meeting of the American Chemical Society, Columbia, Mo., 1972. (b) Graduate Fellow, Medical Scientist Training Program (GM02016). (c) National Chemical Laboratory, Poona 8, India. (d) Established Investigator, American Heart Association (AHA-70-111).
(2) (a) G. R. Marshall and H. E. Bosshard, *Circ. Res., Suppl. II*, 43 (1972); (b) G. R. Marshall, H. E. Bosshard, N. E. Eilers, and P. Needleman, "Chemistry and Biology of Peptides", J. Meienhofer, Ed., Ann Arbor Science Publishers, Ann Arbor, Mich., 1972, p 629.
(3) V. Z. Pletney, E. P. Gromon, and E. M. Popov, *Khim. Prir. Soedin*, 224 (1973).
(4) A. W. Burgess and S. J. Leach, *Biopolymers*, **12**, 2599 (1973).
(5) P. A. Levene and R. E. Steiger, *J. Biol. Chem.*, **76**, 299 (1968).
(6) N. C. E. Kendrick, Ph.D. Thesis, Washington University, 1973.
(7) H. R. Almond, D. T. Manning, and C. Nieman, *Biochemistry*, **1**, 243 (1962).
(8) C. G. Baker, S.-C. J. Fu, S. M. Birnbaum, H. A. Sober, and J. P. Greenstein, *J. Am. Chem. Soc.*, **74**, 4701 (1952).
(9) S.-C. J. Fu and S. M. Birnbaum, *J. Am. Chem. Soc.*, **75**, 918 (1953).
(10) W. S. Fones and M. Lee, *J. Biol. Chem.*, **201**, 847 (1953).
(11) W. H. Vine, D. A. Brueckner, P. Needleman, and G. R. Marshall, *Biochemistry*, **12**, 1630 (1973).
(12) G. A. Stein, H. A. Bronner, and K. Pfister, *J. Am. Chem. Soc.*, **77**, 700 (1955).
(13) K. Kurona, *Biochem. Z.*, **134**, 434 (1922).
(14) F. Weygand and R. Geiger, *Chem. Ber.*, **84**, 647 (1955).
(15) E. E. Schallenberg and M. Calvin, *J. Am. Chem. Soc.*, **77**, 2770 (1955).
(16) S. Terashima, K. Achiwa, and S. Yamado, *Chem. Pharm. Bull.*, **14**, 1138 (1966).
(17) F. W. Bollinger, *J. Med. Chem.*, **14**, 373 (1971).
(18) R. B. Merrifield, *Biochemistry*, **3**, 1385 (1964).
(19) K. Inoye, K. Watanabe, K. Nambe, and H. Otsuke, *Bull. Chem. Soc. Jpn.*, **43**, 3873 (1970).
(20) E. C. Jorgenson, S. Rapaka, and G. C. Windridge, *J. Med. Chem.*, **14**, 905 (1961).
(21) E. Schnabel, *Justus Liebigs Ann. Chem.*, **702**, 188 (1967).
(22) U. Ragnarsson, S. K. Karlsson, B. E. Sandberg, and L. Larsson, *Org. Synth.*, **53**, 25 (1973).
(23) W. König and R. Geiger, "Chemistry and Biology of Peptides", J. Meienhofer, Ed., Ann Arbor Science Publishers, Ann Arbor, Mich., 1972, p 343.

Ring Opening of 3-Chloro-4-nitroisothiazole with Amines

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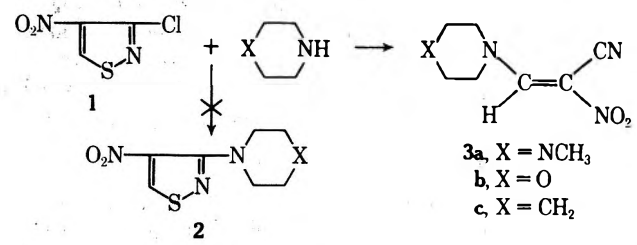
In an attempt to prepare 3-(*N*-methylpiperazino)-4-nitroisothiazole (**2a**), 3-chloro-4-nitroisothiazole (**1**)[1] was treated with *N*-methylpiperazine. Unexpectedly, a ring opening occurred leading to the enamine **3a** rather than **2** (Scheme I). The evidence for this is as follows.

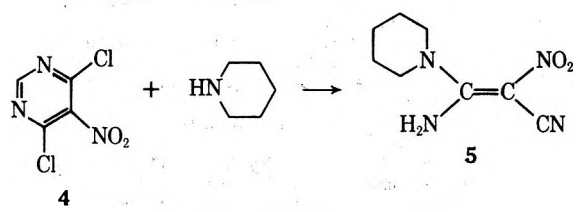
Scheme I



The product did not contain sulfur and analyzed as $C_8H_{12}N_4O_2$. The ir spectrum showed a C≡N band (2200 cm^{-1}), a strong C=C band (1620 cm^{-1}), and an NO_2 band (1280 and 1490 cm^{-1}) which had been shifted to longer wavelength owing to conjugation with an amino group. A normal C=C—NO_2 should have peaks at 1524 ± 4 and 1353 ± 6 cm^{-1}.[2] The NMR chemical shift of the olefinic proton (δ 8.50) enabled us to assign the configuration of **3a** as having a trans relationship between the amine and NO_2 nitrogens. Matter et al.[3] have shown that the equation $\delta = 5.25 + Z_{gem} + Z_{trans} + Z_{cis}$ is useful in determining the chemical shift of protons on substituted ethylenes where *Z*'s are parameters for various substituents listed in his paper. Together with the parameter for NO_2 determined by Descotes et al.,[4] one can calculate the chemical shift for the olefinic proton of **3a** as follows. δ = 5.25 + 1.17 (conjd NR_2) + 0.55 (*trans*-CN) + 1.67 (*cis*-NO_2) = 8.64. The calculated chemical shift for the other isomer is δ = 5.25 + 1.17 + 0.75 (*cis*-CN) + 0.46 (*trans*-NO_2) = 7.63. Clearly the observed value (8.50) is closer to that calculated for **3a** than its isomer.

There are no other 3-amino-2-nitroacrylonitriles reported in the literature, the nearest analog being **5**.[5] This compound, prepared by ring opening of the dichloronitropyrimidine **4** (Scheme II), shows ir maxima at 1643 cm^{-1} (C=C).

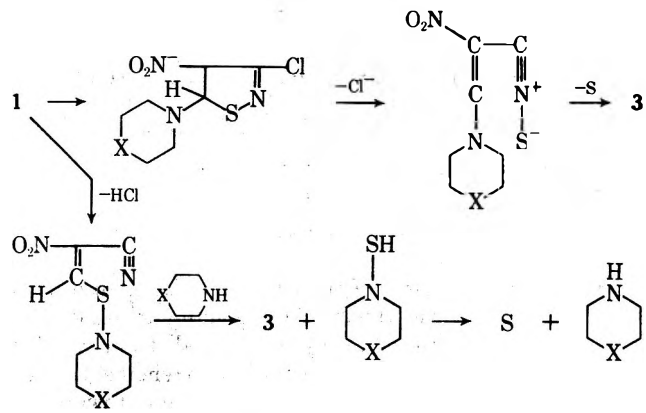
Scheme II



The monobasic amines, morpholine and piperidine, react in a like manner if triethylamine is present.

Two possible mechanisms for the formation of **3** are given in Scheme III. The first involves a nitrile sulfide in-

Scheme III



termediate. The species has been proposed by Howe and Franz as an intermediate in the decomposition of 1,3,4-oxathiazol-2-ones.[6] The second involves nucleophilic attack on sulfur.[7] Several ring openings of isothiazoles have been shown to involve attack on the ring sulfur.[8-11] At this point it is not possible to decide between the two mechanisms.

Experimental Section

3-(4-Methyl-1-piperazino)-2-nitroacrylonitrile (3a). To 5.00 g of 3-chloro-4-nitroisothiazole[1] in 25 ml of isopropyl alcohol at 0°, 3.25 g of *N*-methylpiperazine in 10 ml of isopropyl alcohol was added dropwise. The solution was kept at room temperature overnight. A pale yellow solid (mp 119°, sulfur, 600 mg) was filtered. The solution was concentrated and cooled, giving 3.32 g of **3a**: mp 83–85°; NMR ($CDCl_3$) δ 2.33 (3 H, s), 2.55 (2 H, t), 2.61 (2 H, t), 3.70 (2 H, t), 4.00 (2 H, t), 8.50 (1 H, s); ir, see text. Anal. Calcd for $C_8H_{12}N_4O_2$: C, 48.98; H, 6.17; N, 28.56. Found: C, 48.80; H, 5.90; N, 28.37; S, 0.0.

3-(1-Morpholino)-2-nitroacrylonitrile (3b). To 5.00 g of 3-chloro-4-nitroisothiazole in 25 ml of benzene at 0°, 2.80 g of morpholine in 5 ml of benzene was added slowly followed by 3.16 g of triethylamine. An exothermic reaction occurred and a solid formed. After 1 hr the solution was treated with dilute HCl and benzene, and the solid was filtered and crystallized from dimethoxyethane to give sulfur (mp 118°, insoluble in DME), and 3.02 g of **3b**, mp 143–145°. Anal. Calcd for $C_7H_9N_3O_3$: C, 45.90; H, 4.90; N, 22.94. Found: C, 45.76; H, 4.82; N, 22.84.

3-(1-Piperidino)-2-nitroacrylonitrile (3c). 3-Chloro-4-nitroisothiazole (5.00 g) and piperidine (2.80 g) were allowed to react as above. The product was soluble in benzene but was crystallized from isopropyl alcohol and then methanol to give 3.54 g of **3c**, mp 116–118°. Anal. Calcd for $C_8H_{11}N_3O_2$: C, 53.03; H, 6.12; N, 23.19. Found: C, 52.80; H, 6.16; N, 23.48.

Acknowledgments. The NMR spectra were done under the direction of Dr. R. Egan, ir under Mr. W. Washburn, and microanalyses by Ms. J. Hood.

Registry No.—**1**, 14217-68-6; **3a**, 54062-82-7; **3b**, 54062-83-8; **3c**, 54062-84-9; *N*-methylpiperazine, 109-01-3; morpholine, 110-91-8; piperidine, 110-89-4.

References and Notes

(1) R. Williams, U.S. Patent 3,285,930 (1967); *Chem. Abstr.*, **66**, 28766r (1967).
(2) L. Bellamy, "The Infrared Spectra of Complex Molecules", 2nd ed, Methuen, London, 1958, p 299.
(3) U. E. Matter, C. Pascual, E. Pretsch, A. Pross, W. Simon, and S. Sternhell, *Tetrahedron*, **25**, 2023 (1969).
(4) G. Descotes, Y. Bahurel, M. Bourillot, G. Pingeun, and R. Rostaing, *Bull. Soc. Chim. Fr.*, 282 (1970).
(5) J. Clark, I. Gelling, I. Southon, and M. Morton, *J. Chem. Soc. C*, 494 (1970).
(6) R. K. Howe and J. E. Franz, *J. Org. Chem.*, **39**, 962 (1974); *J. Chem. Soc., Chem. Commun.*, 524 (1973).
(7) The author thanks one of the referees for pointing out this possibility.
(8) W. R. Hatchard, *J. Org. Chem.*, **29**, 660 (1964).
(9) W. D. Crow and I. Gusney, *Aust. J. Chem.*, **19**, 1693 (1966); **20**, 2729 (1967).
(10) M. P. L. Caton, D. H. Jones, R. Slack, and K. R. H. Wooldridge, *J. Chem. Soc.*, 4616 (1964).
(11) K. R. H. Wooldridge, *Adv. Heterocycl. Chem.*, **14**, 19 (1972).

Monoesters of Cyclohexane-1β,3β,5β-triol

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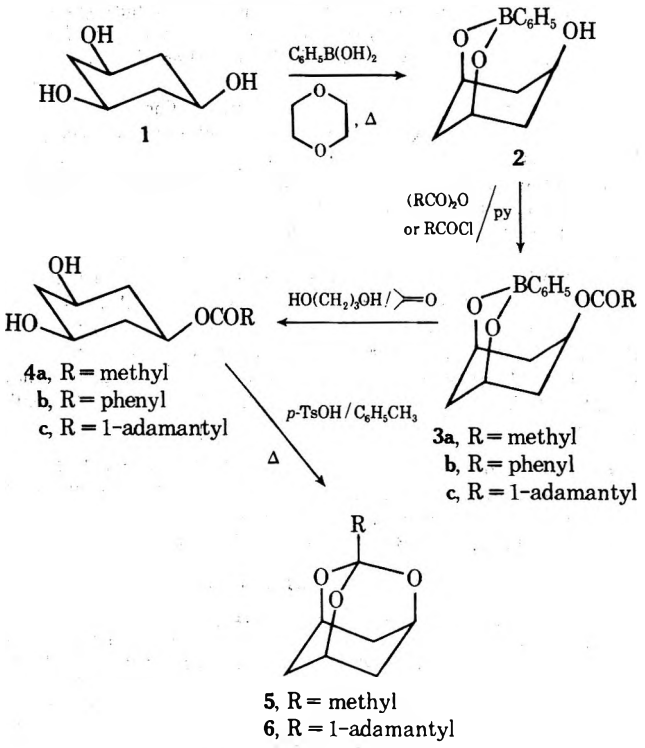
We required a series of the title compounds in order to study their cyclization to the corresponding trioxaadamantanes. This ring system, hitherto prepared[2] from cyclohexane-1β,3β,5β-triol (α-phloroglucitol, **1**) (Scheme I) and a trialkyl ortho ester, is reported[3] to be stable toward Grignard reagents and has seen limited use as a carboxylic acid protecting group.[4] We describe herein the synthesis of three monoesters of **1** and some preliminary cyclization results.

Scheme I



Starting triol **1** was obtained highly stereoselectively by high-pressure hydrogenation[2] of 1,3,5-trihydroxybenzene (phloroglucinol) over a rhodium catalyst. Efforts to conveniently prepare monoesters of **1** by direct acylation with 1 equiv of acylating agent in pyridine were thwarted by the qualitative observation that partially acylated phloroglucitols appeared to be more susceptible to further acylation than **1** itself. Likewise, partial saponification of fully acylated derivatives (for example, α-phloroglucitol tribenzoate) with 2 equiv of base produced mixtures in which the desired monoacyl product did not predominate.

Success was achieved through reaction of **1** with phenylboronic acid[5] in refluxing dioxane, producing α-phloroglucitol phenylboronate (**2**) in 99% yield. This last substance was treated with 1 equiv of the acid chloride or anhydride in pyridine, leading to the corresponding acyl derivatives **3** in good yields (79–99%). The phenylboronate group was then cleaved using propane-1,3-diol in acetone,[5] affording the title compounds **4** in yields of ca. 80%.

While monoacetate **4a** could be cyclized to trioxaadamantane **5** in 40% yield with refluxing toluene containing toluenesulfonic acid, esters **4b** and **4c** proved much more resistant to cyclization. For example, reaction of **4c** with toluenesulfonic acid in boiling xylene afforded trioxaadamantane **6** [mp 142–144°, tentative assignment based on a high-resolution mass spectrum, *m/e* 276.176 (calcd, 276,173)] in less than 1% yield.

Experimental Section

Melting points were determined on a Kofler hot stage or in a sealed capillary in an oil bath and are uncorrected. Infrared spectra were recorded with a Beckman IR-5 spectrophotometer. NMR spectra were recorded on a Varian A-60, HA-100, or XL-100 high-resolution spectrometer. Chemical shifts are reported in parts per million downfield from internal Me_4Si. Mass spectra (70 eV) were determined on a CEC 110-2B double-focusing mass spectrometer equipped with a direct inlet. Elemental analyses were performed at the University of Oregon by Dr. S. Rottschaefer.

Cyclohexane-1β,3β,5β-triol (1). A mixture of 10.9 g of phloroglucinol (Aldrich), 5 g of 5% rhodium on alumina (Engelhard), and 70 ml of 95% ethanol (distilled from Raney nickel) was shaken in an atmosphere of hydrogen at 2900 psi and 98° for 18 hr. Filtration of the hot mixture and concentration of the filtrate afforded 6.55 g (58%) of crystalline **1** as a hydrate, mp 110–112° (lit.[2] mp 110°). Anhydrous **1**, mp 185° (lit.[2] mp 184°), used in subsequent experiments, was obtained by heating the hydrate overnight at 50° (10 mm). The NMR spectrum of the original mother liquors of **1** revealed only the presence of **1** and unreacted phloroglucinol.

Cyclohexane-1β,3β,5β-triol Phenylboronate (2). A mixture of 220 ml of dioxane (distilled from $LiAlH_4$), 3.0 g (0.023 mol) of anhydrous **1**, and 2.8 g (0.023 mol) of phenylboronic acid (Aldrich) was refluxed while the dioxane–water azeotrope was slowly removed by fractional distillation over a 90-min period. Removal of the remaining solvent (ca. 150 ml) in vacuo afforded 4.9 g (99%) of **2**, mp 109–111°. Two successive sublimations (100°, 0.25 mm) gave the analytical specimen as colorless prisms: mp 114–115°; ir ($CHCl_3$) 1441 (m, B–Ar stretch[6]), 1312 cm^{-1} (s, B–O stretch[6]); NMR ($CDCl_3$) δ 1.58 (m, 3, axial methylene protons), 2.19 (m, 3, equatorial methylene protons), 4.24 (m, 3, methine protons), 7.0–7.9 (m, 5, aromatic protons); mass spectrum *m/e* 218 (M^+), 210, 186, 177.

Anal. Calcd for $C_{12}H_{15}BO_3$: C, 66.10; H, 6.93. Found: C, 66.13; H, 7.09.

Acylation of 2. The synthesis of **3b** is representative. To a solution of 1.35 g (6.2 mmol) of **2** in 15 ml of dry pyridine was added 710 μl (6.2 mmol) of benzoyl chloride. After a 2-hr period at 25° the solvents were removed *in vacuo*, and the residual solid was extracted with hot benzene. Evaporation of the extract afforded 1.95 g (99%) of crystalline **3b**, mp 125–127°. Two recrystallizations from benzene–hexane gave the analytical specimen as colorless pentagonal clusters: mp 137–137.5°; ir ($CHCl_3$) 1447 (m, B–Ar stretch), 1309 cm^{-1} (s, B–O stretch); NMR ($CDCl_3$) δ 1.5–2.8 (m, 6, $-CH_2-$), 4.48 (m, 2, –CHOB–), 5.45 (m, 1, –CHOCO), 6.5–7.9 (m, 10, aromatic protons); mass spectrum *m/e* 322 (M^+), 245, 200, 172.

