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NOTES

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Preferred Ring Sizes of Cyclic Transition States in Bifunctional Catalysis of the Dedeuteration of Isobutyraldehyde-2-*d* by Polyethylenimines†[1a,b]

Jack Hine* and Robert L. Flachskam, Jr.[1c]

Department of Chemistry, The Ohio State University, Columbus, Ohio 43210

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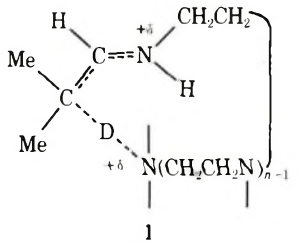
Polyethylenimines (PEI's) act as bifunctional catalysts for the dedeuteration of isobutyraldehyde-2-*d* by using primary amino groups to reversibly complex the aldehyde, partly as iminium ions, and then using other amino groups to remove deuterium from the iminium ion groups in the same molecule. The exchange of 0.05 *M* aldehyde at pH 8.5 in the presence of 1 *N* PEI's, where almost all the reaction is due to complexed aldehyde, proceeds at relative rates of 1:1.19:1.24:1.38 for PEI's with average molecular weights of 600, 1200, 1800, and 50,000, respectively. The reaction under these conditions is catalyzed by 1,4-diazabicyclo[2.2.2]octane (Dabco), which attacks the complexed aldehyde. The relative rates of attack by Dabco are 1.46:1.32:1.15:1 on aldehyde complexed to PEI-600, PEI-1200, PEI-1800, and PEI-50,000, respectively. These and previous observations show that attack by internal amino groups on the complexed aldehyde is ineffective when the chain separating the amino and complexed aldehyde groups is either too long or too short. A computer-simulated polymerization process is used to estimate the detailed structure of the polymers. With data on various reference reactions this is used in an argument that the complexed aldehyde is probably dedeuterated most efficiently by amino groups that are 3–6 monomer units from the complexed aldehyde.

Earlier papers in this series described evidence that polyethylenimines (PEI's) act as bifunctional catalysts in the dedeuteration of isobutyraldehyde-2-*d*.[2,3] A primary amino group on the polymer transforms the aldehyde to an imine, which is in equilibrium with the corresponding iminium ion. Then, in the rate-controlling step of the reaction, another amino group in the polymer removes the activated α-deuterium atom *via* a transition state, such as 1, arising from the trans form of the iminium ion. Cyclic



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transition states are probably rather common in enzymatic reactions. The dedeuteration of acetone-d_6 by acetoacetate decarboxylase, for example, probably involves the formation of an iminium ion by the ϵ-amino group of a lysine unit followed by removal of deuterium by another basic group in the same molecule.[4] For these reasons it was of interest to learn what ring sizes are preferred in the formation of transition states like 1 from PEI's for which a wide variety of ring sizes are possible. We have therefore measured the catalytic activities of PEI's under various conditions and made experimental measurements and computer calculations to estimate the relative numbers and basicities of the primary, secondary, and tertiary amino groups in these PEI's.

Results

The kinetics of the deuterium exchange of isobutyraldehyde-2-*d* were studied as described previously.[5] The reactions were stopped by acidifying the reaction mixture to neutralize the basic catalyst and liberate the aldehyde from any complex formed with the catalyst. The aldehyde was then extracted and its deuterium content was determined by proton magnetic resonance measurements. First-order rate constants obtained in the presence of various PEI's are listed in Table I. PEI-*X* is a polymer with a number-average molecular weight of *X*. Normalities refer to the number of equivalents of amino groups per liter. The aldehyde forms complexes with the catalysts in equilibria that are much faster reactions than the deuterium exchanges. In the presence of 1.0 *N* PEI's the aldehyde is very largely complexed, so that the rate constants listed in these cases are essentially those of the complexed aldehyde.

To help in estimating the catalytic efficiencies of the secondary amino groups of the PEI's, diethylamine was studied as a catalyst. Rate constants obtained in the presence of several diethylamine buffers are listed in Table II. Ultraviolet measurements showed that 0.2 *M* diethylamine transforms less than 1% of 0.07 *M* isobutyraldehyde

† This paper contains "miniprint." See Editorial regarding miniprint on p 8A of the Jan 11, 1974, issue.

Table I
Rate Constants for Exchange of Isobutyraldehyde-2-*d* in the Presence of PEI's in Water at 35° [a]

PEI	pH	10^5k, sec^{-1}
1.00 *N* PEI-600	8.49	10.2
1.00 *N* PEI-600[b]	8.50	24.1
1.00 *N* PEI-1200	8.51	12.1
1.00 *N* PEI-1200[b]	8.48	24.6
1.00 *N* PEI-1800	8.54	12.6
1.00 *N* PEI-1800[b]	8.51	23.5
1.00 *N* PEI-50,000	8.52	14.1
1.00 *N* PEI-50,000[b]	8.50	23.6
0.099 *N* $(H_2NCH_2CH_2)_2NH$	8.51	0.90
0.099 *N* PEI-146[c,d]	8.48	2.0
0.100 *N* PEI-190[c,e]	8.51	3.0
0.103 *N* PEI-600	8.47	7.5
0.153 *N* PEI-600	8.42	9.5
1.01 *N* PEI-600	7.40	8.1
1.01 *N* PEI-600	7.78	9.6
1.01 *N* PEI-600	7.91	11.1
1.01 *N* PEI-600	8.15	10.8
1.01 *N* PEI-600	8.37	9.9
1.01 *N* PEI-600	8.40	9.8
0.100 *N* PEI-50,000	8.60	6.5
0.30 *N* PEI-50,000	8.51	11.5
0.60 *N* PEI-50,000	8.52	15.0
1.00 *N* PEI-50,000	6.81	14.9
1.00 *N* PEI-50,000	7.55	22.5
1.00 *N* PEI-50,000	7.96	21.0
1.00 *N* PEI-50,000	8.56	14.9

[a] $[Me_2CDCHO]_0$ = 0.054 *M*. All concentrations listed are total concentrations, regardless of states of protonation or complexing. [b] 0.100 *M* 1,4-diazabicyclo[2.2.2]octane also present. [c] Labeled as a PEI because it is a mixture of polyethylenepolyamines; the molecular weight given is that of its principal component. [d] Eastman Technical triethylenetetramine. [e] Eastman Technical tetraethylenepentamine.