Anal. Calcd for $C_{19}H_{19}BO_4$: C, 70.84; H, 5.94. Found: C, 70.82; H, 5.93.

Similarly prepared using acetic anhydride was **3a**, mp 74–75° (hexane).

Anal. Calcd for $C_{14}H_{17}BO_4$: C, 64.65; H, 6.59. Found: C, 64.64; H, 6.69.

Similarly prepared using adamantane-1-carbonyl chloride was **3c**, mp 149–151° (hexane).

Anal. Calcd for $C_{23}H_{29}BO_4 \cdot H_2O$: C, 69.36; H, 7.84. Found: C, 69.06; H, 7.69.

Monoesters 4a–c of Cyclohexane-1β,3β,5β-triol. The synthesis of **4b** is representative. To a solution of 504 mg (1.56 mmol) of **3b**, mp 125–127°, in 5 ml of dry acetone was added 1.0 ml (14 mmol) of propane-1,3-diol. The solution was stirred at 25° for 2.5 hr and then the volatiles were removed under vacuum (1 mm) overnight. The residue was taken up in 5 ml of ethyl acetate and washed with water. The organic phase was dried and evaporated, affording 306 mg (83%) of **4b**, mp 110–116°. Recrystallization from toluene gave the analytical specimen as colorless, chunky prisms: mp 114°; NMR (acetone-d_6) δ 1.35 [q, J = 11.5 Hz, 1, axial methylene proton –CHOHCH$_2$(a,e)CHOH–], 1.50 [q, J = 11.5 Hz, 2, axial methylene protons CH$_2$(a,e)CHOCOC$_6$H$_5$CH$_2$(a,e)–], 2.28 (m, 3, equatorial methylene protons), 3.83 (t of t, 2, –CHOH–), 3.93 (brs, 2, OH), 5.02 (t of t, 1, –CHOCOC$_6$H$_5$), 7.3–8.1 (m, 5, aromatic protons); mass spectrum *m/e* 236 (M^+), 218, 200, 123.

Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 65.90; H, 6.71.

Similarly prepared from **3a** was **4a**, mp 131–132° (acetone–hexane).

Anal. Calcd for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found: C, 54.96; H, 8.23.

Similarly prepared from **3c** was **4c**, mp 175–176° (toluene).

Anal. Calcd for $C_{17}H_{26}O_4$: C, 69.36; H, 8.90. Found: C, 69.50; H, 9.03.

Cyclohexane-1β,3β,5β-triol Tribenzoate. To a solution of 100 mg (0.75 mmol) of anhydrous **1** in 2 ml of pyridine was added 0.90 ml (7.7 mmol) of benzoyl chloride. After 1 hr at 25° the usual work-up gave 262 mg (78%) of the title compound which was recrystallized from chloroform–methanol, affording the analytical specimen as colorless prisms, mp 177–178°.

Anal. Calcd for $C_{27}H_{24}O_6$: C, 72.96; H, 5.44. Found: C, 72.79; H, 5.38.

Cyclization of 4a. A mixture of 69.5 mg of **4a** in 3 ml of toluene containing 7 mg of toluenesulfonic acid monohydrate was refluxed for 4 hr with continuous removal of water by means of a Dean-Stark trap. The solvent was removed and the residue was taken up in chloroform, washed with 2% $NaHCO_3$, dried, and the chloroform then evaporated. Sublimation (12 hr, 60°, 760 mm) of the residue afforded 24.5 mg (40%) of **5**, mp 126° (lit.[7] mp 126°).

Acknowledgment. We thank the National Science Foundation (09413) for generous financial support.

Registry No.—**1**, 50409-12-6; **2**, 53951-24-9; **3a**, 53951-25-0; **3b**, 53951-26-1; **3c**, 53951-27-2; **4a**, 53951-28-3; **4b**, 53951-29-4; **4c**, 53951-30-7; **5**, 27761-63-3; phloroglucinol, 108-73-6; phenylboronic acid, 98-80-6; benzoyl chloride, 98-88-4; acetic anhydride, 108-24-7; adamantyl-1-carbonyl chloride, 2094-72-6; propane-1,3-diol, 504-63-2; cyclohexane-1β,3β,5β-triol tribenzoate, 53951-31-8.

References and Notes

(1) Alfred P. Sloan Foundation Fellow, 1972–1974. Recipient of a NIH Research Career Development Award (1 K4 70156).
(2) H. Stetter and K. H. Steinacker, *Chem. Ber.*, **85**, 451 (1952).
(3) H. Stetter and K. H. Steinacker, *Chem. Ber.*, **87**, 205 (1954); R. H. DeWolfe, "Carboxylic Ortho Acid Derivatives", Organic Chemistry, A Series of Monographs, Vol. 14, Academic Press, New York, N.Y., 1970.
(4) J. M. Osbond, P. G. Philpott, and J. C. Wickens, *J. Chem. Soc.*, 2779 (1961); F. Bohlmann and W. Sucrow, *Chem. Ber.*, **97**, 1839, 1846 (1964).
(5) R. J. Ferrier and D. Prasad, *J. Chem. Soc.*, 7425, 7429 (1965).
(6) L. J. Bellamy, W. Gerrard, and M. F. Lappert, *J. Chem. Soc.*, 2412 (1958).
(7) H. Stetter and K. H. Steinacker, *Chem. Ber.*, **86**, 790 (1953).

On the Specificity of Amine Solvation

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The question arose whether proton exchange of a cyclic amine obeys the mechanism now widely accepted for acyclic aliphatic amines:[2]

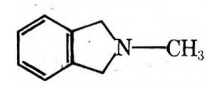
$$R_3NH^+\cdots OH_2 + HOH \underset{k_{-a}}{\overset{k_a}{\rightleftharpoons}} R_3N\cdots HOH + H_3O^+$$

$$R_3N\cdots HOH \xrightarrow{k_H} R_3N + HOH$$

$$R_3N + H_3O^+ \xrightarrow{fast} R_3NH^+\cdots OH_2$$

Since the rate parameters, especially k_H, are sensitive to subtle interactions between the water and the alkyl groups,[3] it was by no means clear how incorporating the amine into a ring would perturb the exchange process.

Proton exchange rates of *N*-methylisoindoline conjugate acid were measured by NMR line-shape analysis of the



doublet-to-singlet transition of the NCH_3 signal as the pH increased from 0 to 2. In this pH range, bimolecular exchange[4] between R_3NH^+ and R_3N was unimportant (the rate constants showed no dependence on amine concentration below the 0.15 *M* amine used in the experiments). Likewise, exchange catalyzed by hydroxide ion[4] did not contribute to the observed rates. If *N*-methylisoindoline exchanges by the mechanism shown above, then the corresponding rate equation (eq 1) predicts that a plot of $1/k_{obsd}$

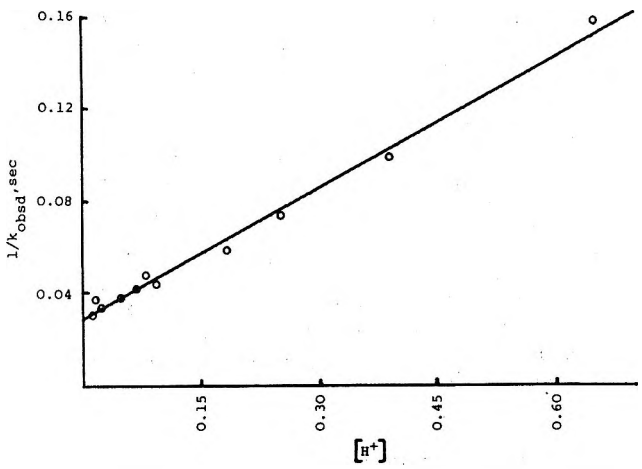


Figure 1. Plot of $1/k_{obsd}$ vs. $[H^+]$ for the proton exchange of the conjugate acid of *N*-methylisoindoline in aqueous HCl at 25°.

$$k_{obsd} = \frac{k_a k_H}{k_H + k_{-a}[H^+]} \quad (1)$$

vs. $[H^+]$ should be linear. This was found to be the case (Figure 1). The slope and intercept of the plot and the pK_a of the amine ($K_a = k_a/k_{-a}$) allowed calculation of all three rate parameters in the mechanism. These are given in Table I along with analogous data for dibenzylmethylamine. The k_a values are seen to differ sevenfold, but this largely reflects the difference in basicity between the two amines. More importantly, the k_H values for *N*-methylisoindoline and dibenzylmethylamine differ by only a small and mechanistically insignificant amount.

Table I
Proton Exchange Data for *N*-Methylisoindoline and Dibenzylmethylamine

Amine	pK_a	k_a, sec^{-1}	k_{-a}, M^{-1} sec^{-1}	k_H, sec^{-1}
N-Methylisoindoline[a]	8.33	35	7.4×10^9	1.1×10^9
Dibenzylmethylamine[b]	7.72	240	1.3×10^{10}	2.7×10^9

[a] 25°, aqueous HCl. [b] 30°, data from ref 3.

Grunwald and Ralph[3] have proposed that *solvent–solute* interactions (rather than *solvent–solvent* interactions) determine the shapes of amine solvation shells. Thus, the solvent molds itself about the contours of the amine; the better the fit, the smaller the rate of desolvation, k_H. If this description is correct, then solvation phenomena can become "extraordinarily specific".[3] Our results show that short-range London dispersion forces between the amine substituents and the water, upon which k_H depends, vary little when the substituents are confined in a ring. In at least one case, therefore, amine solvation is certainly *not* sufficiently form fitting to distinguish a cyclic amine from a conformationally different acyclic analog.[5] This work points out the need to specify the effect of shape on k_H more clearly.

Experimental Section

Materials. *N*-Methylisoindoline was prepared by reducing *N*-methylphthalimide with $LiAlH_4$ in ether in the presence of $MgSO_4$.[6] After the excess $LiAlH_4$ was destroyed with aqueous ethanol, the mixture was filtered and the ether layer was separated and dried over $MgSO_4$. The ether was then removed, leaving a dark residue which was distilled under vacuum, bp 92–93° (25 mm) [lit.[6] bp 81–82° (13 mm)], to give colorless *N*-methylisoindoline in approximately 15% yield. Redistillation gave material of high purity as judged by GLC and an elemental analysis. Although *N*-methylisoindoline was found to be oxygen sensitive to a much greater degree than simple acyclic amines, the compound was quite stable when stored under nitrogen in a freezer. The compound was also found to be stable in >1 *M* aqueous HCl (with a corresponding decrease in stability with increasing pH). All kinetic studies were performed with freshly distilled amine.

Kinetics. Observed rate constants at 25.0 ± 0.8° for NH-proton exchange of *N*-methylisoindoline in aqueous HCl were determined from the singlet-to-doublet transition of the NCH_3 NMR signal. The instrumental settings and treatment of the NMR data were similar to those described in a previous publication.[7] Rate constants in Table I determined at Emory with a Jeol JNM-MH-100 spectrometer were within 10% of those determined at Georgia with a Hitachi Perkin-Elmer R-20 spectrometer. Solutions were used immediately after their preparation, and pH values were measured both before and after each kinetic run. The pK_a of *N*-methylisoindoline (Table I) was obtained by differential potentiometric titration.

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

Registry No.—*N*-Methylisoindoline, 3474-87-1.

References and Notes

(1) Recipient of a Camille and Henry Dreyfus Foundation Teacher–Scholar Grant and a National Institutes of Health Research Career Development Award.
(2) E. K. Ralph, III, and E. Grunwald, *J. Amer. Chem. Soc.*, **89**, 2963 (1967).
(3) E. Grunwald and E. K. Ralph, *Acc. Chem. Res.*, **4**, 107 (1971).
(4) D. E. Leyden and W. R. Morgan, *J. Phys. Chem.*, **73**, 2924 (1969).
(5) Unless the phenyl rings of dibenzylmethylamine are proximate, the acyclic and cyclic amines are conformationally distinct at the nitrogen.
(6) L. M. Rice, C. H. Grogan, and E. M. Reig, *J. Am. Chem. Soc.*, **77**, 616 (1953).
(7) F. M. Menger and G. Salto, *J. Am. Chem. Soc.*, **95**, 6848 (1973).

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s-Triazines. VI.[1] Novel Reaction Products from *s*-Triazinylation of 2-Acyl-1-methylpyrroles Using 2,4,6-Trichloro-*s*-triazine

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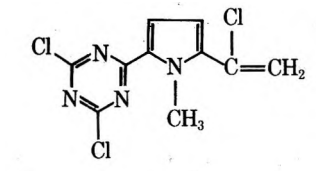
The direct *s*-triazinylation reactions using 2,4,6-trichloro-*s*-triazine (cyanuric chloride) on pyrrole and various substituted pyrroles to give 2,4-dichloro-6-(pyrrolyl)-*s*-triazines have been described in our earlier paper.[2] Here we report on the novel reaction products obtained by treating cyanuric chloride with 2-acyl-1-methylpyrroles.

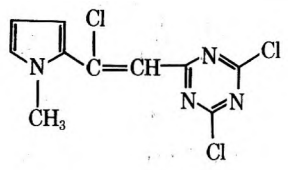
2-Acetyl-1-methylpyrrole (**3**), when treated with 1 equiv of cyanuric chloride in refluxing bromobenzene, led to an equimolar mixture of two isomeric products, **1** and **2**. The ir spectrum in either case did not show any carbonyl or hydroxyl absorptions. The NMR spectrum in CCl_4 for **1** exhibited two vinyl protons at δ 5.62 (d) and 5.77 (d) ($J \simeq 1.5$ Hz) besides the expected pyrrole ring protons. The single olefinic proton in **2** appeared as a singlet at δ 6.72 amidst a multiplet at δ 6.65–6.86 due to two other pyrrole protons. However, in C_6D_6 the olefinic proton appeared as a sharp singlet at δ 6.42 and the three pyrrole ring protons in a normal ABX pattern. Mass spectra (20 eV) for both compounds show the same parent ion, M^+ 288. The relative abundance ratios of the four peaks corresponding to the molecular ion group at 288, 290, 292, and 294 are consistent with the expected ratios 27:27:9:1 for three chlorine atoms. The loss of a chlorine atom in each case is shown by the

close agreement of the isotopic ratios at *m/e* 253, 255, and 257 with the expected values 9:6:1. In compound **1**, the characteristic feature is shown by the presence of the ion *m/e* 227 due to loss of the chlorovinyl side chain, which is absent in **2**.

The chlorovinylpyrrole **4**, which is a likely initial product from **3** and cyanuric chloride,[3] is suggested as an intermediate in the formation of **1** and **2**.[4,5] From a similar reaction with 1-methyl-2-propionylpyrrole only the corresponding 5-triazinyl-substituted pyrrole (**5**) was isolated. Attack at the olefinic site may have been hindered by steric factors.



1



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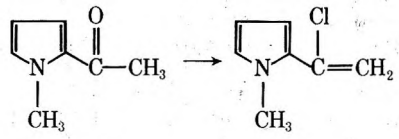
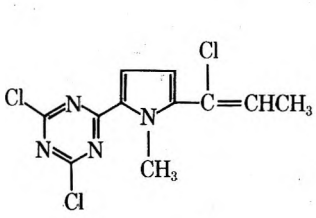


3 **4**



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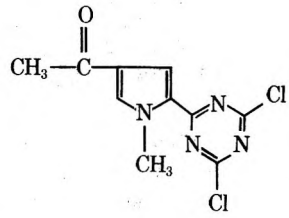

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In view of our failure to produce an acylpyrrole substituted with an *s*-triazinyl group by the above reaction, we turned to acylation of pyrroles already having a triazinyl substituent. Thus, Friedel–Crafts acetylation of 2,4-dichloro-6-(1-methylpyrrol-2-yl)-*s*-triazine with acetic anhydride in the presence of $SnCl_4$ produced mainly the 4-acetyl derivative (**6**). This is consistent with our previous observation on electrophilic substitution reactions with pyrroles having a triazinyl group at the 2 position.[6]

Experimental Section

Melting points are not corrected. Spectra were measured with Perkin-Elmer 457, Unicam SP800, Varian A-60A, and LKB-9000S spectrometers.

2,4-Dichloro-6-[5-(α-chlorovinyl)-1-methylpyrrol-2-yl]-*s*-triazine (1) and 2,4-Dichloro-6-[2-chloro-2-(1-methylpyrrol-2-yl)vinyl]-*s*-triazine (2). A mixture of 2-acetyl-1-methylpyrrole (5.0 g, 0.04 mol) and cyanuric chloride (7.4 g, 0.04 mol) in dry bromobenzene (150 ml) was refluxed for 20 hr; the solvent was evaporated under vacuum at 50° and the residue extracted repeatedly with diethyl ether. The extract on chromatography on a silica gel column eluting with CH_2Cl_2 afforded two fractions. Compound **1** was a pale yellow solid: 3.6 g (31%); mp 108–110° (*n*-hexane); ir (KBr) 890, 850 cm^{-1}; NMR (CCl_4) δ 5.62 (d) and 5.77 (d) ($J \simeq 1.5$ Hz, $=CH_2$), 6.35 (d, H_3), 7.42 (d, H_4, $J_{3,4} \simeq 4.2$ Hz), 4.1 (s, NCH_3); MS *m/e* 288 (M^+), 253 ($M^+ - Cl$), 227 ($M^+ - CCl{=}CH_2$), 140 ($M^+ - C_3N_3Cl_2$); λ_{max} (MeOH) 345 nm (log ε 4.5).

Anal. Calcd for $C_{10}H_7Cl_3N_4$: C, 41.47; H, 2.43; N, 19.34; Cl, 36.73. Found: C, 41.24; H, 2.52; N, 19.57; Cl, 36.86.

Compound **2** was an intense yellow solid: 3.3 g (29%); mp 124–126° (*n*-hexane); ir (KBr) 860, 840 cm^{-1}; NMR (CCl_4) δ 6.72 (s, =CH–), 6.65–6.85 (m, H_5, H_3), 6.12 (dd, H_4), 3.87 (s, NCH_3); NMR (C_6D_6) δ 6.42 (s, =CH–), 6.68 (dd, H_3), 5.99 (dd, H_4), 6.15 (dd, H_5), 2.87 (s, NCH_3); MS *m/e* 288 (M^+), 253 ($M^+ - Cl$); λ_{max} (MeOH) 400 nm (log ε 4.25).

Anal. Calcd for $C_{10}H_7Cl_3N_4$: C, 41.47; H, 2.43; N, 19.34; Cl, 36.73. Found: C, 41.30; H, 2.39; N, 19.49; Cl, 36.66.

2,4-Dichloro-6-[5-(1-chloro-1-propenyl)-1-methylpyrrol-2-yl]-*s*-triazine (5) was similarly prepared from 1-methyl-2-propionylpyrrole in ca. 31% yield: mp 108–110° (*n*-hexane); ir (KBr) 850 cm^{-1}; NMR (CCl_4) δ 6.09 (q, =CH–), 6.23 (d, H_3), 7.41 (d, H_4, $J_{3,4} \simeq 4.5$ Hz), two signals at 2.11 (d), 1.98 (d) for C–CH_3 and 4.07 (s), 4.03 (s) for NCH_3 in each case indicated a mixture of cis/trans isomers in the ratio of ca. 1:9; MS *m/e* 302 (M^+), 287 ($M^+ - CH_3$), 267 ($M^+ - Cl$), 154 ($M^+ - C_3N_3Cl_2$); λ_{max} (MeOH) 348 nm (log ε 4.56).

Anal. Calcd for $C_{11}H_9Cl_3N_4$: C, 43.51; H, 2.98; N, 18.45; Cl, 35.03. Found: C, 43.83; H, 2.84; N, 18.25; Cl, 34.78.

2,4-Dichloro-6-(4-acetyl-1-methylpyrrol-2-yl)-*s*-triazine (6). To 2,4-dichloro-6-(1-methylpyrrol-2-yl)-*s*-triazine[2,6] (2.3 g, 0.01 mol) and Ac_2O (1.02 g) in dry benzene (25 ml) was added dropwise $SnCl_4$ (2.6 g, 0.01 mol) with stirring at room temperature; stirring was continued for 2 hr. The reaction mixture was evaporated to dryness and partitioned between $CHCl_3$ and water. The chloroform layer was separated, dried ($MgSO_4$), treated with charcoal, and evaporated to give a solid residue (2.2 g, 81%). This on sublimation at 130° (0.02 mm) produced analytically pure compound: mp 172–174°; ir (KBr) 1675, 1665 cm^{-1}; NMR ($CDCl_3$) δ 7.85 (d, H_3), 7.53 (d, H_5, $J_{3,5} \simeq 2.0$ Hz), 2.43 (s, C–CH_3), 4.12 (s, NCH_3); λ_{max} (MeOH) 232 nm (log ε 4.24), 328 (4.43).

Anal. Calcd for $C_{10}H_8Cl_2N_4O$: C, 44.30; H, 2.97; N, 20.66; Cl, 26.15. Found: C, 44.51; H, 2.97; N, 20.38; Cl, 26.33.

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Registry No.—**1**, 53993-20-7; **2**, 53993-21-8; **3**, 932-16-1; **5**, 53993-22-9; **6**, 53993-23-0; cyanuric chloride, 108-77-0; 1-methyl-2-propionylpyrrole, 17180-59-5; 2,4-dichloro-6-(1-methylpyrrol-2-yl)-*s*-triazine, 35252-42-7.

References and Notes

(1) Part V: J. K. Chakrabarti, A. F. Cockerill, G. L. O. Davies, T. M. Hotten, D. M. Rackham, and D. E. Tupper, *J. Chem. Soc., Perkin Trans. 2*, 861 (1974).
(2) J. K. Chakrabarti and D. E. Tupper, *J. Heterocycl. Chem.*, **11**, 417 (1974).
(3) J. R. Sandler, *J. Org. Chem.*, **35**, 3967 (1970).
(4) Similar nucleophilic substitutions of cyanuric chloride by the ethylenic double bond of ketene diethyl acetal (a) and by diazomethane (b) are known: (a) E. Kober, *J. Org. Chem.*, **26**, 4705 (1961). (b) C. Grundmann and E. Kober, *J. Am. Chem. Soc.*, **79**, 944 (1957).
(5) We are grateful to one of the reviewers for this suggestion.
(6) J. K. Chakrabarti, R. W. Goulding, and A. Todd, *J. Chem. Soc., Perkin Trans. 1*, 2499 (1973).

Polymer-Protected Reagents. III. Acetal Formation with Polymer-Protected Aluminum Chloride

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Previous communications from this laboratory demonstrated polymer-protected aluminum chloride (Ⓟ-$AlCl_3$) to be an effective catalyst for the formation of ethers[3] and esters.[4]

As an adjunct to these studies we wish to report the use of Ⓟ-$AlCl_3$ as a catalyst for acetal formation. Our results indicate that Ⓟ-$AlCl_3$ is useful for most acid-catalyzed dehydration reactions.

The scope of the reaction of various aldehydes and alcohols with Ⓟ-$AlCl_3$ and noncatalyzed conditions is shown in Table I. These results indicate that the more sterically hindered alcohols react more slowly and that electron-withdrawing groups attached to the benzaldehyde enhance acetal formation. The latter point is demonstrated by compet-

Table I
Acetal Formation

Registry no.	Aldehyde	Alcohol	Mole ratio aldehyde/alcohol	Temp, °C	Time, hr	% yield[a] No catalyst	% yield[a] Ⓟ-$AlCl_3$[b]
100-52-7	Benzaldehyde	1-Butanol[c]	0.21	95	2.5	8	21
	Benzaldehyde	2-Butanol[d]	0.21	95	92	0	0
552-89-6	*o*-Nitrobenzaldehyde	1-Butanol	0.21	45	3	1	40
	o-Nitrobenzaldehyde	1-Butanol	0.21	95	18	0	62
104-88-1	*p*-Chlorobenzaldehyde	1-Butanol	0.21	95	18	1	32
123-11-5	*p*-Anisaldehyde	1-Butanol	0.21	95	93	0	0
90-02-8	*o*-Salicylaldehyde	1-Butanol	0.21	95	47	0	0
535-16-8	*p*-Nitrobenzaldehyde	1-Butanol	0.21	95	24	0	48

[a] Yields determined by VPC with added internal standard of *m*-chlorotoluene. [b] One-half gram of Ⓟ$AlCl_3$ used per 20 mmol of aldehyde [c] Registry no., 71-36-3. [d] Registry no., 78-92-2.

Table II
Competitive Rate Factors for Dibutyl Acetal Formation from Para-Substituted Benzaldehydes[a]

Substituent	k_x/k_H
NO_2	1.36
$N(CH_3)_2$[b]	0.00
H	1.00
Cl	1.06

[a] 20 mmol of substituted benzaldehyde, 20 mmol of benzaldehyde, excess 1-butanol, and 0.55 g of Ⓟ$AlCl_3$ stirred at 55°. [b] Registry no., 100-10-7.

itive rate data (see Table II) for various para-substituted benzaldehyde reactions with 1-butanol and Ⓟ-$AlCl_3$.

Consistency of Ⓟ-$AlCl_3$ preparation was demonstrated by two different batches which gave yields of the acetal from *o*-nitrobenzylaldehyde and 1-butanol within 0.1%. Some catalysis by polymer (styrene–1.8% divinylbenzene copolymer) alone was also shown in the case of the *o*-nitrobenzaldehyde–1-butanol reaction. Yields of 67% acetal compared to the Ⓟ-$AlCl_3$ catalysts were observed. The cross-linked polystyrene alone probably works as an entrapment agent for the water formed in the reaction. The total catalytic activity of Ⓟ-$AlCl_3$ is no doubt derived from both its Lewis acid nature of the bound aluminum chloride plus the ability of the cross-linked polystyrene to entrap water.

The Ⓟ-$AlCl_3$ was also an effective catalyst for the hydrolysis of acetals. For example, heating the diethyl acetal of *o*-chlorobenzaldehyde with Ⓟ-$AlCl_3$ in benzene–methanol–water (2:6:1) for 17.5 hr gave a 61% yield of *o*-chlorobenzaldehyde together with 34% of *o*-chlorobenzaldehyde dimethyl acetal and 5% of a product tentatively identified as the methyl ethyl acetal. Under similar conditions a blank containing all reagents but Ⓟ-$AlCl_3$ produced only 4% of the aldehyde and 2% of the mixed methyl ethyl acetal.

Ⓟ-$AlCl_3$ is a useful catalyst for synthetic reactions which require both a dehydrating agent and a Lewis acid. Though its versatility is rather limited, on a larger scale, it may be quite useful because the reagents can be recycled and because the catalyst's reactivity is somewhat attenuated because of the presence of the polymer. For reactions requiring an acid catalyst in compounds with a sensitive secondary functional group, Ⓟ-$AlCl_3$ may well be the reagent of choice. Extensive electron microscopic studies detailing the exact structure of Ⓟ-$AlCl_3$ will be published shortly.

Experimental Section

All alcohols and aldehydes were reagent grade and the latter were redistilled prior to use. Ⓟ-$AlCl_3$ was prepared as before.[3]

General Procedure. Reactant concentrations, temperatures, times, product, and yield data are given in Table I. The aldehyde, alcohol, anhydrous benzene (5 ml/20 mmol of aldehyde), and 0.5 g of Ⓟ-$AlCl_3$ per 20 mmol of aldehyde were stirred in a closed reaction tube for the appropriate temperature. After the desired reaction time, aliquots were removed and analyzed by gas–liquid chromatography on a Hewlett-Packard Model 5750 flame ionization gas chromatograph. The columns used were 6 ft × 0.125 in. 3% silicon gum rubber on Chromosorb W and 10% Carbowax 20M on Chromosorb P. Yields were determined by the addition of the internal standard of *m*-chlorotoluene. Preparative reactions were performed as above. Isolation of products was accomplished by filtration of Ⓟ-$AlCl_3$ and distillation of the filtrate. Products were identified by VPC, NMR, ir, and comparison with authentic samples.

Acknowledgment. We thank the National Science Foundation (Grant No. GP-33566) and the Research Corporation for support. In addition, support from the National Institutes of Health—General Medical Sciences for a special postdoctoral fellowship for one of us (E.C.B.) is gratefully acknowledged.

Registry No.—*p*-Nitrobenzaldehyde dibutyl acetal, 19706-87-7; *p*-(dimethylamino)benzaldehyde dibutyl acetal, 53951-32-9; benzaldehyde dibutyl acetal, 5395-08-4; *p*-chlorobenzaldehyde dibutyl acetal, 53951-33-0; *o*-nitrobenzaldehyde dibutyl acetal, 53951-34-1; $AlCl_3$, 7446-70-0.

References and Notes

(1) On leave from Rollins College, 1972–1973.
(2) Fellow of the Alfred P. Sloan Foundation, 1971–1973.
(3) D. C. Neckers, D. A. Kooistra, and G. W. Green, *J. Am. Chem. Soc.*, **94**, 9284 (1972).
(4) E. C. Blossey, L. M. Turner, and D. C. Neckers, *Tetrahedron Lett.*, 1823 (1973).

Application of an Optically Active Nuclear Magnetic Resonance Shift Reagent to Configurational Problems

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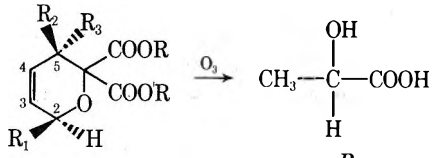
The use of an optically active NMR shift reagent, such as $Eu(hfac)_3$, offered an interesting approach to the problem of the determination and correlation of configuration, or the evaluation of the optical yield of reactions. The principal effect of such optically active shift reagents is the separation of NMR signals for the corresponding enantiomers by the selective complexation of one enantiomer. In this study we report the application of $Eu(hfac)_3$ (europium 3-trifluoroacetyl-*d*-camphorate) to the determination of the configuration at C-2 of a series of derivatives of 2-methyl-

Scheme I



1

Compd	R	R_1	R_2	R_3
1	H	CH_3	H	H
2	C_2H_5	CH_3	H	H
3	CH_3	CH_3	H	H
4	C_2H_5	CH_3	CH_3	H
5	C_2H_5	CH_3	H	CH_3

5,6-dihydro-α-pyran 6,6-diacids. The five compounds we used were (2*R*)-2-methyl-5,6-dihydro-α-pyrano-6,6-dicarboxylic acid (**1**), the dimethyl ester of this acid (**3**), diethyl 2-methyl-5,6-dihydro-α-pyrano-6,6-dicarboxylate (**2**), diethyl *cis*-2,5-dimethyl-5,6-dihydro-α-pyrano-6,6-dicarboxylate (**4**), and diethyl *trans*-2,5-dimethyl-5,6-dihydro-α-pyranodicarboxylate (**5**). The conformation of this family of compounds has recently been established.[1-3] The working principle of our study is that the ozonolysis of optically active compound **1** (or **3**) gives the lactic acid[4] (Scheme I). Comparison of the NMR spectra of model optical isomers of lactic acid (*R* or *S*) and the lactic acid obtained from the ozonolysis—recorded in the presence of $Eu(hfac)_3$ in ethanol-*d*—permitted us to conclude that the lactic acid from the ozonolysis is 70% *R*. In fact, the induced shifts of CH and CH_3 protons were different for the isomers of lactic acid. These shifts are bigger for the complex of the *R* acid and $Eu(hfac)_3$. We reexamined the 220-MHz NMR spectra of compounds **1** and **3** (optically active) and their racemic derivatives **2**, **4**, and **5**. The spectrum of **3** recorded in the presence of $Eu(hfac)_3$ revealed that the induced shifts of the H-2 and CH_3-2 protons are δ 0.98 and 0.52,[5] respectively (Table I).

The direct application of $Eu(hfac)_3$ to the racemic compounds **2–5** showed a separation of the signals for H-2 and CH_3-2. Comparison of the values of the induced shift for the racemic and the optically active (*R*)-**3**—with the same quantity of the shift reagent—permitted us to conclude that of the pairs of optical isomers the one with a larger $\Delta\delta$ has the *R* configuration. On searching for the verification of this conclusion, we observed a similar splitting of signals for the ester **2**, which means that the complex *R* ester-*d* shift reagent showed a slightly larger $\Delta\delta$ than the epimeric complex *S* ester-*d* shift reagent. The quasiracemate formation between the optically active shift reagent and the asymmetric center of the compound is characterized by the smaller $\Delta\delta$. This is a different representation of the fact that the lanthanide complex has its own symmetry.

For the two diastereomers **4** and **5** (asymmetric centers at C-2 and C-5), the corresponding racemic mixtures are composed of *R,S* + *S,R* and *R,R* + *S,S*, respectively. A separation of signals by the same method was observed for the protons of H-2 and CH_3-2 but the corresponding signals of H-5 and CH_3-5 remained unchanged. These results can be explained by the position of the complexation site, which for the dihydropyranol esters is known to be on the oxygen close to C-2.[1]

The successful application of the optically active shift reagent technique to the reactions of epimerization, racemization, asymmetric induction, or simply to the identification of configuration depends mainly on the use of a high-resolution spectrometer and an appropriate solvent, and on the asymmetric center being relatively close to the complexation site.

Table I
Chemical Shifts of Selected Protons[a]

		H-2	CH_3-2	H-5	CH_3-5	H-3	H-4
Lactic acid	(*R*)[b]	4.50	1.34				
Lactic acid	(*S*)[b]	4.28	1.19				
1	(*R*)	4.84	1.45	3.10		5.52	5.92
2	(2*R*)	5.01	1.62	3.19		5.55	5.86
	(2*S*)	4.90	1.52			5.51	
3	(2*R*)	5.12	1.57	3.22		5.82	6.17
	(2*S*)	4.90	1.49				
4	(2*R*,5*S*)	5.22	1.81	3.25	1.25	5.66	6.03
	(2*S*,5*R*)	5.11	1.73			5.62	
5	(2*R*,5*R*)	4.89	1.64	3.30	1.28	5.73	6.02
	(2*S*,5*S*)	4.78	1.53			5.70	

[a] After addition of 0.1 mol of $Eu(hfac)_3$ in $CDCl_3$ (10.0%). [b] In ethanol-*d*.

Experimental Section

The prefix *dl* has been omitted from the names of most racemic compounds described. The NMR spectra in $CDCl_3$, CD_3OD, or C_2D_5OD were registered on a Varian HR 220 MHz spectrometer. The shift reagent $Eu(hfac)_3$ was purchased from Norell Chemical Co., Ltd. The compounds **1–5** were prepared in a bomb tube and purified by preparative VPC.[1,4] The ozonolysis was carried out in the Mathieson ozonizer in 10% methanol solution. The physical constants of the compounds follow: **1**, mp 112–114° (yield 60%); **2**, bp 79° (0.1 mm) (55%); **3**, mp 92–93° (50%); **4**, bp 82° (0.17 mm) (47%); and **5**, bp 84° (0.12 mm) (34%). The separation of the optical isomers of **1** [αD (H_2O) +14°] has been carried out through the brucine salt recrystallization. The (*R*)-lactic acid [αD (H_2O) +3.8°] was bought from Sigma Chemicals Co.

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Registry No.—**1**, 53951-35-2; **2** (2*R*), 53951-36-3; **2** (2*S*), 53951-37-4; **3** (2*R*), 53951-38-5; **3** (2*S*), 53951-39-6; **4** (2*R*,5*S*), 53991-02-9; **4** (2*S*,5*R*), 53991-03-0; **5** (2*R*,5*R*), 53991-04-1; **5** (2*S*,5*S*), 53991-05-2; lactic acid (*R*), 10326-41-7; lactic acid (*S*), 79-33-4; europium 3-trifluoroacetyl-*d*-camphorate, 34830-11-0.

References and Notes

(1) K. Jankowski and J. Couturier, *J. Org. Chem.*, **37**, 3997 (1972).
(2) O. Achmatowicz, J. Jurczak, A. Konowal, and A. Zamojski, *Org. Magn. Reson.*, **2**, 55 (1970).
(3) (a) R. J. Ferrier and G. H. Sankey, *J. Chem. Soc.*, 581 (1969); 1417 (1967); (b) K. Jankowski and R. Luce, *Tetrahedron Lett.*, 2069 (1974).
(4) O. Achmatowicz and A. Zamojski, *Rocz. Chem.*, **35**, 1251 (1961).
(5) K. Jankowski, *Bull. Acad. Pol. Sci., Ser. Sci. Chim.*, **21**, 741 (1973).
(6) The spectrum of **3** showed also the residual signals corresponding to the partially racemized compound.
(7) G. N. LaMar, *J. Chem. Phys.*, **42**, 1985 (1965).

Deamination of 2-Amino-1-cyclopropylethanol

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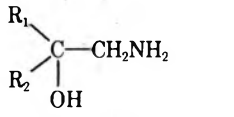
The 1,2 shift of cyclopropyl to an electrophilic center relative to hydride, alkyl, and phenyl shifts has been investigated in a number of reactions. In the reaction with nitrous acid of 2-cyclopropylethylamine[2] and in the solvolysis of

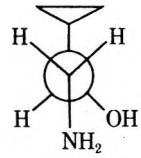
alkyl brosylates and tosylates,[3] the ratio of cyclopropyl to hydride and methyl shifts was greater than 1, but solvolysis reactions of cyclopropyl have often been complicated by ring-opening reactions[4,5] and diazotization reactions of aliphatic amines have given contradictory results in other cases. Although hydride shift predominates over alkyl or cycloalkyl group shifts in most reactions reported, it is difficult, for example, to interpret the variations in the hydride:alkyl shift ratio from 1.3–1.6 found in the reaction with nitrous acid of isobutylamine[6] to the predominant methyl shift found in the reaction of *threo*-3-phenyl-2-butylamine[7] and to the strong predominance of hydride over ethyl and cyclohexyl shift products (93:4.5:2.5) in the reaction of (*S*)-1-amino-2-cyclohexylbutane investigated by Kirmse.[8] We have sought to compare cyclopropyl vs. hydride shifts in a reaction with fewer complications.