Table II
Diethylamine Catalysis of the Deuterium Exchange of Isobutyraldehyde-2-*d* in Water at 35°

$[Et_2NH]$	$[Et_2NH_2^+]$	10^5k_p, sec^{-1}	$10^5k_h[OH^-]$, sec^{-1}	$10^3k_{Et_2NH}$, M^{-1} sec^{-1}
0.0241	0.0774	8.77	1.40	3.06
0.0247	0.164	8.42	0.76	3.10
0.0498	0.136	17.9	1.8	3.24
				Av 3.13

to carbinolamine (or any other adduct). In view of this fact and the earlier observation that secondary amines do not give any detectable catalysis of the dedeuteration of isobutyraldehyde-2-*d* *via* iminium ion formation,[6] these exchange reactions were assumed to follow eq 1, where k_p is

$$k_p = k_{Et_2NH}[Et_2NH] + k_h[OH^-] \quad (1)$$

the pseudo-first-order rate constant obtained in a given run. (The catalysis constant for water[5] is so small that such catalysis may be neglected in all the runs described in the present paper.) As shown in Table II, the corrections for hydroxide ion catalysis (calculated from the catalysis constant for hydroxide ions[5]) do not exceed 16% of the total reaction, and the values obtained for k_{Et_2NH} are reasonably constant.

One method of determining the fraction of the amino groups in PEI's that are tertiary is to treat the material with excess acetic anhydride to transform the primary and secondary amino groups to amide groups and then to titrate the remaining basic groups with *p*-toluenesulfonic acid in acetic acid–acetic anhydride.[7] It seems possible that, if too many tertiary amino groups are located near each other in the polymer, the protonation of some of them will so decrease the basicity of the remaining ones

Table III
Titrations with *p*-Toluenesulfonic Acid at 63 ± 1% Acetic Acid–37 ± 1% Acetic Anhydride

Amine	Concn, *M*	[*p*-TsOH],[a] *M*	Equiv of base/mol of amine
$(Me_2NCH_2CH_2)_2NMe$	0.022	0.200	2.99
$(Me_2NCH_2CH_2NMeCH_2)_2$	0.0070	0.100	3.96
$(Me_2NCH_2CH_2)_3N$[b]	0.0065	0.100	3.00
$(AcNHCH_2CH_2)_3N$[c]	0.107	0.200	1.02

[a] In glacial acetic acid. [b] The 3.7% $(Me_2NCH_2CH_2NMeCH_2)_2$ present as an impurity was assumed to take up 4 equiv of acid/mol of amine. [c] The starting material was $(H_2NCH_2CH_2)_3N$ containing 13.2% of triethylenetetramine as an impurity. The material was acetylated in the manner used for PEI's, and the impurity was assumed to leave no base that would be titrated under the conditions used.

Table IV
Tertiary Amine Content of PEI's as Determined by the Acetylation–Titration Method

PEI	% tertiary[a]
PEI-600	21.6
PEI-1200	25.2
PEI-1800	26.0
PEI-50,000	26.5

[a] The number of tertiary amino groups divided by the total number of amino groups and multiplied by 100.

Table V
Thermodynamic pK_a Values in Water at 25°

Amine	pK_1	pK_2	pK_3
$(Me_2NCH_2CH_2)_2NMe$	9.32	8.24	
$(Me_2NCH_2CH_2)_3N$	9.42	8.34	6.66
$(Me_2NCH_2CH_2NMeCH_2)_2$	9.16	8.17	4.62

that the number of amino groups determined will be smaller than the number actually present. To test this possibility, four model compounds were titrated, and the averages of the results obtained are shown in Table III. The potentiometric titration curves obtained were essentially the same as those obtained in titrations of acetylated PEI's, except that the end points were slightly sharper in the case of the model compounds. The number of tertiary amino groups determined is correct in every case except that of tris(2-dimethylaminoethyl)amine, where only three of the four amino groups present were protonated during the titration. We therefore conclude that a tertiary amino group in a PEI will not be protonated in the titration if the three nearest amino groups are protonated, but that protonation of a tertiary amino group is not prevented by protonation of two of the three nearest amino groups (*cf.* the first two compounds in Table III). The tertiary amino contents of PEI's listed in Table IV were determined by the standard acetylation–titration method and have not been corrected for the possibility that some of the tertiary amino groups escaped titration. Essentially the same results were obtained in several cases where the acetylation was varied from the standard 4 hr to as little as 15 min and as much as 6 hr.

The pK_a values of three of the model compounds were determined by potentiometric titration in aqueous solution, with the results shown in Table V.

Discussion

The rate constants for the dedeuteration of 0.053 *M* isobutyraldehyde-2-*d* in the presence of ethylenediamine and its five N-ethylated derivatives, all at concentrations of

0.10 *M*, at pH 8.5 and 35° range from 0.20×10^{-5} sec^{-1} for the unsubstituted compound to 0.55×10^{-5} sec^{-1} for the triethyl derivative.[2,3] The relative reactivities are a complicated function of the fraction of the aldehyde that is complexed, the fraction of the amine that is protonated at pH 8.5, the amount of reaction that involves two molecules of catalyst, and other factors. The rate of dedeuteration in the presence of ethylenediamine around pH 8.5 increases to a maximum at diamine concentrations around 0.03 *M*, decreases to a minimum around diamine concentrations of 0.10 *M*, and then increases with increasing concentrations of diamine.[8] These and similar observations show that the relative catalytic activities of ethylenediamine and its N-ethylated derivatives are functions of the concentrations of aldehyde and diamine used. The fact that diethylenetriamine is about 60% more efficient than the best of the N-ethylated ethylenediamine catalysts may suggest that bifunctional catalysis has become important, but there are a number of possible alternative explanations. In fact, in view of the evidence that the exchange of isobutyraldehyde *via* iminium-ion formation involves only the trans iminium ions[6,9-13] and that more than six carbon (or other) atoms are needed between the primary amino group and the basic catalyzing group for bifunctional catalysis *via* a trans iminium ion,[13] it seems unlikely that diethylenetriamine is acting bifunctionally. All the compounds listed as PEI's in Table I have pairs of amino groups separated by a large enough number of atoms that a molecular model of a transition state for bifunctionally catalyzed dedeuteration *via* a trans iminium ion may be constructed without obvious major strain. In view of all the additional evidence described, particularly for PEI-1800,[2,3] it seems likely that bifunctional catalysis is significant for all these PEI's. The reactions in all cases will include a component from free aldehyde and a component from complexed aldehyde, with all the bifunctionally catalyzed reaction being included in the latter component. Therefore, in order to learn more about the bifunctionally catalyzed reaction, we shall give particular attention to the relative reactivities determined in the presence of 1.0 *N* PEI's, where the complexed aldehyde is responsible for almost all the observed reaction.

In Figure 1 are plots of the rate constants for deuterium exchange of 0.054 *M* isobutyraldehyde-2-*d* *vs.* pH in the presence of 1.0 *N* PEI-600, PEI-1800, and PEI-50,000. Whether one compares the rate constants at a given pH, such as 8.5, where the largest amount of data exists, or at the respective maxima for the various PEI's, the catalytic activities are seen to increase with increasing molecular weight of the PEI's. This increasing reactivity of the complexed aldehyde suggests either that as the molecular weight of the PEI increases the complexed aldehyde becomes increasingly reactive toward attack by a base (*e.g.*, because of a larger fraction of it being present as iminium ions), or that there is an increase in the number and/or basicity of internal amino groups that can attack complexed aldehyde, or that both of the preceding factors are important. In view of the results obtained when Dabco was present in the reaction solution, the first alternative seems unlikely. The effect of 0.200 *N* Dabco on the exchange rate in the presence of 1.00 *N* PEI's increases in the order PEI-50,000 < PEI-1800 < PEI-1200 < PEI-600. This sequence is reasonably explained by assuming that aldehyde complexed to PEI-600 is somewhat more reactive than that complexed to PEI-50,000 because a somewhat larger fraction of it is complexed as iminium ions, but it is also possible that aldehyde complexed to the larger PEI's is more sterically hindered. A larger fraction of iminium ions would be expected in the aldehyde complexed to the lower molecular weight PEI's because these have a larger fraction of primary amino groups, which can yield imines and iminium ions, in contrast to the secondary amino groups, which yield carbinolamines, imidazolidines, and perhaps larger ringed heterocycles. The greater rate of deuterium exchange of aldehyde complexed to the higher molecular weight PEI's is therefore most plausibly explained in terms of the larger number of amino groups in the same molecule that are capable of removing deuterium from those isobutyraldehyde-2-*d* molecules that are complexed as iminium ions. However, the reactivity of complexed aldehyde is not simply proportional to the number of other amino groups present in the molecule (even if a correction is made for differences in susceptibilities of complexed aldehyde to attack by bases as judged from the effect of Dabco on exchange rates). Aldehyde that is complexed to PEI-1800 must have about three times as many amino groups in the same molecule with it as does aldehyde that is complexed to PEI-600, and yet the PEI-1800-complexed aldehyde is only about 24% more reactive. PEI-50,000-complexed aldehyde is only 5–90% (depending on the pH at which the comparison is made) more reactive than PEI-1800-complexed aldehyde, in spite of having about 30 times as many amino groups. If we make the plausible assumption that an amino group (of a given basicity, etc.) separated from a complexed aldehyde by a given number of atoms has about the same rate constant for deprotonating it in one PEI as in a PEI of much different molecular weight, it follows that most of the amino groups in PEI-50,000 are separated from the average complexed aldehyde by such a long chain of atoms that they rarely collide with it and are thus quite inefficient at deprotonating it.

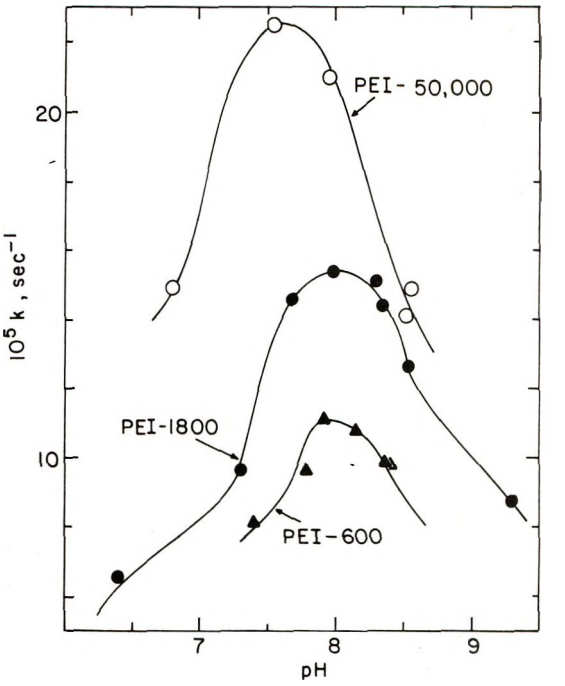

Figure 1. Plot of rate constants for dedeuteration of isobutyraldehyde-2-*d* in water at 35° in the presence of, ▲, 1.01 *N* PEI-600; ●, 0.97 ± 0.03 *N* PEI-1800; ○, 1.00 *N* PEI-50,000.