The reaction of amino alcohols with nitrous acid has served in somewhat the same way as the pinacol rearrangement as a test of the relative ability of substituent groups to donate an electron pair to an electrophilic site.[9,10] Relative shifts are known to be affected by the conformational equilibria of the amino alcohols.[10,11] To equalize these, we have compared the cyclopropyl and isopropyl shift products with hydride shift products formed in the reaction with nitrous acid of amines 1 and 2.

2-Amino-1-cyclopropylethanol (1) and 1-amino-3-methyl-2-butanol (2) were synthesized from cyclopropanecarboxaldehyde and 2-methylpropanal by condensation with nitromethane and reduction of the nitro alcohols.



1, R_1 = H; R_2 = cyclopropyl
2, R_1 = H; R_2 = isopropyl
4, R_1 = phenyl; R_2 = isopropyl



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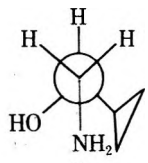

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The reaction of nitrous acid with 1 yielded cyclopropylacetaldehyde, cyclopropanecarboxaldehyde (in an overall 40% yield of carbonyl compounds, cyclopropylacetaldehyde was the major portion) and cyclopropyloxirane (**3**, 10%). The formation of cyclopropanecarboxaldehyde probably resulted from oxidative cleavage of the starting material or of cyclopropylethylene glycol. Under similar conditions, propylene glycol gave rise to carbonyl compounds, one of which was tentatively identified as acetaldehyde. The cyclopropyl shift was the only one observed; it is estimated that less than 2% of cyclopropyl methyl ketone could have been formed.

It is possible under certain conditions for alkyl epoxides to isomerize to aldehydes in the presence of acid;[12] so it was necessary to determine whether the cyclopropylacetaldehyde might have resulted from the ring opening of protonated **3**, a reaction path which would involve no 1,2-cyclopropyl shift. To investigate this possibility, **3** was prepared in 31% yield by the action of dimethylsulfonium methylide on cyclopropanecarboxaldehyde and in very low yield by the epoxidation of vinylcyclopropane. When **3** was subjected to the identical reaction conditions used in the reaction of **1** with nitrous acid no cyclopropaneacetaldehyde was formed.

The reaction of nitrous acid with **2** yielded 3-methyl-2-butanone (30%) and 3-methyl-1,2-epoxybutane (10%). The presence of 3-methyl-2-butanone and the absence of any detectable quantity of 3-methylbutanal in the product indicates that the isopropyl group is unable to compete successfully with hydride for migration.

In this case also the possibility that the 3-methyl-2-butanone was formed via the intermediate 3-methyl-1,2-epoxybutane was tested. 3-Methyl-1,2-epoxybutane was prepared by the epoxidation of 3-methyl-1-butene. When this epoxide was subjected to the identical reaction conditions used in the reaction with nitrous acid of 1-amino-3-methyl-2-butanol, no carbonyl compound was formed.

It is expected[10] that the conformation of the hydroxy diazonium ion formed from **1** should be a major factor in determining relative shifts; related amino alcohols have been shown[13] to have hydroxyl and amino functions in gauche conformation. The ratio of conformation **5** (preferred), with the bulky group trans to the amino group, to conformation **6**, with β hydrogen trans to the amino group, should differ little between cyclopropyl and isopropyl. There is precedence for the marked predominance of 1,2 shift of a group in which anchimeric assistance is facile in the work of House,[14] who found 99% phenyl shift in the reaction with nitrous acid of **4**. The formation of 3-methyl-2-butanone is consistent with the predominant shift of hydride in the nitrous acid reaction of aminobutanes.[8] The formation of cyclopropylacetaldehyde is consistent with conformational preferences and with earlier observations[2–5] of anchimeric assistance by cyclopropyl. The stabilization of an intermediate leading to cyclopropyl shift may be attributed to a π complex as suggested by Dewar and Harris.[4] This interpretation is related to our earlier explanation of the results of deamination of 2-cyclopropylethylamine.[2] Whatever the explanation, the marked difference in behavior of **1** and **2** is further evidence of the ready participation of cyclopropyl in reactions involving a neighboring electrophilic center.

Experimental Section[15]

1-Cyclopropyl-2-nitroethanol. To a stirred solution of 70 g (1.0 mol) of cyclopropanecarboxaldehyde and 61 g (1.0 mol) of nitromethane in 150 ml of methanol, cooled in ice, 40 g (1.0 mol) of sodium hydroxide in 150 ml of water was added dropwise. A white solid precipitated during the 1-hr addition; after stirring for an additional 30 min, 62 g (1.0 mol) of glacial acetic acid was added dropwise. The organic layer was combined with ether extracts (2 × 500 ml) of the aqueous layer and dried with anhydrous sodium sulfate. Solvent was then removed under vacuum and gentle warming, and 119 g (90%) of 2-nitro-1-cyclopropylethanol, bp 74–74.5° (2.0 mm), was obtained. Anal.[16] Calcd for $C_5H_9NO_3$: C, 45.80; H, 6.92; N, 10.68. Found C, 45.58; H, 7.44; N, 10.98.

2-Amino-1-cyclopropylethanol (1). 1-Cyclopropyl-2-nitroethanol, 100 g (0.76 mol), in 250 ml of dry ether was added dropwise during 3 hr to a stirred refluxing slurry of 64 g (1.7 mol) of lithium aluminum hydride in 2 l. of dry ether. Reflux was maintained for 2 hr, and the mixture was decomposed by dropwise addition of 600 ml of 2-propanol followed by 170 ml of water saturated with sodium chloride. After stirring for 5 hr, the mixture was filtered and the white precipitate of aluminum and lithium hydroxide was continuously extracted with 1:3 2-propanol–ether. The extracts and the original filtrate gave 40 g (51%) of **1**, bp 89–94° (12 mm). Anal.[16] Calcd for $C_5H_{11}NO$: C, 59.37; H, 10.96; N, 13.84. Found: C, 59.40, 59.30; H, 10.53, 10.67; N, 14.10.

Reaction of 1 with Nitrous Acid. A solution of 10.5 g (0.15 mol) of sodium nitrite in 50 ml of water was added dropwise to a stirred solution of 15 g (0.15 mol) of **1**, 12 ml of 12 *M* hydrochloric acid, and 150 ml of water. The temperature was kept below 5° during the addition and for 1 hr afterwards. The reaction mixture was then warmed to 50° until evidence of nitrogen evolution had ceased and extracted with 10 ml of ether, and the extract was dried over anhydrous sodium sulfate. Vapor chromatography on columns A and B[17] showed only two peaks. The smallest one of these was shown to have retention times on both columns identical with those of a sample of **3** which was synthesized for reference.[18] The larger peak exhibited retention times that were different from that of cyclopropyl methyl ketone and identical with those of both cyclopropanecarboxaldehyde and cyclopropylacetaldehyde on both columns. Silica gel TLC of the 2,4-dinitrophenylhydrazone derivative of the crude reaction mixture (3:1 benzene–petroleum ether) indicated the presence of both aldehydes. Identification was made

by preparing and chromatographing samples of the dinitrophenylhydrazones. Fractional crystallization of the crude mixture of 2,4-dinitrophenylhydrazones from ethanol gave a sample (mp 131–132°) which did not depress the melting point of a known sample of cyclopropylacetaldehyde 2,4-dinitrophenylhydrazone.

Cyclopropyloxirane (3). Cyclopropanecarboxaldehyde, 7.0 g (0.10 mol), was stirred under nitrogen with 28.6 g (0.14 mol) of trimethylsulfonium iodide in 60 ml of dimethyl sulfoxide. A solution of 14.0 g of potassium *tert*-butoxide in 150 ml of dimethyl sulfoxide was added dropwise with stirring during 30 min while cooling. After stirring for an additional 15 min, 300 ml of water was added slowly while cooling with ice. The solution was extracted with ether (3 × 500 ml) and the extract was washed with water and dried over molecular sieves. Distillation on a Teflon spinning band column gave, after removal of ether and *tert*-butyl alcohol, 2.6 g of **3**: bp 85–90° (lit.[12b] bp 100°); NMR (neat) δ 0.1–0.4 (m, 4 H, cyclopropyl CH_2), 0.5–0.8 (m, 1 H, cyclopropyl CH), 2.4–2.7 (m, 2 H, oxirane CH_2), 2.1–2.3 (m, 1 H, oxirane CH).[18] Anal.[19] Calcd for C_5H_8O: C, 71.39; H, 9.59. Found: C, 71.12; H, 9.75.

Cyclopropyloxirane (**3**) was first prepared from vinylcyclopropane but the amount was not sufficient for complete identification. A solution of 35 g (0.20 mol) of *m*-chloroperoxybenzoic acid in 60 ml of dry ether was added dropwise during 1 hr to a stirred solution of 10.5 g (0.15 mol) of vinylcyclopropane[20] maintained at 20°. After stirring for 2 hr, the mixture was extracted with 10% sodium hydroxide solution, washed with water, and dried. After removal of the ether, VPC using column B[17] indicated one volatile product in addition to ether and a small amount of vinylcyclopropane.

Reaction of Nitrous Acid with 3. A solution of 1.66 g (0.024 mol) of sodium nitrite in 8.0 ml of water was added dropwise to a stirred solution of 2.0 g (0.024 mol) of **3**, 1.9 ml of 12 *M* hydrochloric acid, and 23.5 ml of water. The conditions of the reaction of **1** with nitrous acid were duplicated. The mixture was extracted with two 4-ml portions of ether and the extracts were dried over molecular sieves. Gas chromatography of the ether solution on column B[17] showed only one major component besides ether. This component had a retention time identical with that of **3** and different from those of cyclopropylacetaldehyde, cyclopropanecarboxaldehyde, and cyclopropyl methyl ketone. Treatment of the product with 2,4-dinitrophenylhydrazine yielded no precipitate.

Reaction of Nitrous Acid with 1-Amino-3-methyl-2-butanol. 1-Amino-3-methyl-2-butanol, bp 88–90° (40 mm) [lit.[21] bp 174° (734 mm)], was prepared in 42% overall yield from 2-methylpropanal by the same route used for 2-amino-1-cyclopropylethanol. Dropwise addition of 32 g (0.45 mol) of sodium nitrite in 100 ml of water to a stirred solution of 45 g (0.45 mol) of 1-amino-3-methyl-2-butanol in 500 ml of water containing 35 ml of 12 *M* hydrochloric acid, maintained below 5°, was followed by stirring (30 min), warming, and refluxing (10 min). The reaction mixture was extracted with two 75-ml portions of ether, and the dried ether solution was concentrated. Vapor chromatography on columns A and B[17] showed the presence of only 3-methyl-1,2-epoxybutane and 3-methyl-2-butanone, in a ratio of 1:3 (in approximate 40% yield), identified by comparison of retention times with those of authentic samples. 3-Methylbutanal, with a different retention time, was not present. The 2,4-dinitrophenylhydrazone, mp 123–124°, was prepared and did not depress the melting point of an authentic sample of 3-methyl-2-butanone 2,4-dinitrophenylhydrazone.

Reaction of 3-Methyl-1,2-epoxybutane with Nitrous Acid. The epoxide was prepared in 63% yield from 3-methyl-1-butene by reaction with *m*-chloroperoxybenzoic acid.[22] A solution containing 2.0 g (0.023 mol) of 3-methyl-1,2-epoxybutane, 1.75 ml of 12 *M* HCl, and 25 ml of water was stirred and the temperature maintained below 5° while a solution of 1.60 g (0.023 mol) of sodium nitrite in 5 ml of water was added dropwise. After 30 min, the stirred solution was warmed to 20° and then refluxed for 10 min. It was then extracted with two 4-ml portions of ether, and the ether extract was dried over molecular sieves. Gas chromatography on column B[17] indicated the presence only of ether and 3-methyl-1,2-epoxybutane. Treatment with 2,4-dinitrophenylhydrazine gave no solid.

Registry No.—**1**, 54120-02-4; **2**, 17687-58-0; **3**, 21994-19-4; 1-cyclopropyl-2-nitroethanol, 54120-03-5; cyclopropanecarboxaldehyde, 1489-69-6; nitromethane, 75-52-5; nitrous acid, 7782-77-6; cyclopropanecarboxaldehyde 2,4-dinitrophenylhydrazone, 36873-36-6; cyclopropylacetaldehyde 2,4-dinitrophenylhydrazone, 54120-04-6; potassium *tert*-butoxide, 865-47-4; 2-methylpropanal, 78-84-2; 3-methyl-1,2-epoxybutane, 1438-14-8; 3-methyl-2-butanone, 563-80-4; 3-methyl-2-butanone 2,4-dinitrophenylhydrazone, 3077-97-2.

References and Notes

(1) Abstracted from the M.S. Theses of Stephen D. Clemans (1963) and Bruce A. Bennett (1971), Rensselaer Polytechnic Institute.
(2) G. E. Cartier and S. C. Bunce, *J. Am. Chem. Soc.*, **85**, 932 (1963).
(3) (a) M. Hanack and H. M. Ensslin, *Tetrahedron Lett.*, 4445 (1965); (b) R. R. Sauers and R. W. Ubersax, *J. Org. Chem.*, **31**, 495 (1966).
(4) M. J. S. Dewar and J. M. Harris, *J. Am. Chem. Soc.*, **92**, 6557 (1970).
(5) R. A. Kent and S. C. Bunce, paper presented at the 160th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1970, Abstract ORGN 109.
(6) J. H. Bayless, A. T. Jurewicz, and L. Friedman, *J. Am. Chem. Soc.*, **90**, 4466 (1968).
(7) D. Y. Curtin and M. C. Crew, *J. Am. Chem. Soc.*, **77**, 354 (1955).
(8) W. Kirmse and W. Gruber, *Chem. Ber.*, **104**, 1789 (1971).
(9) Y. Pocker, "Molecular Rearrangements", P. de Mayo, Ed., Wiley, New York, N.Y., 1963, Chapter 1.
(10) C. J. Collins, *Acc. Chem. Res.*, **4**, 315 (1971).
(11) B. M. Benjamin, H. J. Schaeffer, and C. J. Collins, *J. Am. Chem. Soc.*, **79**, 6160 (1957).
(12) Y. Pocker, *Chem. Ind. (London)*, 332 (1959); (b) W. Kirmse and B. Kornrumpf *Angew. Chem., Int. Ed. Engl.*, **8**, 75 (1969).
(13) O. Bastiansen, H. Seip, and J. E. Boggs, *Perspect. Struct. Chem.*, **4**, 60 (1971).
(14) H. O. House and E. J. Grubbs, *J. Am. Chem. Soc.*, **81**, 4733 (1959).
(15) Melting points are corrected. Infrared spectra were measured on a Perkin-Elmer 137 Infracord spectrophotometer, NMR spectra with Varian A-60 and T-60 instruments, and mass spectra with a Perkin-Elmer Hitachi mass spectrometer.
(16) Analysis by Dr. F. B. Strauss Microanalytical Laboratory, Oxford, England OX2 7SA.
(17) A, 20% di-2-ethylhexyl sebacate on Chromosorb W; B, 20% Carbowax 4000 on Chromosorb P; C, 10% diethylene glycol adipate on Chromosorb W.
(18) A report of the preparation of **3** (ref 12b) appeared subsequently; our physical constants (boiling point, NMR spectrum) are somewhat at variance, but the spectral data are obtained under different conditions.
(19) Analysis by Instranal Laboratory, Inc., Rensselaer, N.Y.
(20) V. A. Slabey, *J. Am. Chem. Soc.*, **74**, 4930 (1952).
(21) K. A. Krasuskii and F. F. Krivonoss, *Ukr. Khem. Zh.*, **4**, 79 (1929); *Chem. Abstr.*, **24**, 1082 (1930).
(22) D. J. Pasto and C. C. Cumbo, *J. Org. Chem.*, **30**, 1271 (1965).

A New Reaction of Trithioorthoacetates. Reaction with Acylating Reagents

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Reactions of trithioorthocarboxylates are relatively unknown.[1] In our earlier work[2] it was found that when aryl trithioorthoacetates $(ArS)_3CCH_3$ were dissolved in trifluoroacetic acid-*d*, rapid and complete isotopic exchange occurred at room temperature and on evaporation of the solvent deuterated compounds $(ArS)_3C-CD_3$ were obtained quantitatively. As an extension of this work trifluoroacetylation of $(ArS)_3C-CH_3$ was tried and we now wish to report the results.

As anticipated, the reaction did proceed quite easily at room temperature, but the products, obtained in high yields, were $(ArS)_2C{=}CHCOCF_3$ instead of $(ArS)_3C-CH_2COCF_3$ (Ar, yield, %: *p*-$CH_3OC_6H_4$, 58; *p*-$CH_3C_6H_4$,

$$(ArS)_3C-CH_3 \xrightarrow[rT]{(CF_3CO)_2O} (ArS)_2C{=}CHCOCF_3$$

98; C_6H_5, 100; *p*-ClC_6H_4, 75). Physical properties together with analytical data for the acylation products are listed in Table I.