In order to get an improved understanding of how the ability of an amino group to deprotonate complexed aldehyde depends on the length of the intervening chain of atoms, we used computer and other techniques to estimate certain aspects of the detailed structures of the PEI's, as described in more detail in the Appendix. We carried out computer simulations of ethylenimine polymerization, using constraints to make some properties of

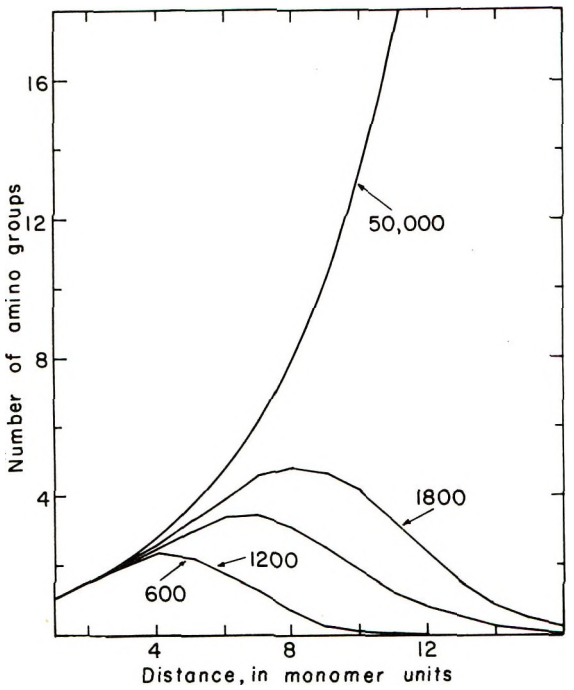

Figure 2. Estimated total number of amino groups at each distance from the average primary amino group in polyethylenimines with average molecular weights of 600, 1200, 1800, and 50,000.

the polymers resemble those observed experimentally but otherwise assuming random reaction. We then estimated the number of primary, secondary, and tertiary amino groups at each possible distance from the average primary amino groups. The estimated total number of amino groups at each distance from the average primary amino group in PEI-600, PEI-1200, PEI-1800, and PEI-50,000 is plotted in Figure 2.

To discuss internal attack on complexed aldehyde simply in terms of the number of amino groups at various distances away that are available for attack neglects several important factors. Other factors being equal, the most basic amino groups will attack most rapidly. However, at the pH's where bifunctional catalysis is most clearly significant, many of the amino groups of a PEI are protonated, and the most basic amino groups will be protonated to the greatest extent. Furthermore, in view of the fact that trimethylamine dedeuterates isobutyraldehyde-2-*d* 20 times as rapidly as triethylamine does, in spite of being only about one-seventh as basic,[5] allowance should also be made for differences in steric hindrance and any other factors that influence the ease with which a base removes α deuterium from an N-substituted isobutylideniminium ion. In order to allow for such factors we subdivided the amino groups in PEI's in aqueous solution at pH 8.5 into a number of categories and estimated the rate constant for the attack of each on *N*-methylisobutylideniminium ions. As described in detail in the Appendix, data on model compounds were used to estimate the basicities of the various types of amino groups in the unprotonated PEI's and the effect of protonation of nearby amino groups on these basicities. Then Brønsted relationships were assumed for the rate constants for dedeuteration of *N*-methylisobutyliden-2-*d*-iminium ions by these various types of amino groups. Rate constants for dedeuteration by the different types of amino groups were then calculated from their respective basicities and the Brønsted relationships. From these results the estimated average rate constants for dedeuteration by the primary, by the secondary, and by the tertiary amino groups of each of the PEI's were calculated. It was then assumed that the *relative* magnitudes of these rate constants for attack on the *N*-methylisobutyliden-2-*d*-iminium ion are the same as those for attack on the isobutyliden-2-*d*-iminium ions formed from any given PEI. This permits us to combine the estimated rate constants and the estimated numbers of primary, secondary, and tertiary amino groups at each of the possible number of units away from the average primary amino group to obtain the relative rate constants that would be expected, for a given PEI, for dedeuteration of complexed aldehyde *via* transition states with each of the possible rings if there were no ring-size effect. A plot of the estimated relative rate constants[14] for attack on complexed aldehyde by the primary, secondary, and tertiary amino groups at each of the possible distances from the average primary amino group in PEI-1800 is shown in Figure 3. The estimated amount of catalysis by tertiary amino groups is seen to be quite small compared with that estimated for primary and secondary amino groups, which are less hindered and, on the average, more basic. The three curves in Figure 3 may be summed to get the total relative rate constants that would be expected if there were no ring-size effect. Before comparing such a summed curve with that for another PEI, a correction was made for differences in ease of removal of deuterium from complexed aldehyde as evidenced by reactivities toward added Dabco. That is, the estimated rate constants for PEI-600, PEI-1200, and PEI-1800 were multiplied by 1.46, 1.32, and 1.15, respectively, since the effects of Dabco on the rate of exchange of aldehyde complexed to PEI-600, PEI-1200, and PEI-1800 are greater by 46, 32, and 15%, respectively, than on the rate of exchange of aldehyde complexed to PEI-50,000 (Table I). A plot of the relative rate constants (relative to that for the average tertiary amino group in PEI-50,000) is shown in Figure 4. (To put the entire plot for PEI-50,000 on the same graph would make those for the smaller polymers too small to see clearly.)