Similarly, reactions of $(ArS)_3C-CH_3$ with $(CCl_3CO)_2O$ (refluxing for 1 day in $CHCl_3$) gave $(ArS)_2C{=}CHCOCCl_3$ (Ar, yield, %: Ph, 76; *p*-$CH_3C_6H_4$, 28). The acid chloride CCl_3COCl can also be used, the yields being improved in

Table I: Products of the Reaction with Acylating Reagents

Registry no.	Products	Mp,[a,e] °C	NMR, τ (CDCl3)[b]	Ir, ν_{CO}[c]	Empirical formula	C[e]	H	S	F	Cl
54083-59-9	$(p\text{-}CH_3OC_6H_4S)_2C{=}CHCOCF_3$	101	2.73 (q, 8 H), 4.02 (s, 1 H), 6.15 (s, 6 H)	1660	$C_{18}H_{15}O_3S_2F_3$	53.99	3.78		14.23	
						53.99	3.66		14.24	
54083-60-2	$(p\text{-}CH_3C_6H_4S)_2C{=}CHCOCF_3$	160	2.38–2.75 (m, 8 H), 4.12 (s, 1 H), 7.61 (d, 6 H)	1662	$C_{18}H_{15}OS_2F_3$	58.68	4.10		15.47	
						58.86	4.38		15.39	
54083-61-3	$(C_6H_5S)_2C{=}CHCOCF_3$	88	2.20–2.76 (m, 10 H), 4.00 (s, 1 H)	1670	$C_{16}H_{11}OS_2F_3$	56.46	3.26		16.74	
						56.93	3.36		16.73	
54083-62-4	$(p\text{-}ClC_6H_4S)_2{=}CHCOCF_3$	119	2.28–2.72 (m, 8 H), 4.08 (s, 1 H)	1670	$C_{16}H_9OS_2F_3Cl_2$	46.96	2.22		13.93	17.32
						47.03	2.12		13.87	17.38
54083-63-5	$(p\text{-}CH_3C_6H_4S)_2C{=}CHCOCCl_3$	182	2.69 (m, 8 H), 3.80 (s, 1 H), 7.56 (d, 6 H)	1673	$C_{18}H_{15}OS_2Cl_3$	51.73	3.62	15.34		25.45
						51.68	3.58	15.11		25.44
54083-64-6	$(C_6H_5S)_2C{=}CHCOCCl_3$	145	2.50 (m, 10 H), 3.85 (s, 1 H)	1670	$C_{16}H_{11}OS_2Cl_3$	49.32	2.84	16.45		27.29
						49.14	2.79	16.25		27.32
54083-65-7	$(p\text{-}CH_3C_6H_4S)_2C{=}CHCOCHCl_2$	142	2.36–2.82 (s, 8 H), 4.02 (s, 1 H), 4.30 (s, 1 H), 7.60 (d, 6 H)	1650	$C_{18}H_{16}OS_2Cl_2$	56.39	4.21	16.73		18.49
						56.38	4.26	16.43		18.29
54083-66-8	$(C_6H_5S)_2C{=}CHCOCHCl_2$	120	2.62 (m, 10 H), 3.98 (s, 1 H), 4.30 (s, 1 H)	1660						
54083-67-9	$(p\text{-}CH_3C_6H_4S)_2C{=}CHCOCH_2Cl$	152	2.35–2.77 (m, 8 H), 4.07 (s, 1 H), 6.11 (s, 2 H), 7.62 (d, 6 H)	1630	$C_{18}H_{17}OS_2Cl$	61.96	4.91	18.38		10.16
						62.06	4.90	18.12		10.21
54083-68-0	$(p\text{-}CH_3C_6H_4S)PhC{=}CHCOCF_3$[d]	104.5	2.70–3.02 (s, 8 H), 3.30 (s, 1 H), 7.78 (s, 3 H)	1680	$C_{17}H_{13}OSF_3$	63.34	4.07		17.68	
						63.14	4.20		17.67	

[a] Melting points are uncorrected. [b] The NMR spectra were recorded on a 60-MHz Hitachi R-24 spectrometer and satisfactory integrations were obtained for all compounds. [c] cm^{-1} (KBr). Recorded on a Hitachi ir spectrometer, Model EP1-G3. [d] Probably the acyl group is cis to the sulfide group. [e] Analysis, % (calcd over found).

this case up to 100 and 76% for the phenyl and *p*-tolyl compounds, respectively.

Acylation of $(ArS)_3C\text{–}CH_3$ with $CHCl_2COCl$ was performed by refluxing in $CHCl_3$ for 15–72 hr, affording $(ArS)_2C{=}CHCOCHCl_2$ (Ar, yield, %: Ph, 54; $p\text{-}CH_3C_6H_4$, 33).

Monochloroacetylation is also possible. For example, $(p\text{-}CH_3C_6H_4S)_3C\text{–}CH_3$ gave after refluxing with $CH_2ClCOCl$ in chlorobenzene for 18 hr $(p\text{-}CH_3C_6H_4S)_2C{=}CHCOCH_2Cl$ in 37% yield, with recovery of some starting material. Neither $(CH_3CO)_2O$ nor CH_3COCl[3] reacted with $(ArS)_3C\text{–}CH_3$.

This reaction can also be applicable to dithioketals; $(p\text{-}CH_3C_6H_4S)_2PhC\text{–}CH_3$ reacted with $(CF_3CO)_2O$ at room temperature to give a 33% yield of $(p\text{-}CH_3C_6H_4S)PhC{=}CHCOCF_3$.

It seems probable that the products $(ArS)_2C{=}CHCOCF_3$ result from electrophilic attack by the acid anhydride on $(ArS)_2C{=}CH_2$, formed by acid-catalyzed elimination of ArSH from the trithioorthoacetates. In favor of this view, ketene dithioacetals react with the acid anhydride to give the same products.[4] Furthermore, although the reaction of trithioorthoacetates is inhibited by adding small amounts of pyridine, if we start with ketene dithioacetals, the reaction proceeds quite favorably in the presence of pyridine, and formation of resinous materials is avoided. However, we have facts indicating that the two reactions are mechanistically different in some respects.

Experimental Section

Trithioorthoacetates. All trithioorthoacetates were prepared by heating corresponding thiolacetates (5 mmol) and thiophenols (10 mmol) for 2 hr at 50° using a small amount of *p*-toluenesulfonic acid as a catalyst and recrystallized from benzene or *n*-hexane. $(C_6H_5S)_3CCH_3$: mp 147°.[5] $(p\text{-}CH_3OC_6H_4S)_3CCH_3$: mp 158°; NMR ($CDCl_3$) τ 2.80 (q, 12 H), 6.17 (s, 9 H), 8.68 (s, 3 H). $(p\text{-}CH_3C_6H_4S)_3CCH_3$: mp 147°; NMR ($CDCl_3$) τ 2.67 (q, 12 H), 7.63 (s, 9 H), 8.64 (s, 3 H). Anal. Calcd for $C_{23}H_{24}S_3$: C, 69.65; H, 6.10; S, 24.25. Found: C, 69.52; H, 6.16; S, 24.04. $(p\text{-}ClC_6H_4S)_3CCH_3$: mp 111°; NMR ($CDCl_3$) τ 2.60 (q, 12 H), 8.62 (s, 3 H). Anal. Calcd for $C_{20}H_{15}S_3Cl_3$: C, 52.46; H, 3.30; S, 21.01; Cl, 23.25. Found: C, 52.31; H, 3.36; S, 20.99; Cl, 23.42.

Acylation of Trithioorthoacetates. In a typical experiment 3 g (14.3 mmol) of trifluoroacetic anhydride was added to a solution of $(p\text{-}CH_3C_6H_4S)_3CCH_3$ (3 g, 7.58 mmol) in $CHCl_3$ (8 ml) and the mixture was stirred for 20 hr at room temperature or for 2 hr at 40°, and gave after evaporation of the solvent 2.74 g (98% yield) of $(p\text{-}CH_3C_6H_4S)_2C{=}CHCOCF_3$ as white needles, mp 160°. If necessary, the raw products were submitted to column chromatography on silica gel and then purified by recrystallization from appropriate solvents. All spectroscopic and analytical data are tabulated in Table I.

H–D Exchange Experiments. For example, a solution of $(C_6H_5S)_3CCH_3$ (0.1 g) in $CDCl_3$ (0.3 ml) was mixed with 0.5 ml of CF_3CO_2H in a NMR tube and its NMR spectrum was recorded immediately at 35°. A peak for methyl at δ 1.40 in $CDCl_3$ shifted to δ 2.93 and disappeared almost completely when CF_3CO_2D was used instead of CF_3CO_2H. In an isolation experiment, evaporation of the solvent gave $(PhS)_3CCD_3$ almost quantitatively. This material, the deuterium content of which was estimated to be more than 90% by NMR integration in $CDCl_3$ was converted back to $(PhS)_3CCH_3$ by dissolving it into CF_3CO_2H and confirmed by mixture melting point.

Acknowledgment. The authors are grateful for the able assistance of Mr. Kōichi Yamane in performing these experiments.

Registry No.—$(C_6H_5S)_3CCH_3$, 14859-20-2; $(p\text{-}CH_3OC_6H_4S)_3CCH_3$, 39141-48-5; $(p\text{-}CH_3C_6H_4S)_3CCH_3$, 35446-98-1; $(p\text{-}ClC_6H_4S)_3CCH_3$, 39141-50-9; $(CF_3CO)_2O$, 407-25-0; $(CCl_3CO)_2O$, 4124-31-6; $CHCl_2COCl$, 79-36-7; $CH_2ClCOCl$, 79-04-9; $(p\text{-}CH_3C_6H_4S)_2PhCCH_3$, 54083-69-1; thiophenol, 108-98-5; *p*-methoxythiophenol, 696-63-9; *p*-methylthiophenol, 106-45-6; *p*-chlorothiophenol, 106-54-7; dithioacetic acid, 594-03-6.

References and Notes

(1) For a review, see R. H. DeWolfe, "Carboxylic Ortho Acid Derivatives," Academic Press, New York, N.Y., 1970, p 348.
(2) M. Hojo and R. Masuda, unpublished work. Presented in part at the 27th Annual Meeting of the Chemical Society of Japan, Oct 12, 1972, Abstracts, III, p 365.
(3) H. Boehme and J. Roehr [*Justus Liebigs Ann. Chem.*, **648**, 21 (1961)] reported a reaction of triethyl trithioorthoacetate with acetyl chloride to form ketene diethyl dithioacetal and thiolacetate. In our experiment with $(ArS)_3CCH_3$ and acetyl chloride, no reaction occurred. However, if a small amount of acetic acid was present, resinous materials were produced, probably derived from the ketene dithioacetal.
(4) M. Hojo and R. Masuda, unpublished work. Acylation of ketene dithioacetals, vinyl sulfides, vinyl ethers, and vinyl amides will be reported in our forthcoming papers.
(5) G. A. Wildschut, H. J. T. Bos, L. Brandsma, and J. F. Arens, *Monatsh. Chem.*, **98**, 1043 (1967).

Homobenzylic and Homoallylic Spin–Spin Coupling Interactions in Some Octahydro- and Hexahydrophenanthridines

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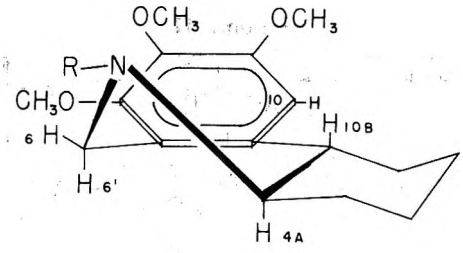
In a previous communication[1] we reported that the signals assigned to H-6′ in the NMR spectra of 1 showed splittings of ca. 1.5 Hz in addition to those expected from geminal coupling between H-6 and H-6′. The conformation of 1 is believed to be that shown here and was derived[1] mainly



1 a R = Me

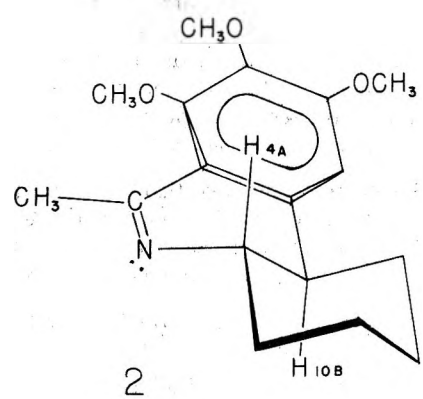
b R = Et

from nmr data. It can be seen that the protons most likely to be responsible for the additional splitting are H-10 (benzylic coupling),[2] H-4a (coupling across four single bonds),[2] or H-10b (homobenzylic coupling).[2] The original suggestion[1] of long-range coupling between H-6′ and H-4a would represent an unusual case of substantial coupling across four single bonds in non-W configuration.[2] An earlier report proposing such a case[3] has been shown to be incorrect.[4]

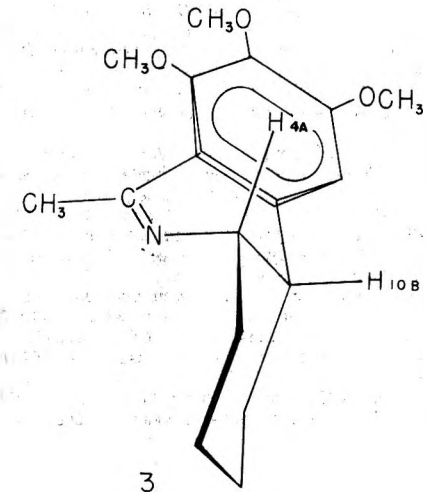
We now present conclusive evidence from 100-MHz multiple resonance studies and from studies on the 4a-deuterio derivative of **1a** that the observed interaction results from homobenzylic coupling between H-6′ and H-10b. The spectra of 1 have been reexamined in $CDCl_3$ at 100 MHz[5] by the Sydney group and, with the aid of multiple resonance experiments, it was established that the proton responsible for the long-range interaction with H-6′ (multiplet, δ 2.52 in **1a**) also interacts with H-10 ($J \simeq 0.8$ Hz, benzylic coupling).[2] Clearly, the resonance at δ 2.52 must be due to H-10b and the long-range interaction responsible for the additional splitting of the signals due to H-6′ is a homobenzylic coupling.[2] An analogous series of results was also obtained for **1b**. A careful measurement of the splittings in the signals due to H-6′, while the residual broadening due to interaction with H-10 was removed by decoupling, showed $J_{6',10b} = 1.88 \pm 0.03$ Hz in **1a** and 1.69 ± 0.03 Hz in **1b**, the largest homobenzylic interactions reported so far.[2,6] The assignment is confirmed by the spectrum of 5-methyl-7,8,9-trimethoxy-4a,10b-*trans*-1,2,3,4,4a,5,6,10b-octahydrophenanthridine-*4a-d*, in which the signal of H-6′ has the same multiplicity as seen with the undeuterated **1a**.

It is significant that these interactions and the similar, slightly smaller, spin–spin coupling in some sterically analogous steroids with ring A aromatic[4] are between trans disposed pseudo-axial protons, which is a particularly favorable juxtaposition for cisoid homoallylic coupling,[7] a related long-range spin–spin interaction.

In a previous communication[8] we have also reported homoallylic coupling constants of about 2 Hz between H-4a and the C-6 methyl protons in 6-methyl-7,8,9-trimethoxy-4a,10b-*trans*- (**2**) and -4a,10b-*cis*-1,2,3,4,4a,10b-hexahydrophenanthridine (**3**). These two compounds represent examples of transoid homoallylic coupling where a methyl group



2



3

assumes the equilibrium conformation in systems where one sp^2 carbon is replaced by an sp^2-hybridized nitrogen atom. In view of the conformational dependence of homoallylic coupling constants,[7] the similarity of the observed homoallylic coupling constants in the trans and cis isomers indicates that H-4a must have essentially the same conformational relationship to the double bond in the two isomers, that is, one in which the dihedral angle between H-4a and the plane of the double bond approaches 90°. This requires that the predominant solution conformation of the cis isomer **3** be that in which the cyclohexane ring has the chair conformation with H-4a in equatorial and H-10b in axial orientations, contrary to what was previously proposed[8] on the basis of chemical shift arguments. The 100-

MHz spectrum of the 1,1,4,4-tetradeuterated derivative of **3** gives chemical shifts of δ 3.35, 2.48, and about 2.5 for H-4a, the methyl group, and H-10b, respectively, and coupling constants of $J_{4a,10b}$ = 4.6 and J_{4a,CH_3} = 2.4 Hz. By analogy, a similar correction seems in order for the proposed solution conformation of the parent 7,8,9-trimethoxy-4a,10b-*cis*-1,2,3,4,4a,10b-hexahydrophenanthridine.[8] The predominance of the conformation where H-4a is equatorial and H-10b axial is also consistent with the observed allylic coupling constant of about 3 Hz (presumably negative) between H-6 and H-4a.[8] Although the alternative conformation, where H-4a approaches coplanarity with the double bond, could lead to positive allylic coupling,[9] the deviation from coplanarity by about 20° should yield a coupling constant of somewhat smaller magnitude than that observed.

The incorporation of deuterium on carbons 1 and 4 of **3** was accomplished by using 1,3-butadiene-*1,1,4,4-d*$_4$[10] in the Diels–Alder condensation step of the synthetic scheme of **3**.[1,8,11] Incorporation of deuterium on the 4a position in **1a** was accomplished by base-catalyzed deuterium exchange on the *trans*-2-(3,4,5-trimethoxyphenyl)nitrocyclohexane intermediate[11] in a mixture of D_2O and tetrahydrofuran. The deuterated nitro compound was reduced to the corresponding amine with iron in acetic acid[12] and was found to contain about 90% deuterium at C-1 by NMR. The amine was converted to the deuterated analog of **1a** by the previously described procedure.[1]

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Registry No.—**1a**, 34035-53-5; **1b**, 34035-58-0; **2**, 34910-05-9; **3**, 34910-07-1.

References and Notes

(1) B. R. Lowry and A. C. Huitric, *J. Org. Chem.*, **37**, 1316 (1972).
(2) (a) S. Sternhell, *Q. Rev., Chem. Soc.*, **23**, 236 (1969); (b) M. Barfield and B. Chakrabarti, *Chem. Rev.*, **69**, 757 (1969); (c) K. D. Bartle, D. W. Jones, and R. S. Matthews, *Rev. Pure Appl. Chem.*, **19**, 191 (1969).
(3) Y. Osawa and M. Neeman, *J. Am. Chem. Soc.*, **85**, 2856 (1963).
(4) F. P. Johnson, A. Melera, and S. Sternhell, *Aust. J. Chem.*, **19**, 1523 (1966).
(5) The NMR spectra were obtained with a Varian Model HA-100 spectrometer operating in the frequency sweep mode. Samples were examined in deuteriochloroform solutions and were degassed.
(6) S. O. Almquist, A. J. Asen, B. Kimland, and C. R. Enzell, *Acta Chem. Scand.*, **25**, 3186 (1971); (b) C. J. Macdonald and W. F. Reynolds, *Can. J. Chem.*, **48**, 1002 (1970); (c) Y. Ishizaki, Y. Tanahashi, T. Takahashi, and K. Tori, *Chem. Commun.*, 551 (1969).
(7) M. Barfield and S. Sternhell, *J. Am. Chem. Soc.*, **94**, 1905 (1972).
(8) B. R. Lowry and A. C. Huitric, *J. Org. Chem.*, **37**, 2697 (1972).
(9) G. P. Newsoroff and S. Sternhell, *Aust. J. Chem.*, **25**, 1669 (1972).
(10) A. C. Cope, G. A. Berchtold, and D. L. Ross, *J. Am. Chem. Soc.*, **83**, 3859 (1961).
(11) W. F. Trager and A. C. Huitric, *J. Pharm. Sci.* **54**, 1552 (1965).
(12) W. F. Trager, F. F. Fincenzi, and A. C. Huitric, *J. Org. Chem.*, **27**, 3006 (1962).

An Unusual 2,3-Disubstitution of Furan Ring

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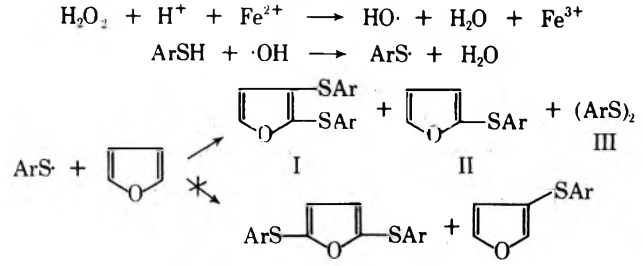
It is well known that furan can react with ionic[1] or radical[2] reagents, giving both substitution and 2,5-addition products; we wish now to report a case in which a 2,3-addition to the furan ring can explain the reaction products.

Furan was allowed to react with *p*-bromophenylthio radicals generated by H_2O_2/Fe^{2+} oxidation of the parent thiol in *tert*-butyl alcohol–water mixture under the conditions of the Fenton reaction.[3] The reaction products were 2,3-bis(*p*-bromophenylthio)furan (I) and 2-(*p*-bromophenylthio)furan (II) in 2:1 ratio; *p*-bromodiphenyl disulfide (III) was also separated. Gas chromatographic analysis of the reaction mixture indicates absence of 2,5-bis(*p*-bromophenylthio)furan or 3-(*p*-bromophenylthio)furan (Scheme I).

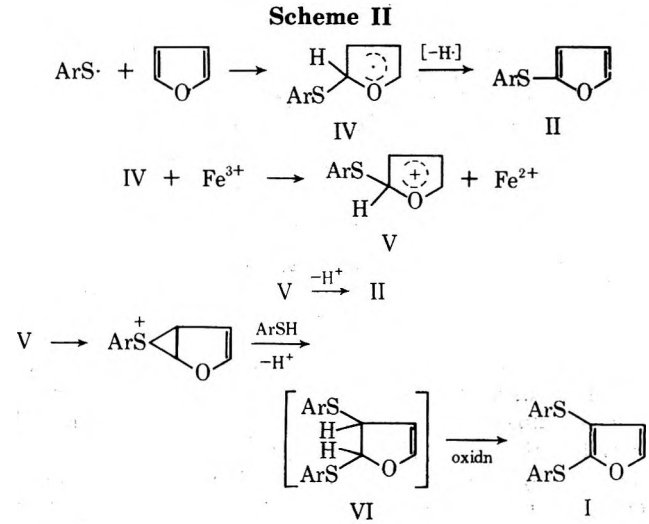
Scheme I



Thio aryl radicals were also generated in furan by hydrogen abstraction with *tert*-butoxy radicals from *p*-bromothiophenol or by cumene hydroperoxide initiated autoxidation[4] of *p*-bromothiophenol; in these cases the only addition product formed was II in low yields.

The products of the Fenton reaction can reasonably be rationalized by a mechanism involving the oxidation of the α complex IV by ferric ions, the cation V formed then reacting with a molecule of thiophenol giving the dihydro derivative VI, readily dehydrogenated to I (Scheme II).

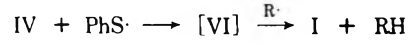
Scheme II



The attack of thiophenol at position 3 of the cation V can be explained by the participation of the lone pair of the sulfur atom attached to the ring; this effect is well known in other systems.

We believe that the fully homolytic pathway that could be devised to explain the formation of I (Scheme III) is not

Scheme III



realistic because of the lack of formation of I in the reaction carried out in the absence of ferric ions. In this case, in fact, the only product is the "normal" 2-substitution product

(II). This is in agreement with the experimental results available in the literature,[5] where no evidence can be found to consider that β-arylthio radicals are bridged.

Compound I could be formed by further substitution on II, but when II was allowed to react under the conditions of the Fenton reaction, no I was identified in the reaction mixture.

Experimental Section

2-(*p*-Bromophenylthio)furan (II). To a solution of *n*-butyllithium [prepared from *n*-butyl bromide (2.29 g) and lithium (0.297 g) in dry ether] was slowly added at −30° 2-iodofuran[6] (3.68 g) in dry ether. The solution was allowed to reach ambient temperature and stirred for 2 hr. The reaction mixture was then cooled again at −70° and 4,4′-dibromodiphenyl disulfide (8.04 g) in dry ether was added. The reaction mixture was left overnight without further cooling, then hydrolyzed with HCl (10%). From the ethereal layer, after concentration and vacuum distillation, was obtained 2-(4-bromophenylthio)furan (3.1 g), bp 120° (0.5 mmHg). Anal. Calcd for $C_{10}H_7BrOS$:C, 47.07; H, 2.77; S, 12.57; Br, 31.32. Found: C, 47.8; H, 3.0; S, 12.8; Br, 32.0.

Oxidation with H_2O_2 in acetic acid gave the corresponding sulfone, mp 123–124°. Anal. Calcd for $C_{10}H_7BrO_3S$: C, 41.81; H, 2.44; S, 11.15; Br, 27.87. Found: C, 41.7; H, 2.3; S, 11.3; Br, 27.6.

In the same way (from *n*-butyllithium, 3-iodofuran,[7] and 4,4′-dibromodiphenyl disulfide) was prepared 3-(*p*-bromophenylthio)furan, bp 110° (0.5 mmHg) (Anal. Found: C, 47.5; H, 2.81; S, 12.8; Br, 31.12.) and the corresponding sulfone, mp 121–123°.

2,5-Bis(*p*-bromophenylthio)furan. 2,5-Bis(chloromercury)-furan[8] (14.7 g) was suspended in dry chloroform (500 ml) and 4-bromosulfenyl chloride[9] (17.8 g) in chloroform (50 ml) was added under vigorous stirring. The mixture was refluxed for 20 min and then washed with water. The dry organic layer was concentrated and the residue was purified by column chromatography on silica gel; 5.0 g of the product, mp 89–90°, was obtained. Anal. Calcd for $C_{16}H_{10}Br_2OS_2$: C, 43.45; H, 2.28; S, 14.5; Br, 36.12. Found: C, 43.5; H, 2.3; S, 14.1; Br, 36.0.

2,3-Bis(*p*-bromophenylthio)furan. A mixture of 3,4-dibromo-2-furoic acid[10] (3 g), copper *p*-bromothiophenate[11] (6.27 g), chinoline (60 ml), and pyridine (5 ml) was stirred at 200–210° for 3 hr. The mixture, originally yellow-orange, turns green, then becomes homogeneous.

To the cooled solution was then added 10% hydrochloric acid (300 ml) and the mixture was extracted with benzene.

Chromatography on silica gel of the concentrated organic layer gave 0.8 g of an oil (Anal. Calcd for $C_{16}H_{10}Br_2OS_2$: C, 43.15; H, 2.28; S, 14.5; Br, 36.08. Found: C, 43.8; H, 2.3; S, 14.5; Br, 36.4.) which was directly oxidized with H_2O_2 in acetic acid to the corresponding disulfone, mp 182–184°. Anal. Calcd for $C_{16}H_{10}Br_2O_5S_2$: C, 37.96; H, 1.99; Br, 31.57. Found: C, 38.0; H, 1.97; Br, 31.7.

Fenton Reaction. To a mixture of furan (70 ml), *p*-bromothiophenol (3.8 g), *tert*-butyl alcohol (40 ml), and water (15 ml) was slowly added an aqueous solution of $FeSO_4 \cdot 7H_2O$ (6.2 g) and concentrated H_2SO_4 (2.2 ml), then, under vigorous stirring, 5.1 ml of 30% H_2O_2 during 1 hr, the temperature of the reaction mixture being 5–10°. The reaction mixture was left overnight at room temperature, then extracted with ether. From the ethereal solution was removed the unreacted thiophenol (3 g) by washing with 10% NaOH.

The residue was chromatographed on silica gel. The following products were separated and identified by analysis and comparison of spectral data (ir, NMR) with those of authentic models: 4,4′-dibromodiphenyl disulfide (0.56 g), 2(*p*-bromophenylthio)furan (0.1 g), and 2,3-bis(*p*-bromophenylthio)furan (0.4 g). The latter product was oxidized to a sulfone, mp 182–184°, identical with that obtained in the previously described independent synthesis. No 2,5-bis(*p*-bromophenylthio)furan or 3-(*p*-bromophenylthio)furan were identified in the reaction products.

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Registry No.—I, 53906-92-6; I disulfone, 53906-93-7; II, 53906-94-8; II sulfone, 53906-95-9; III, 5335-84-2; furan, 110-00-9; *p*-bromophenylthio radical, 31053-90-4; 3-(*p*-bromophenylthio)furan, 53906-96-0; 3-(*p*-bromophenylsulfonyl)furan, 53906-97-1; 2,5-bis(*p*-bromophenylthio)furan, 53906-98-2.

References and Notes

(1) See, for instance, P. Bosshard and C. H. Engster, *Adv. Heterocycl. Chem.*, **7**, 377 (1966).
(2) K. E. Kolb and W. A. Black, *Chem. Commun.*, 1119 (1969); L. Benati, N. La Barba, M. Tiecco, and A. Tundo, *J. Chem. Soc. B*, 1253 (1969).
(3) Ya. L. Gold'farb, G. P. Pokhil, and L. I. Belenkii, *Dokl. Akad. Nauk SSSR*, **167**, 826 (1966).
(4) A. L. J. Beckwith and B. S. Low, *J. Chem. Soc.*, 1304 (1961).
(5) L. Kaplan, "Bridged Free Radicals," Marcel Dekker, New York, N.Y., 1972, p 305.
(6) Z. N. Nazarova and Yu. A. Babaev, *Zh. Obshch. Khim.*, **33**, 1431 (1963).
(7) H. Gilman, H. E. Mallory, and G. F. Wright, *J. Am. Chem. Soc.*, **54**, 733 (1932).
(8) H. Gilman and G. F. Wright, *J. Am. Chem. Soc.*, **55**, 3302 (1933).
(9) W. E. Truce and M. F. Adams, *J. Am. Chem. Soc.*, **73**, 3015 (1951).
(10) L. D. Tarazova and Ya. L. Gold'farb, *Izv. Akad. Nauk SSSR*, 2013 (1965).
(11) R. Adams, W. Reifschneider, and N. D. Nair, *Croat. Chem. Acta*, **29**, 279 (1957).

The Anionic Addition of Dimethylamine to Isoprene

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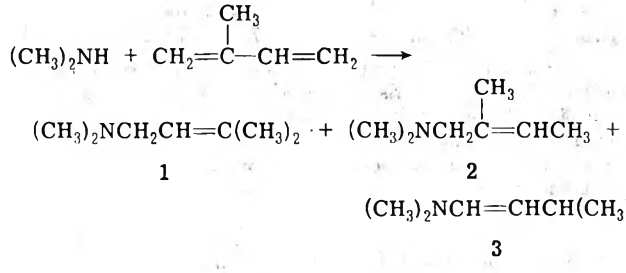
The alkali metal catalyzed anionic addition of amines and ammonia to olefins and conjugated dienes affords an excellent route to alkyl-substituted amine systems.[1-9] Yields as high as 76% have been reported with various amines and olefins using lithium, sodium, or potassium metal or their corresponding hydrides.[6,9] Butyllithium has been employed to form the lithium amide intermediate, which readily adds to both vinyl aromatics and conjugated dienes.[1] The use of sodium metal for the addition of amines to conjugated dienes has been studied extensively. In fact, the sodium-catalyzed addition of dimethylamine to isoprene was originally reported to give 95% *N,N*,3-trimethyl-2-butenylamine (1) and 3% of an enamine.[4] However, subsequent investigations have shown that the formation of *N,N*,2-trimethyl-2-butenylamine (2) and 4% of an unidentified material, presumably **3**, also occurred.[10,11] Since the



base-catalyzed rearrangement of allyl amines to enamines is known,[12,13] the formation of **3** under these conditions is not unlikely. In fact, the presence of **3** in the reaction mixture has been confirmed by the isolation of the 2,4-dinitrophenylhydrazone of isovaleraldehyde from the acid hydrolysis of the reaction mixture and the sodium-catalyzed rearrangement of **1** to **3** has been studied.[13] This anionic addition presented an interesting problem in the possible control of the ratio of 1,4-addition product to 4,1-addition products, which are formed during the reaction, by changing the alkali metal catalyst used.

The sodium-catalyzed addition of dimethylamine to isoprene was conducted and gave three product peaks when

the reaction mixture was analyzed by GLC. The major component, *N,N*,3-trimethyl-2-butenylamine (**1**), had a boiling point of 120° and was obtained in about 70% yield but always contained about 7% of **3** that could not be separated by distillation. The NMR spectrum of **1** had a triplet centered at 5.3 ppm for the lone vinyl proton, a doublet at 2.9 ppm for the methylene between the vinyl group and the nitrogen, a singlet at 2.2 ppm for the amino methyls, and two singlets at 1.8 and 1.7 ppm for the vinylic methyls. The shift in one of these methyl absorptions is due to its being cis to the dimethylamino moiety.

Compound **2** had a boiling point at 76° and was isolated GC pure in 23% yield by spinning band distillation. The NMR spectrum of **2** had a multiplet for the lone vinyl proton centered at 5.4 ppm, a singlet at 2.9 ppm for the methylene protons between the vinyl group and the nitrogen, a singlet at 2.15 ppm for the amino methyls, a singlet at 1.6 ppm for one vinylic methyl, and a doublet at 1.55 ppm for the other vinylic methyl. The latter is partially obscured by the absorption for the other vinylic methyl. Although the nature of the sterochemistry about the double bond cannot be assigned from this data, the cis product is expected because of the nonpolar nature of the reaction media.[1]

In our experiments **3** could not be separated from **1** either by spinning band distillation or by preparative gas chromatography.

Our specific interest in maximizing the yield of **1** led us to investigate the effects of various alkali metal catalysts[9] on the product ratio for this reaction. These results are summarized in Table I.

Table I
Alkali Metal Catalyzed Additions of Dimethylamine to Isoprene

Metal	Addition temp, °C	Addition time, hr	Reaction time, hr[b]	Product percentage[a] 1	2	3	Total yield, %
Potassium	22–24	1.5	4	64.4	32.2	3.5	70
Sodium	0	2.5	1	71.8	22.4	4.0	90
Sodium	20–30	3		75.0	21.0	4.0	92[e]
Lithium	0	2	16	76.3	14.7	8.9	70
Lithium	0	6	14	74.2	18.1	7.7	72
Lithium	22–25	2	3	76.6	16.6	6.8	70
Lithium[c]	0	2	14	66.3	20.7	13.1	12
Lithium[d]	23–25	2	3	76.5	13.9	9.6	71

[a] Determined by GLC on a 12 ft × 0.25 in. stainless steel column packed with 15% 1,2,3-tris(2-cyanoethoxy)propane on Chromosorb W at 60°. [b] Time at room temperature. [c] Lithium dimethylamide prepared from lithium metal and then isoprene added. [d] Tetramethylethylenediamine added to activate the lithium amide. [e] Reference 10.

The yield of 4,1-addition products in this reaction can be thought of as the total of the amounts of **1** and **3**, since **3** arises from **1** by anionic rearrangement.[13] Thus, the amount of 4,1-addition increases along the series K < Na < Li under the same reaction conditions, which is in the same order as the increasing tightness of the metal–amide ion pair in nonpolar media. The addition of a small amount of tetramethylethylenediamine to the lithium-catalyzed reaction produced a slight increase in the percentage of 4,1 products from 83.4 to 86.1%. Since detailed kinetic studies of the reaction were not undertaken, mechanistic implications of the data in Table I have not been considered.

Total yields were lower when both potassium and lithium were used as catalysts than when sodium was used. With potassium, the low yield was the result of low conversion, which was shown by a large isoprene peak in GLC analysis, while with lithium, a large amount of a white solid was formed. The infrared spectrum of the white solid was compared to that of an authentic sample of polyisoprene and was found to be identical.

When lithium was used as a catalyst, long room-temperature reaction times resulted in increased amounts of **3**. Longer addition times at lower temperatures seemed to give increased amounts of **2**. These results would be consistent with the need for amine coordination with the metal–amide for enhancement of 4,1-addition. These addition reactions were performed by adding the dimethylamine to a suspension of the metal in isoprene. When lithium dimethylamide was prepared first and the isoprene added to the reaction mixture, only a low total yield of product was obtained that contained large amounts of **2** and **3**.

In conclusion, the ratio of 1,4-addition product to 4,1-addition products from the anionic addition of dimethylamine to isoprene was altered by changing the alkali metal catalyst. A higher yield of 4,1-addition products was realized when lithium metal was used but the total product yield was lower owing to the concurrent formation of polyisoprene. The best total yield of product was obtained using sodium and very low conversions were realized with potassium.

Experimental Section

Gas chromatography was performed on a Perkin-Elmer Model 900 chromatograph using a 12 ft × 0.25 in. stainless steel column packed with 15% 1,2,3-tris(2-cyanoethoxy)propane on Chromosorb W. The NMR spectra were run on a Jeol JNM-MH-100 100-MHz spectrometer. Distillations were carried out on a Nester-Faust Auto Annular Teflon Spinning Band Distillation column.

Anionic Addition of Dimethylamine to Isoprene. The general procedure that was followed was to weigh 34 g (0.5 mol) of freshly distilled dry isoprene and 0.015 mol of the alkali metal into a three-necked flask equipped with a magnetic stirrer, thermometer, and Dry Ice condenser and add 22.5 g (33.0 ml, 0.5 mol) of dimethylamine (J. T. Baker) slowly by bubbling it through the reaction mixture. The reaction temperature was controlled as desired by the use of an ice–methanol bath. After the addition was complete, the reaction mixture was stirred at room temperature to complete the reaction. The conditions are summarized in Table I. After the reaction was complete, the product ratio was measured by GLC. In one case (sodium catalyst), the product was distilled on a Teflon spinning bond column to obtain **1**, bp 120° (lit.[13] bp 114–118°), and **2**, bp 76°.

Registry No.—**1**, 17945-72-1; **2**, 40267-41-2; **3**, 18495-55-1; dimethylamine, 124-40-3; isoprene, 78-79-5; potassium, 7440-09-7; sodium, 7440-23-5; lithium, 7439-93-2.