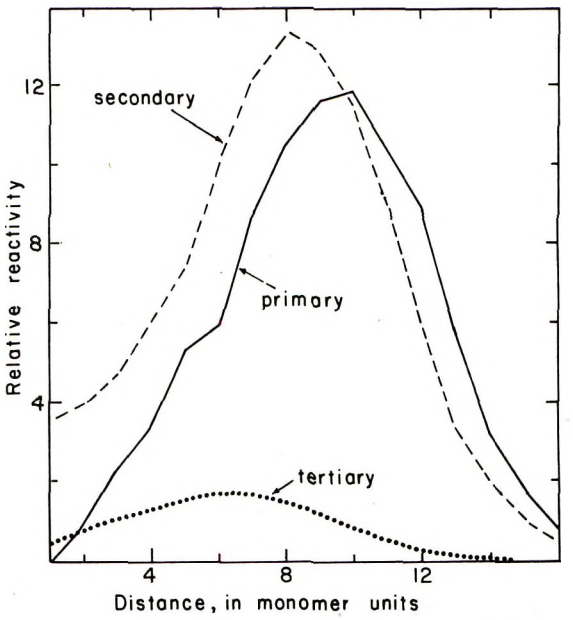

Figure 3. Estimated reactivities (relative to that of a tertiary amino group), in dedeuteration of $Me_2CDCH{=}N^+H{-}$ groups, of the primary, secondary, and tertiary amino groups at various distances from the average primary amino group in PEI-1800.

If there were no ring-size effect, the relative rate constants for the exchange of complexed aldehyde would be essentially equal to the relative areas under the curves shown in Figure 4. Thus, aldehyde complexed to PEI-1200, PEI-1800, and PEI-50,000 would exchange 2.0, 2.7, and 70 times as fast as aldehyde complexed to PEI-600.

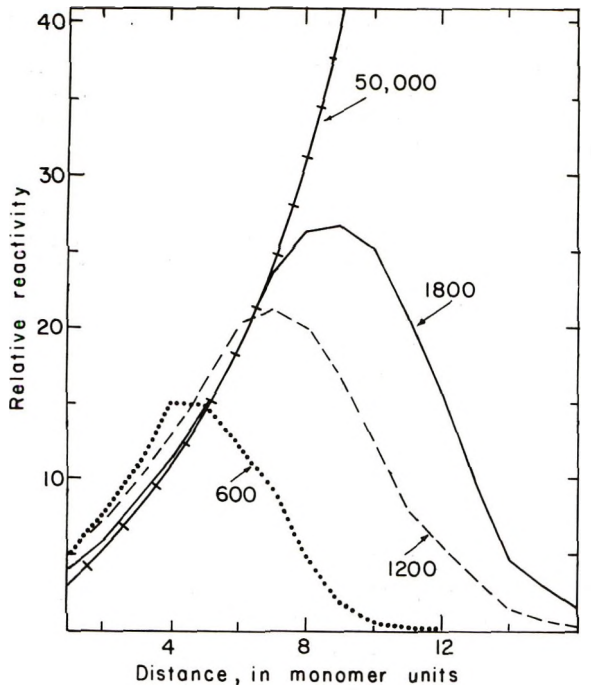

Figure 4. Estimated reactivities (relative to that of the average tertiary amino group in PEI-50,000), in dedeuteration of internal $Me_2CDCH{=}N^+H$- groups, of amino groups at various distances from the average primary amino group in four PEI's.

These figures are quite different from the observed ratios of 1.19, 1.24, and 1.38, which may be calculated from the data on runs using 1.0 *N* PEI's at pH 8.5 in Table I. We assume that these differences would largely disappear if each of the rate constants for reaction *via* a transition state with a given ring size were multiplied by the proper ring-size factor.

There are, of course, an infinite number of sets of ring-size factors that will give the desired agreement, but they are not all equally plausible. We have assumed that whatever value of n makes 1 the most favorable transition state, the next most favorable one will be one with one more or one less ethylenimine unit in the ring. More precisely, we have assumed that the ring-size factors will be a Gaussian function of ln n, as shown in eq 2. In this equation r, the ring-size factor, is the number by which the relative rate constants, such as those plotted in Figure 4, should be multiplied to correct them for the ring-size effect; n_{op} is the value of n in the optimum transition state; and C is a constant that controls the sharpness of the Gaussian function. A logarithmic function is used so that

$$\ln r = -C\left(\ln \frac{n_{op} - 1}{n - 1}\right)^2 \qquad (2)$$

r will be undefined for negative values of n but still positive for any large n. A function of $n - 1$ is used to make r zero for an n value of 1, since models of the appropriate transition state 1 can be constructed only with obvious enormous strain. With n_{op} restricted to integers, a very large value of C corresponds to essentially all the reaction proceeding *via* the transition state in which n is equal to n_{op}. An n_{op} value of 5.5, for example, corresponds to the transition states for which n is 5 and 6 being about equally favorable. A very small value of C corresponds to essentially identical ring-size factors for all values of n, which, as explained earlier, corresponds to much greater relative catalytic activity for the larger PEI's than that found experimentally.