References and Notes

(1) R. J. Schlott, J. C. Falk, and K. W. Narducy, *J. Org. Chem.*, **37**, 4243 (1972).
(2) G. T. Martirosyan, E. A. Grigoryan, and A. T. Babayan, *Izv. Akad. Nauk Arm. SSR, Khim. Nauki*, **18**, 161 (1965).
(3) G. T. Martirosyan, E. A. Grigoryan, and A. T. Babayan, *Izv. Akad. Nauk Arm. SSR, Khim. Nauki*, **17**, 517 (1964).
(4) G. T. Martirosyan and E. A. Grigoryan, *Izv. Akad. Nauk Arm. SSR, Khim. Nauki*, **16**, 31 (1963).
(5) J. E. Hyre and A. R. Boder, *J. Am. Chem. Soc.*, **80**, 437 (1958).
(6) B. W. Hawk, E. L. Little, S. L. Scott, and G. M. Whitman, *J. Am. Chem. Soc.*, **76**, 1899 (1954).
(7) J. D. Danforth, U.S. Patent 2,495,890 (1950).
(8) R. Wegles and G. Pieper, *Chem. Ber.*, **83**, 1 (1950).
(9) G. T. Martirosyan, E. M. Arakelyan, and A. T. Babayan, *Arm. Khim. Zh.*, **20**, 518 (1967).
(10) D. I. Hoke, D. L. Surbey, and W. R. Ovialt, *J. Polym. Sci., Part A-1*, **10**, 595 (1972).
(11) G. B. Butler and M. F. Hoover, Abstracts, 166th National Meeting of the American Chemical Society, Chicago, Ill., Aug 26–31, 197 POLY 17; *J. Polym. Sci.*, Symposium No. 45, 1 (1974).
(12) J. Sauer and H. Prehl, *Chem. Ber.*, **102**, 1917 (1969).
(13) G. T. Martirosyan, M. G. Indzhikyan, E. A. Grigoryan, and A. T. Babayan, *Arm. Khim. Zh.*, **20**, 275 (1967).

Photochemistry of Dimethylamine in Hydrocarbon Solvents. Striking Differences between Solution- and Gas-Phase Photochemical Reactivity

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Generation of dimethylamino radicals both thermally and photochemically from a variety of chemical precursors has produced discordant results.[1-4] However, one widely accepted generalization has been that dimerization to tetramethylhydrazine is a prominent reaction of dimethylamino radicals;[1b,3,4h] indeed, the reaction has even been touted as a practicable synthetic route to the hydrazine.[3a,c] Complicating interpretation of dimethylamino radical reactivity have been numerous other reaction products, apparently varying with the precursor, medium, and method for generating the dimethylamino moiety.[2-4] Among these, *N,N,N',N'*-tetramethylmethanediamine (**1**) has often been found,[2,3a,c,5] but never adequately explained.

We wish to report the results of our study of the solution-phase photochemistry of dimethylamine (**2**) in hydrocarbon solvents, which (a) contrast sharply with the gas-phase photochemistry of dimethylamine;[3,4] (b) indicate that dimerization of dimethylamino radicals may be almost totally suppressed under some reaction conditions; (c) offer an extremely clean, easy, and high-yield synthesis of the interesting[6] diamine **1**; and (d) support for the first time a viable mechanism for the formation of **1** from dimethylamino radicals.

Hydrocarbon (most conveniently, *n*-nonane; cf. Experimental Section) solutions of **2** (*ca.* 1 *M*) were degassed and irradiated at 35° with a Vycor-filtered mercury arc; reaction was monitored by GLC (Carbowax 20M on firebrick). At about 70% conversion, 100 mmol of **2** gave (eq 1) 22

$$\underset{2}{Me_2NH} \xrightarrow[C_9H_{20}]{h\nu} \underset{1}{Me_2NCH_2NMe_2} + \underset{3}{MeNH_2} + \text{trace products} \quad (1)$$

mmol of diamine **1**, 7 mmol of methylamine (**3**), and traces (<2%) of two minor products (vide infra). Diamine **1** was isolated by spinning-band distillation (alternatively, preparative GLC) and identified by comparison with authentic material. It is noteworthy that, assuming the minimum 3:1 stoichiometry demanded for the **2** → **1** reaction, the observed yields of **1** are above 90% and thus synthetically quite attractive.[7] The two minor products were identified by GLC–MS techniques as *N,N,N'*-trimethylmethanediamine (**4**) and tetramethylhydrazine (**5**). No methane, solvent

$$\underset{4}{Me_2NCH_2NHMe} \qquad \underset{5}{Me_2N{-}NMe_2}$$

reaction products, or *N,N'*-dimethylethanediamine were observed within our detection limits (estimated at ca. 1%); no analysis for hydrogen was made. Monitoring the reaction with time by GLC and NMR showed only continued and proportional increases in the yields of the four volatile products (**1**, **3**, **4**, and **5**) with increasing time of irradiation; no transient accumulation of **4**, **5**, or other species was detected. Oligomerization was minimal, judging from the relatively small nonvolatile photolysate residue.

Formation of **1** from **2** may thus be explained mechanistically (Scheme I) in terms of consecutive (i) photolytic scission of the N–H bond of **2** (eq 2), generating dimethylamino radicals **6**;[3,4] (ii) oxidation of **6** to *N*-methylenemethylamine (**7**) via autodisproportionation (eq 3a), bimolecular

Scheme I

$$\underset{2}{Me_2NH} \xrightarrow{h\nu} \underset{6}{Me_2N\cdot} + H\cdot \quad (2)$$

$$[Me_2N\cdot + H\cdot] \longrightarrow H_2 + \underset{7}{MeN{=}CH_2} \quad (3a)$$

and/or

$$\underset{6}{2Me_2N\cdot} \longrightarrow 2 + \underset{7}{MeN{=}CH_2} \quad (3b)$$

and/or

$$RH \xrightarrow{Me_2N\cdot \text{ or } H\cdot} R\cdot \xrightarrow{Me_2N\cdot} \underset{7}{MeN{=}CH_2} + RH \quad (3c)$$

$$\underset{2}{Me_2NH} + \underset{7}{CH_2{=}NMe} \longrightarrow \underset{4}{Me_2NCH_2NHMe} \quad (4)$$

$$\underset{4}{Me_2NCH_2NHMe} + \underset{2}{Me_2NH} \longrightarrow \underset{1}{Me_2NCH_2NMe_2} + \underset{3}{MeNH_2} \quad (5)$$

disproportionation (eq 3b), and/or a hydrogen transfer sequence involving solvent (eq 3c);[9] (iii) addition of **2** to **7**, giving **4** (eq 4); and (iv) transamination of **4** with **2** (eq 5) to give **1** and **3**, the observed products.

An alternative a priori explanation would have the sequence of events as primary photochemical conversion of **2** to hydrazine **5**, followed by secondary photolysis of **5** to the observed products. However, the failure to detect (GLC–NMR monitoring) short-term accumulation of **5** in the photochemical reaction of **2** suggests that hydrazine **5** is not involved as a cul-de-sac for dimethylamino radicals.

In the proposed mechanism the photochemical cleavage and disproportionation steps are well documented.[3,4] The subsequent addition and transamination steps follow not only from isolation of **4** from reaction mixtures after irradiation of **2**, but also from the observed stoichiometry and general absence of other by-products. However, conversion of independently synthesized **4** to **1** under the conditions employed for photosynthesis of **1** from **2** needs to be demonstrated before the transamination step is unequivocally established. The smaller than theoretical yields of **3** may be attributed both to analytical limitations and to the known photolability of **3**. Irradiation of **3** gives **7**,[11] which would then give **4** and, ultimately, **1**.

Resemblance of the photolytic conversion of **2** to **1** in nonane to the photochemical behavior of dimethylamine in chlorocarbons[2] is compatible with the intermediacy of **6** in both mechanisms. However, in nonane, photolysis of **2** gives **6** directly; in chlorocarbons, photodissociation of the charge-transfer complex of **2** gives the aminium cation radical (**8**), which then generates **6** in a hydrogen transfer reaction with **2** (eq 6). Thus, although diamine **1** and methyl-

$$Me_2NH\cdot CCl_4 \xrightarrow[\text{Pyrex}]{h\nu}$$

$$Cl_3C\cdot + \underset{8}{[Me_2\overset{+}{N}H]Cl^-} \xrightarrow{Me_2NH} \underset{9}{Me_2NH\cdot HCl} + \underset{6}{Me_2N\cdot} \quad (6)$$

amine **3** are the major amine photoproducts from **2** in both nonane and carbon tetrachloride, involvement of the charge-transfer mechanism in the chlorocarbon solvent leads to formation of by-products (amine hydrochloride **9** and chloroform) which are absent when the photochemical reaction is carried out in a hydrocarbon solvent.

Results of our investigation contrast dramatically with earlier studies of the dimethylamino radical under gas-phase conditions,[3,4a,b,h] since we observed only minimal levels of radical recombination (to give hydrazine **5**) and very little formation of higher molecular weight oligomers

of imine 7 (e.g., 1,3,5-trimethylhexahydro-*s*-triazine, polymeric material). The smaller proportion of oligomers seems clearly due to efficient trapping of 7 in solution by excess dimethylamine. The minimum yields of hydrazines are of less certain origin, corresponding to an unusual situation in which a radical dimer product is formed in the gas phase, but not in solution. An explanation involving intermediacy of the isomeric C-centered radicals in solution rather than **6**, an a priori possibility in light of Allan and Swan's photochemical studies of diethylamine,[12] seems incompatible with the absence of *N,N'*-dimethylethanediamine here and the known proclivity of α-aminoalkyl radicals toward recombination rather than disproportionation.[1a,12] The most likely explanation would appear to be the source of the dimethylamino radical. When **6** is generated from **2** by photolysis in solution, oxidation to imine **7**, either via autodisproportionation within the solvent cage (eq 3a) or via the hydrogen transfer sequence with solvent as hydrogen carrier (eq 3c), should be optimized, conditions favoring subsequent formation of **1**. In contrast, when **6** is generated from tetramethyltetrazene or even from **2** in the gas phase, conditions for oxidation of **6** to **7** are no longer optimal; diffusion and recombination reactions of **6** become more important.

Our observations differ superficially from those of Niu and Stenberg,[10] who reported 90% yields of imines analogous to **7** (and no diamines analogous to **1**) resulting from photodehydrogenation of several secondary amines (e.g., **10**, eq 7). Although shorter periods of irradiation were employed in the **10** → **11** (eq 7) conversion (6 hr[10] vs. 96 hr for

$$(n\text{-}C_6H_{13})_2NH \xrightarrow[\text{cyclohexane}]{h\nu,\ 6\ \text{hr}} n\text{-}C_6H_{13}N{=}CHC_5H_{11} \qquad (7)$$

10 **11**

2 → **1**), unreported sample size in the earlier study[10] makes direct, meaningful comparisons difficult. It is likely, however, that the failure to detect even transient buildup of **7** from **2** during the NMR–GLC monitoring of photolyses of **2** partly reflects the higher concentrations of amine (≥ 1 *M*) used in our study than in Niu and Stenberg's work (10^{-2} *M*[10]), since higher concentrations of amine would lead to more efficient bimolecular destruction of imine (Scheme I, eq 4). Similar concentration dependence of imine yields in secondary amine photolysis has been reported by Ratcliff and Kochi.[1a] Another important factor in accounting for the differing reactivities of **2** and amines such as **10** may be stereochemical. Relative to imine **7**, the imine **11** derived from **10** may be less reactive toward nucleophilic addition of amine (as in eq 4) because of the steric hindrance posed by bulky substituents in **10** and **11**.

Finally, the origin of diamine **1**, which was once considered "obscure,"[3a] and later considered to be the reaction of methyl radicals with trimethylamine,[3c] is, in all likelihood, neither. Unlike previous mechanisms offered for formation of **1**, the one outlined in Scheme I involves only species whose presence in photolysates is now well documented.

Experimental Section

Photolysis of Dimethylamine in Nonane. In a typical experiment, a 1.3 *M* solution of dimethylamine (3.77 g, 83.7 mmol) in 65 ml of *n*-nonane in a quartz tube was degassed by three freeze–pump–thaw cycles, then sealed, and irradiated at 35° with an adjacent Vycor-filtered mercury arc lamp (Hanovia medium-pressure 450-W). Progress of reactions was monitored by NMR and by GLC on a 5 ft × 0.25 in. column of 20% w/w alkali-treated Carbowax 20M on 60/80 firebrick at 65°. After 96 hr, NMR, mass spectral, and GLC analysis indicated 68% reaction, with 27 mmol of dimethylamine remaining, formation of 18 mmol (95% yield) of *N,N,N',N'*-tetramethylmethanediamine, 6 mmol of methylamine, and traces (<2% each) of tetramethylhydrazine and *N,N,N'*-trimethylmethanediamine (identified by tandem GC–MS). Prolonged irradiation was inefficient in raising the yield of *N,N,N',N'*-tetramethylmethanediamine because of secondary photochemical reactions. Similar procedures were followed for irradiating samples containing from 2 to 100 mmol of dimethylamine, with approximately proportional irradiation times and with identical results.

Nitrogen was bubbled through the photolysate to remove most of the methylamine and some of the dimethylamine. *N,N,N',N'*-tetramethylmethanediamine was isolated from the residue by spinning-band distillation, bp 82–84° (lit.[8] bp 82–84°), of larger samples or by preparative GLC of smaller ones in ca. 85% yields; it was identified by comparison of ir, NMR, and mass spectra to those of authentic material.[2,8]

Use of pentane or cyclohexane as solvent gave comparable results by GLC analysis; however, isolation by distillation was facilitated using the higher boiling *n*-nonane as solvent (and distillation chaser).

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Registry No.—**1**, 51-80-9; **2**, 124-40-3; nonane, 111-84-2.

References and Notes

(1) For brief discussions, see (a) M. A. Ratcliff, Jr., and J. K. Kochi, *J. Org. Chem.*, **37**, 3268 (1972); (b) J. R. Roberts and K. U. Ingold, *J. Am. Chem. Soc.*, **95**, 3228 (1973).
(2) (a) K. G. Hancock and D. A. Dickinson, *J. Chem. Soc., Chem. Commun.*, 783 (1973); (b) K. G. Hancock and D. A. Dickinson, *J. Org. Chem.*, **39**, 331 (1974).
(3) (a) J. S. Watson, *J. Chem. Soc.*, 3677 (1956); (b) F. O. Rice and C. J. Grelecki, *J. Am. Chem. Soc.*, **79**, 2679 (1957); (c) B. G. Gowenlock, and D. R. Snelling, *Adv. Chem.*, **36**, 150 (1962); (d) B. G. Gowenlock, P. P. Jones, and D. R. Snelling, *Can. J. Chem.*, **41**, 1911 (1963).
(4) (a) C. H. Bamford, *J. Chem. Soc.*, 17 (1939); (b) G. H. Booth and R. G. W. Norrish, ibid., 188 (1952); (c) B. R. Cowley and W. A. Waters, ibid., 1228 (1961); (d) D. Mackay and W. A. Waters, *J. Chem. Soc. C*, 813 (1966); (e) S. G. Hadley and D. H. Volman, *J. Am. Chem. Soc.*, **89**, 1053 (1967); (f) D. E. Wood and R. V. Lloyd, *J. Chem. Phys.*, **53**, 3932 (1970); (g) W. C. Danen and T. T. Kensler, *J. Am. Chem. Soc.*, **92**, 5235 (1970); (h) P. W. Jones and H. D. Gesser, *J. Chem. Soc., B*, 1873 (1971); (i) R. W. Dennis and B. P. Roberts, *J. Organomet. Chem.*, **43**, C2 (1972).
(5) (a) F. Klages, G. Nober, F. Kircher, and M. Bock, *Justus Liebigs Ann. Chem.*, **547**, 1 (1941); (b) G. Smith and G. A. Swan, *J. Chem. Soc.*, 886 (1962); (c) W. H. Urry and J. Sheeto, *Photochem. Photobiol.*, **4**, 1067 (1965).
(6) Among the interesting properties of diamine **1** may be mentioned its apparent tumor cytostatic effect; cf. H. Schönenberger and A. Adam, *Arzneim.-Forsch.*, **14**, 1168 (1964).
(7) Both yield and operational simplicity appear to distinguish this method from the alternatives.[2,8]
(8) J. K. Lindsay and C. R. Hauser, *J. Org. Chem.*, **22**, 355 (1957); L. Henry, *Bull. Cl. Sci., Acad. R. Belg.*, **26**, 203 (1893).
(9) Which pathway predominates depends on other reaction conditions,[1,3,4,10] and has not yet been determined under the conditions we employed for photochemical synthesis of **1**.
(10) C. H. Niu and V. I. Stenberg, *Chem. Commun.*, 1430 (1971).
(11) J. S. Watson and B. deB. Darwent, *J. Chem. Phys.*, **20**, 1041 (1952).
(12) L. T. Allan and F. A. Swan, *J. Chem. Soc.*, 4822 (1965).

3-Thiabicyclo[3.2.0]hepta-1,4-dienes. Synthesis of Tetraphenyl-2,5-dithiabisnorbiphenylene

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3-Thiabicyclo[3.2.0]hepta-1,4-dienes are members of a class of strained heterocyclic systems which have only recently been prepared.[1-4] Two of the reported synthetic routes[1,3] involve closure of the four-membered ring as the final synthetic step, one the formation of the thiophene ring[2] and in the other formation of both rings in one reac-

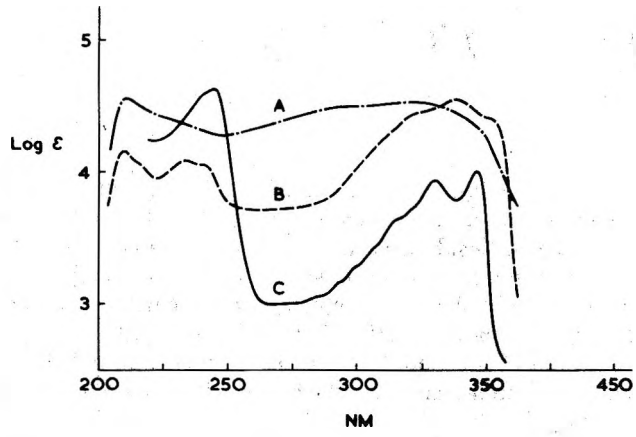
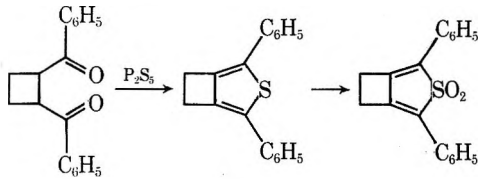


Figure 1. Electronic spectra of (A) tetraphenyl-2,5-dithiabisnorbiphenylene (**5**) in ether, (B) 2,4-diphenyl-3-thiabicyclo[3.2.0]hepta-1,4-diene (**2**) in ether, and (C) 2-thianorbiphenylene in ethanol.

tion.[4] We now report a fifth method which also involves formation of the heterocycle in the final reaction and illustrates its application by the preparation of tetraphenyl-2,5-dithiabisnorbiphenylene (**5**), the first biphenylene analog containing two five-membered heterocycles.[5]

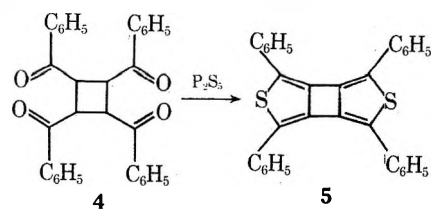
The observed stabilities of the 3-thiabicyclo[3.2.0]hepta-1,4-diene system once it is formed[1-3] encouraged us to examine the classical method of synthesizing five-membered heterocycles from 1,4 diketones. When the diketone **1**[6] was treated with P_2S_5 in tetralin or pyridine then 2,4-diphenyl-3-thiabicyclo[3.2.0]hepta-1,4-diene (**2**), mp 150–150.5°, was obtained in 6% yield. The NMR spectrum (CCl_4) showed a multiplet centred at τ 2.70 with a singlet at 6.77 (5.2) and the electronic spectrum (Figure 1) is very similar to that of the 2,4,6,7-tetraphenyl derivative.[3]

Oxidation of **2** with *m*-chloroperoxybenzoic acid gave the sulfone **3**, mp 244–246° (40%). The NMR spectrum of **3** showed the expected downfield shift of the cyclobutyl ring protons.[2]



1 **2** **3**

When the tetraketone **4**[7] was treated with P_2S_5 in pyridine, tetraphenyl-2,5-dithiabisnorbiphenylene (**5**), mp 194–194.5°, was obtained in 3% yield.[8] The NMR spectrum ($CDCl_3$) showed only a multiplet centered at τ 2.60, and the electronic spectrum (Et_2O) showed a shoulder at 298 nm (ϵ 31,500) and a maximum at 322 (34,800).