We determined how well the observed relative reactivities of aldehyde complexed to the four polymers could be

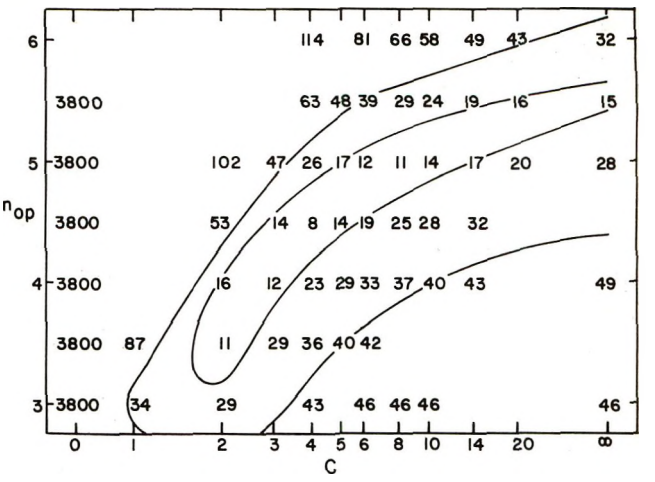

Figure 5. Per cent standard deviations in the fit to the observed catalytic activities of four PEI's obtained using eq 2 and various values of n_{op} and C.

fit (as measured by the standard per cent deviations) by various pairs of values of n_{op} and C. The results are shown in Figure 5, in which two contour lines have been drawn, one at a standard deviation of 17% and the other at a standard deviation of 40%. It is seen that for any value of C from one to infinity there are values of n_{op} that permit our data to be fit with standard deviations of 40% or less. For this reason, we feel that all we can say about C is that its value is probably not much less than 1.0. The plot is much more restrictive as to the probable value of n_{op}, however. If a 40% standard deviation from the experimental values is taken as satisfactory, n_{op} must be in the range 3–6. If it is demanded that the standard deviation not exceed 17%, n_{op} is probably either 4 or 5.

The preceding conclusions are relatively insensitive to some of the details of the treatment used. In alternative treatments we assumed that the number of amino groups at a given distance from the average primary amino group agreed with the number calculated for an infinitely large polymer out to 20 ethylenimine units (instead of 13, as in the treatment that gives Figure 5), neglected catalysis by amino groups more than 20 units away, replaced the terms $n_{op} - 1$ and $n - 1$ in eq 2 by $n_{op} - 2$ and $n - 2$, and took the reactivity of tertiary amino groups as the same in all the polymers. Although these alternative treatments were not carried out in as much detail, in no case was there any evidence that C is significantly smaller than 1.0 or that n_{op} is outside the range 3–6. The range 3–6 of n_{op} corresponds to a ring size of 13–22 atoms for the optimum cyclic transition state. Models of transition states of the type of 1 can be constructed without obvious strain in bond lengths or bond angles (but perhaps with unfavorable nonbonded interactions and torsional strains around single bonds) for any value of n equal to 3 or more. Bifunctional catalysis by 1-dimethylamino-8-amino-2-octyne, which should give a transition state with a 13-membered ring, has been observed.[13] The compounds $H_2N(CH_2)_mNH_2$, where m was 11 and 12 (corresponding to cyclic transition states with 16- and 17-membered rings), did not appear to be bifunctional catalysts,[13] but this may result from the greater energy required to achieve the necessary gauche conformations in a polymethylene chain. The range 13–22 atoms obtained for the optimum cyclic transition state in the present case may depend significantly on the polyethylenimine nature of most of the ring. It would take more data to learn how extrapolatable the present results are to compounds with other types of relatively flexible chains between the pri-

mary amino group and the other basic group in bifunctional catalysts for deuterium exchange *via* the trans form of aldiminium ions.

Experimental Section

Reagents. Polyethylenimines with average molecular weights of 600 (Montrek-6, lot no. 534-1-47), 1200 (Montrek-12, lot no. 534-2-2), and 1800 (Montrek-18, lot no. TA09028BON) were obtained from the Dow Chemical Co. as viscous, colorless liquids containing less than 3% water. PEI-50,000 (Montrek-600, lot no. 01047BOI, said to have a number-average molecular weight of 40,000–60,000) was obtained as a "~33% solution in water." The elemental analysis agreed best with a 34.6% solution of PEI containing 0.88%[15] hydrochloric acid.

Anal. Calcd for 34.6% $(C_2H_5N)_x$–0.88% HCl–64.5% H_2O: C, 19.30; H, 11.29; N, 11.25; Cl, 0.86. Found: C, 19.52; H, 11.28; N, 11.11; Cl, 0.86.

Volhard analysis showed 0.19, 0.24, and 0.51 wt % chloride in the PEI-600, -1200, and -1800, respectively. These amounts were taken as hydrochloric acid already in the samples, and they were therefore added to the per cents of tertiary amino group determined by acetylation and titration[7] to give the results shown in Table IV.

The *N,N*-bis(2-dimethylaminoethyl)methylamine (Ames Laboratories) used was found by glpc to be at least 99.8% pure. After purification by recrystallization of their hydrochlorides, *N,N'*-bis-(2-dimethylaminoethyl)-*N,N'*-dimethylethylenediamine (Ames) and tris(2-dimethylaminoethyl)amine [prepared by methylation of tris(2-aminoethyl)amine][16] were found by glpc to be >99.8 and 96.3% pure, respectively; the 3.7% impurity in the latter tetramine was the former tetramine.