4 **5**

The electronic spectrum of **5** is shown in Figure 1, together with that of **2** and 2-thianorbiphenylene.[4] The spectrum is clearly different from that of **2**, probably owing to interaction of the thiophene rings and an out-of-plane preference of the phenyl groups. The extent of the paratropic contribution of the potential cyclobutadiene in dithianorbiphenylenes must await the synthesis of less substituted derivatives.

Experimental Section

NMR spectra were obtained on either a Varian T-60 or HA-100 spectrometer. Mass spectra were taken on an AEI MS-9 spectrometer at 70 eV. Infrared spectra were recorded on a Unicam SP 200 spectrophotometer and only strong and medium bands are reported. Electronic spectra were determined on a Unicam SP-800 recording spectrophotometer. Melting points were measured on a Kofler hot stage microscope.

Silica for preparative thin layer chromatography was Merck Kieselgel PF_{254} (type E). Solvents were purified and dried by standard methods.

Synthesis of 2,4-Diphenyl-3-thiabicyclo[3.2.0]hepta-1,4-diene (2). A mixture of phosphorus pentasulfide (250 mg, 1.0 mmol), sand (0.5 g), and tetralin (15 ml) was stirred and heated to 150°. *trans*-1,2-Dibenzoylcyclobutane (528 mg, 2.0 mmol) was dissolved in hot tetralin (10 ml) and the hot solution was added dropwise to the stirred mixture over 5 min. The mixture was stirred for a further 15 min at 150–155°, the resulting red solution was filtered, and the filtrate was extracted with hot water (50 ml), 5% NaOH solution (50 ml), and dried ($MgSO_4$). The solution was passed through alumina (150 g), eluting with dichloromethane–petroleum ether (60–80) (1:1), and the solvent and eluted tetralin were removed by distillation under reduced pressure. Preparative TLC of the oily residue on silica, eluting with dichloromethane–pentane (1:9), gave **2** (30 mg, 0.11 mol, 6%): white crystals (EtOH); mass spectrum *m/e* 262.081 (calcd for $C_{18}H_{14}S$, 262.082); ir (KBr) 3025, 2920, 1598, 1539, 1484, 1450, 1360, 1180, 1079, 1020, 925, 908, 760, 744, 698, 670 cm^{-1}; for nmr, see discussion; for electronic spectrum, see discussion.

Anal. Calcd for $C_{18}H_{14}S$: C, 82.39; H, 5.38. Found: C, 82.56; H, 5.45.

Oxidation of 2. Compound **2** (13 mg, 0.05 mmol) was dissolved in $CDCl_3$ (1.5 ml) in an NMR tube and *m*-chloroperoxobenzoic acid (40 mg, 0.23 mmol) was added. The reaction was monitored by NMR, and, on complete disappearance of the signals due to the cyclobutyl protons of **2**, the solution was extracted with $NHCO_3$ solution (3 × 10 ml) and water (10 ml) and dried ($MgSO_4$). Evaporation of the solvent gave a yellow solid which on crystallization (CCl_4) gave yellow crystals of the sulfone **3** (6 mg, 0.02 mmol, 40%): mass spectrum *m/e* 294.073 (calcd for $C_{18}H_{14}SO_2$, 294.072); ir (KBr) 1500, 1455, 1285, 1140, 1120, 765, 690 cm^{-1}; nmr (CCl_4) τ 2.50 (m, 10 H), 6.40 (s, 4 H); λ^{max} (Et_2O) 231 nm (ϵ 19,000), 383 (14,900).

Anal. Calcd for $C_{18}H_{14}SO_2$: C, 73.44; H, 4.79; S, 10.89; O, 10.87. Found: C, 73.32; H, 4.64; S, 10.95; O, 10.85.

Synthesis of Tetraphenyl-2,5-dithiabisnorbiphenylene (5). *cis,trans,cis*-1,2,3,4-Tetrabenzoylcyclobutane (460 mg, 0.975 mmol) was added to pyridine (25 ml) and the solution was heated to boiling. This solution was then added rapidly to a boiling mixture of phosphorus pentasulfide (400 mg, 1.79 mol) in pyridine (5 ml) under N_2. The mixture was heated under reflux for 2 hr, and the solvent was removed under reduced pressure. The black residue was chromatographed on silica (150 g) eluting with dichloromethane–pentane (1:4) to give **5** (13 mg, 0.028 mmol, 3%): mass spectrum *m/e* 468.102 (calcd for $C_{32}H_{20}S_2$, 468.101); ir (KBr) 1600, 1500, 1460, 1080, 1040, 920, 862, 764, 715, 700, 695 cm^{-1}; for nmr, see discussion; for electronic spectrum, see discussion.

Anal. Calcd for $C_{32}H_{20}S_2$: C, 82.01; H, 4.30. Found: C, 81.46; H, 4.65.

Acknowledgment. One of us (S.B.N.) thanks University College London for the award of a Thomas Witherden Batt Scholarship.

Registry No.—**1**, 54120-34-2; **2**, 54120-35-3; **3**, 54120-36-4; **4**, 54120-37-5; **5**, 54120-38-6.

References and Notes

(1) S. W. Longworth and J. F. W. McOmie, *Chem. Commun.*, 623 (1972).
(2) P. J. Garratt and D. N. Nicolaides, *Chem. Commun.*, 1014 (1972); *J. Org. Chem.*, **39**, 2222 (1974).
(3) M. P. Cava, M. V. Lakshmikantham, and M. Behforouz, *J. Org. Chem.*, **39**, 206 (1974).
(4) H. Hauptmann, *Tetrahedron Lett.*, 3589 (1974).
(5) For the related 2-thianorbiphenylene, see P. J. Garratt and K. P. C. Vollhardt, *J. Am. Chem. Soc.*, **94**, 7087 (1972).
(6) T. Y. Kao and R. C. Fuson, *J. Am. Chem. Soc.*, **54**, 1120 (1932).
(7) G. W. Griffin, A. F. Vellturo, and K. Furukawa, *J. Am. Chem. Soc.*, **73**, 2725 (1961).
(8) Griffin et al.[7] report that they were unable to prepare the bisfuran analog of **5** by treatment with P_2O_5. We have also failed to obtain any of the desired product in this reaction.

Additions and Corrections

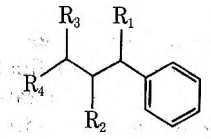
Vol. 40, 1975

Stan S. Hall* and Frank J. McEnroe: Alkylation–Reduction of Carbonyl Systems. IV. The Convenient and Selective Synthesis of Simple and Complex Aromatic Hydrocarbons by Phenylation–Reduction of Aldehydes and Ketones.

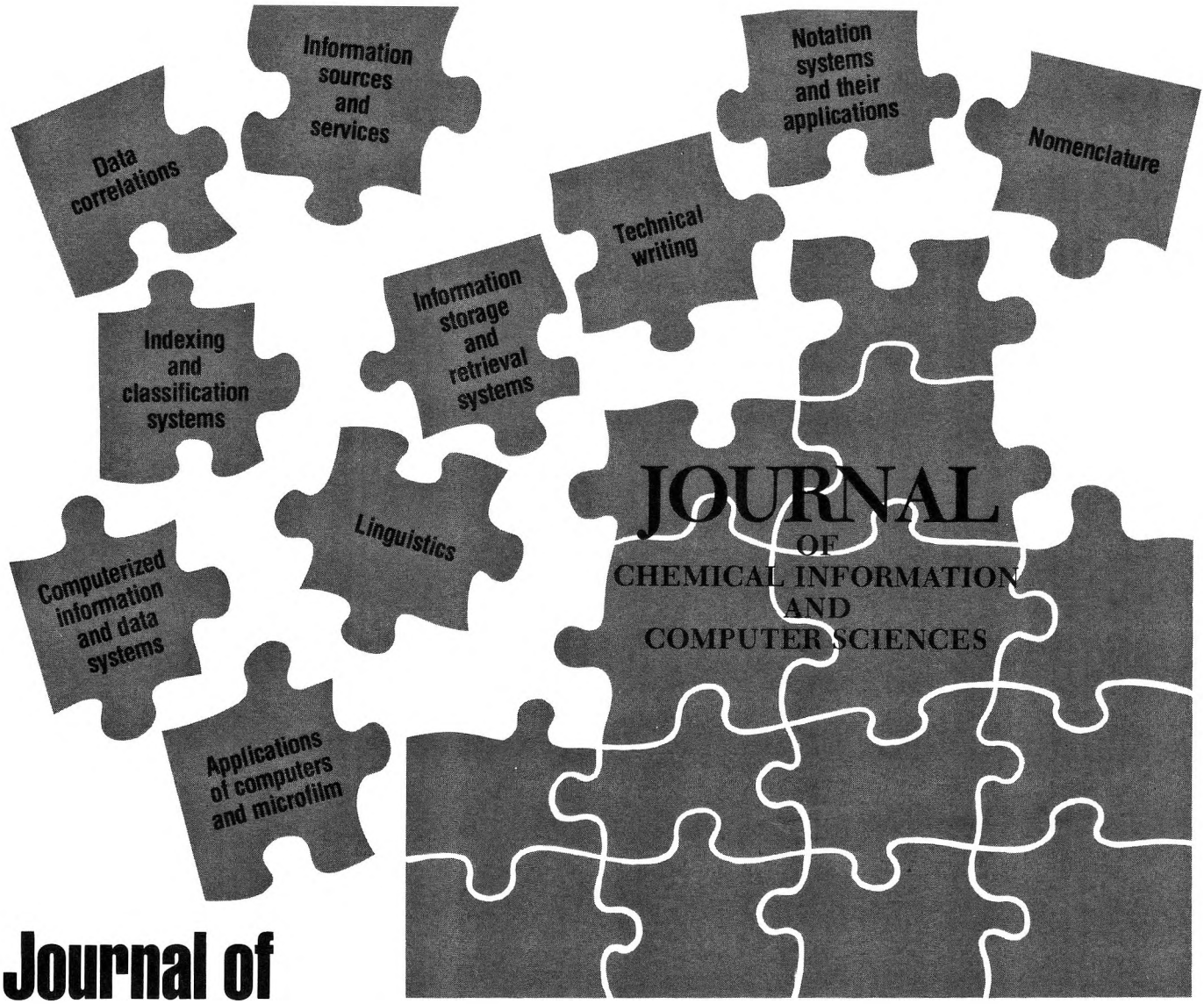
Page 271. Column 2. The second paragraph should read

Careful inspection of the products listed in Table I reveals that almost all of these structural features or functional groups were compatible with the conditions of the procedure. The only carbonyl compound that resisted reduction, after phenylation, was menthone (**3**), which is probably due to steric interactions.[5,12] An example of overreduction occurred with β-ionone (**9**). With such a system (see Scheme I), after the initial reduction of the benzyl alcohol,[13] a 1,3-diene system still remains which is vulnerable and reduces, as one would predict,[7] by 1,2-addition to the less substituted double bond. The phenylation–reduction of two α,β-unsaturated ketones, piperitone (**7**) and 4-cyclohexyl-*trans*-3-buten-2-one (**8**), led to mixtures of the corresponding olefin and aromatic hydrocarbon, a result which did not change substantially by varying the amount of lithium used for the reduction step. The only carbonyl compound found to be completely incompatible with the reductive conditions was methyl 2-thienyl ketone. Phenylation–reduction of this ketone, which is not included in Table I, led to a complex mixture which was difficult to purify and characterize, but the data on the crude product material did indicate that the thiophene ring was being destroyed.[11b-e]

Page 273. Structure **46** in Scheme II should be



46



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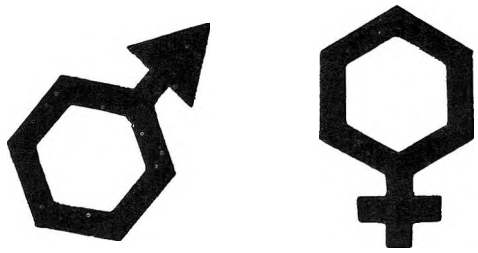

Ph-SeX (X = Br, Cl or PhSe)

The observation that alkyl phenyl selenoxides undergo eliminations at room temperature to form olefins [1-3] is the basis for a new and convenient synthesis of allylic alcohols,[4] allylic ethers and acetates,[5] and α,β-unsaturated carbonyl compounds.[6-8] **Diphenyl diselenide** is a yellow, odorless, air-stable solid which is easily converted into the highly colored phenylselenenyl halides. The oxidations are conveniently carried out at or below room temperature using a variety of oxidants (peracetic acid, sodium periodate, hydrogen peroxide, etc.)

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References:
1) K.B. Sharpless and R.F. Lauer, *J. Amer. Chem. Soc.*, **94**, 7154 (1972); D.N. Jones, D. Mundy, and R.D. Whitehouse, *Chem. Commun.*, 86 (1970).
2) K.B. Sharpless and R.F. Lauer, *J. Org. Chem.*, **37**, 3973 (1972).
3) K.B. Sharpless, M.W. Young, and R.F. Lauer, *Tetrahedron Lett.*, 1979 (1973); K.B. Sharpless and M.W. Young, *J. Org. Chem.*, **40**, 947 (1975), this issue.
4) K.B. Sharpless and R.F. Lauer, *J. Amer. Chem. Soc.*, **95**, 2697 (1973); D. Seebach and A.K. Beck, *Angew. Chem., Intern. Ed Engl.*, in press.
5) K.B. Sharpless and R.F. Lauer, *J. Org. Chem.*, **39**, 429 (1974).
6) K.B. Sharpless, R.F. Lauer, and A.Y. Teranishi, *J. Amer. Chem. Soc.*, **95**, 6137 (1973).
7) H.J. Reich, I.L. Reich, and J.M. Renga, *J. Amer. Chem. Soc*, **95**, 5813 (1973).
8) D.L.J. Clive, *Chem. Commun.*, 695 (1973).

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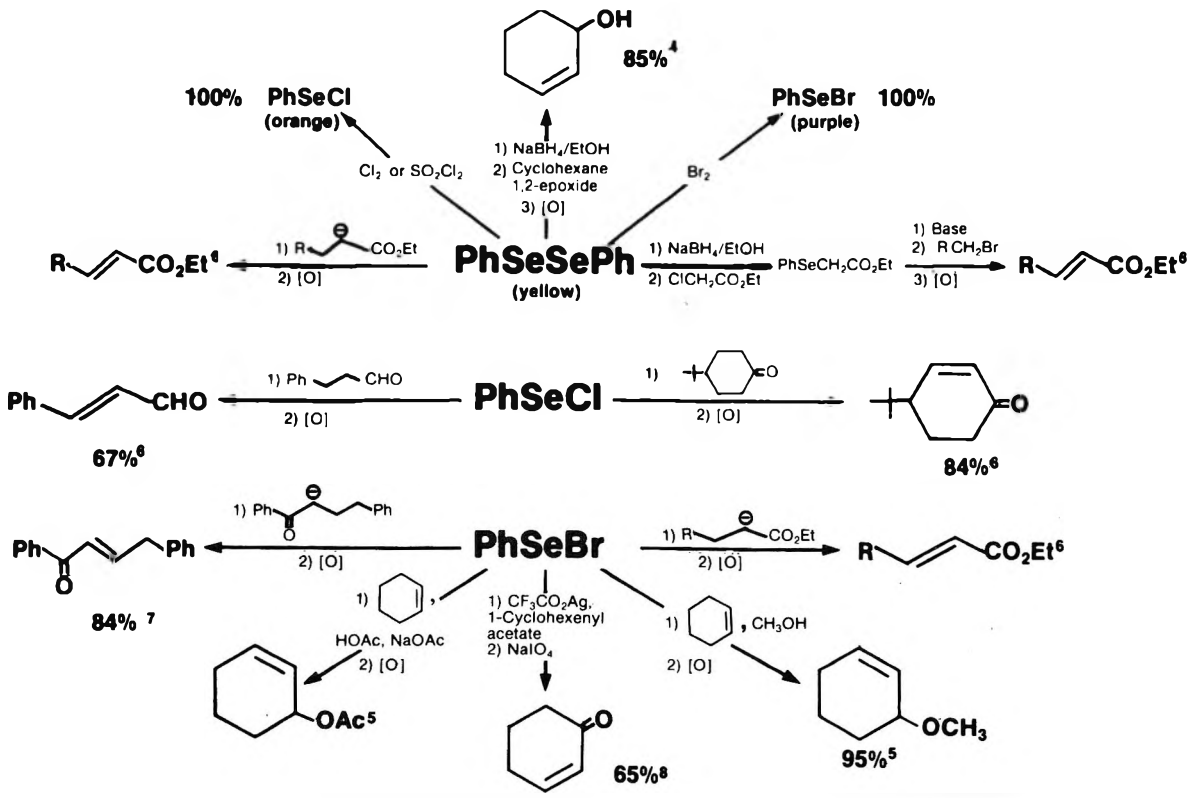

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