Both Eastman Technical triethylenetetramine and tetraethylenepentamine showed a large number of peaks on glpc.

p*K* Determinations. The p*K* values listed in Table V were determined by potentiometric titration of aqueous amine solutions in the concentration range 0.02–0.03 *M* with 1.00 *M* hydrochloric acid using a Radiometer Model 26 pH meter and G202B glass and K401 reference electrodes. Values of pK_1, pK_2, and pK_3 (when determinable) were calculated, using a computer program, so as to minimize the sum of the squares of the deviations of the calculated from the observed pH values for at least eight experimental points. Equation 3 was used to calculate activity coefficients.[17] The reliability of the p*K* values obtained probably stands in the order $pK_1 > pK_2 > pK_3$ because of the uncertainties in calculating the activity coefficients of multicharged ions at the higher ionic strengths present when the diprotonated and triprotonated amines were the principal amine species present.

$$\log \gamma = -0.509Z^2\left(\frac{\sqrt{\mu}}{1+\sqrt{\mu}} - 0.2\mu\right) \qquad (3)$$

Acknowledgment. We thank Drs. Frank C. Schmalstieg, F. E. Rogers, and R. E. Notari for preliminary studies in the area of this investigation, the Dow Chemical Co. for gifts of the polyethylenimines used, and the Instruction and Research Computer Center of The Ohio State University for making its facilities available.

Registry No.—Isobutyraldehyde-2-*d*, 4303-51-9.

Miniprint Material Available. Full-sized photocopies of the miniprinted material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the mini-

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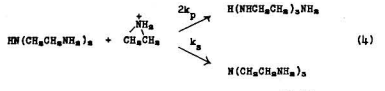
Appendix

Estimation of Distribution of Various Types of Amino Groups.--For the purpose of estimating the environment of the average primary, secondary, and tertiary amino groups in the various PEI's, the polymerization of ethylenimine was taken as involving nucleophilic attack by primary or secondary amino groups in the growing polymer on protonated ethylenimine (eq 4). Although it appears that nucleophilic



(4)

attack by ethylenimine is even more important,[18,19]

(18) G. D. Jones, D. C. MacWilliams, and N. A. Braxtor, J. Org. Chem., 30, 1994 (1965).

(19) C. R. Dick and G. E. Ham, J. Macromol. Sci., Chem., 4, 1301 (1970).

allowance for such a pathway would have complicated our treatment greatly, and it is not clear that it would have changed the results significantly. Although both ethylenediamine and diethylenetriamine are used in the polymerization

JOC-33-2

of ethylenimine[18,20] reaction by the mechanism used would

(20) Cf. J. G. Schneider, C. R. Dick, and G. E. Ham, British Patent 1,195,338; Chem. Abst., 73, 46222j (1970).

pass through the latter in either case. We therefore carried out a computer-simulated polymerization starting with diethylenetriamine and assuming that the reactivity of any amino group in the growing polymer depends only on whether the amino group is primary, secondary, or tertiary. Since quaternary nitrogen is known to be virtually absent from the polymer, the tertiary amino groups were assigned a relative reactivity of zero. This leaves only one parameter, k_p/k_s, the reactivity of any primary amino group relative to that of any secondary amino group. Each simulated polymerization was carried out with a given value of k_p/k_s, which was used with a random number generator to decide which amino group in the growing polymer with n ethylenimine units attacked ethyleniminium ions to give the polymer with $n+1$ units. To simulate PEI-600, PEI-1200, and PEI-1800, polymers with 14, 28, and 42 amino groups (molecular weights 576, 1178, and 1780, respectively) were generated. After 50 polymers of a given type had been generated using a given value of k_p/k_s, the fractions of the amino groups in these polymers that were primary, secondary, and tertiary were calculated, and then the fraction of tertiary amino

JOC-33-3

groups was corrected by subtracting those tertiary amino groups that would not be protonatable in acetic acid solution (because the amino group in question would have three protonated tertiary amino groups adjacent to it) to get the fraction of analyzable tertiary amino groups. When the value 4.0 was used for k_p/k_s the calculated fractions were all smaller than the experimental values and when 2.5 was used they were larger. The value 3.0 gave calculated fractions of analyzable tertiary amino groups of 22.4, 24.0, and 25.0% for PEI-600, PEI-1200, and PEI-1800, which are probably within the experimental uncertainty of the observed values of 21.6, 25.2, and 26.0%, respectively. The PEI-50,000 polymer is much too large for the computer simulated polymerization method used to be practical. However, a total tertiary amine content of 29% was estimated by extrapolation of the observed contents of analyzable tertiary amino groups for the smaller PEI's and the estimates of 0.4, 1.0, and 1.5% unanalyzable tertiary amino groups in PEI-600, PEI-1200, and PEI-1800, respectively. This value is near the 30% total tertiary amine content that may be calculated from the k_p/k_s value of 3.0 and the expression $2/[3+\sqrt{4(k_p/k_s)+1}]$ for the fraction of total tertiary amine in an infinitely large PEI, which may be derived on the following basis.

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If P and S represent primary and secondary amino groups the following relations are evident. As the molecular weight

$$d[P]/dt = k_s[S] \qquad (5)$$

$$d[S]/dt = k_p[P] - k_s[S] \qquad (6)$$

$$\frac{d[S]}{d[P]} = \frac{k_p[P]}{k_s[S]} - 1 \qquad (7)$$

of the polymer approaches infinity the ratio $d[S]/d[P]$ must approach $[S]/[P]$. The fraction of tertiary amino groups may then be calculated from eq 7 and the fact that there would be essentially equal numbers of primary and tertiary amino groups in an infinitely large PEI molecule.

Let us estimate the number of amino groups of various kinds that are at each of the various possible distances from the average primary amino group in an infinitely large PEI. If f is the fraction of amino groups that are primary then the fraction tertiary is also f and the fraction secondary is $1-2f$. It then follows that if E is one of the ethylene units that joins the amino groups the fraction of N-E bonds that are of the type P-E is $f/2$, the fraction of T-E bonds is $3f/2$, and the fraction of S-E bonds is $1-2f$. If the bonds are arranged randomly one might at first think that the fraction of P-E that leads on to give

JOC-33-5

the partial structure P-E-S would be $1-2f$. However, this ignores the fact that since we are dealing with a very large polymer the structure P-E-P, which would simply be ethylenediamine, is impossible. When this restriction is made, the fraction of the amino groups one unit away from the average primary that are secondary, which we shall denote s_1, is $(2-4f)/(2-f)$, and t_1 is $3f/(2-f)$. In calculating p_2, s_2, and t_2, the fractions of the amino groups two units away that are primary, secondary, and tertiary, respectively, we allow for the impossibility of the structures P-E-S-E-P and P-E-T(E-P)$_2$. The total number

$$p_2 = 2t_1f(2-f)/(4-f^2)$$

$$s_2 = s_1^2 + 8t_1(1-2f)/(4-f^2)$$

$$t_2 = s_1t_1 + 12t_1f/(4-f^2)$$

of amino groups two units from the average primary (a_2), that is, the sum $p_2 + s_2 + t_2$, is just $s_1 + 2t_1$. In fact, in general a_{n+1} is equal to $s_n + 2t_n$. Detailed calculations of random distributions of amino groups gave values of s_1, s_2, s_3, and s_4. If it were not for the disturbance in the calculations arising from the nonexistence of P-E-P, P-E-S-E-P, etc., the ratio a_{n+1}/a_n would always have the value $1+f$. Because of these disturbances, which decrease with increasing n, the ratios s_1/s_2, s_2/s_3, and s_3/s_4 are 1.509, 1.380, and 1.334, respectively, when f is 0.29. We

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extrapolated to larger values of n by assuming that s_4/s_5 differed from the limiting value 1.29 by half as much as s_3/s_4 did, and then that s_2/s_3 differed from 1.29 by half this amount, etc. With the added assumption that s_n/t_n, which was relatively constant over the range $n = 1$ to 3, does not change, values of p_n, s_n, and t_n may be calculated for any n (although we did not use values for any n larger than 20).

The number of amino groups at each distance from the average primary amino group in PEI-50,000 was assumed to be the same as for an infinitely large polymer for distances up to 13 monomer units away (where less than 10% of the amino groups in PEI-50,000 have been accounted for). A plot of these numbers, which were calculated as described in the preceding paragraph, and the numbers obtained by counting amino groups in the polymers generated by computer simulation for PEI-600, PEI-1200, and PEI-1800 is shown in Figure 2. The agreement between the four curves, up to the points where those for the smaller polymers begin to fall off, supports both the treatments used, which were based on considerably different assumptions. It was then assumed that the rest of the curve for PEI-50,000, beyond an n value of 13, was fit by an equation of the type shown in eq 8, in which n is the number of units away and the c's

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$$f(n) = a_1(n + a_2)^{a_3}/(a_4 + e^{a_5 n}) \quad (8)$$

are disposable parameters. For each of the three required functions (for values of p_n, s_n, and t_n) values of the four parameters were obtained by imposition of four restraints. It was required that $f(n)$ have the same value for $n = 1$ and $n = 13$ as obtained from the treatment of the infinite polymer described in the preceding paragraph. It was also required that the total area under the plot of $f(n)$ *vs.* n be equal to the number of amino groups of the given type in the polymer and that the area under the plot between $n = 1$ and the maximum in the plot be plausible in light of the areas of the similar curves for the smaller polymers. Thus, for example, in the case of tertiary amino groups, 47% of the total are found between $n = 1$ and the maximum in the case of PEI-600, 45% in the case of PEI-1200, and 44% in the case of PEI-1800. For PEI-50,000 the figure was assumed to be 43%, and corresponding figures of 61% and 53% were similarly taken for the primary and secondary amino groups. These restraints gave a_1, a_2, a_3, and a_4 values of 2.56, 1.08, 110, and 0.150 for the p_n curve, 6.75, 1.75, 103, and 0.193 for the s_n curve, and 4.96, 1.84, 76.9, and 0.281 for the t_n curve. The resulting estimated numbers of primary, secondary, and tertiary amino groups at various distances from the average primary amino group are plotted in Figure 6.

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Estimation of the Basicity and Reactivity of the Various Types of Amino Groups.--In estimating the average reactivity of the various types of amino groups in the PEI's, it is useful to subdivide the various P-E, S-E, and T-E bonds into subcategories, depending on the nature of neighboring amino groups. When P-E bonds lead to a secondary amino group they will be denoted Ps and when they lead to tertiary amino groups, Pt. There will be no Pp, which could exist only in ethylenediamine. Similarly, pSt represents an S-E bond in which the E is attached to a tertiary and the S to a primary amino group (through an ethylene unit). The T-E bonds are merely subdivided into Tp, Ts, and Tt categories; a more complete subdivision (like that used for S-E bonds) would be too complicated and also less worthwhile since it happens that tertiary amino groups are so weakly basic and so hindered that they contribute relatively little to internal basic catalysis. From the fraction of the amino groups in a given PEI that are primary, secondary, and tertiary the total number of P-E, S-E, and T-E bonds may be calculated. The first of these will be equal to the sum Ps + Pt, the second to pSs + pSt + sSp + sSs + sSt + tSp + tSs + tSt, and the third to Tp + Ts + Tt. This gives three equations for the 13 unknowns. Four more, such as Tp = Pt and sSp = pSs, come from symmetry considerations. Two more, such as Ps = pSs + pSt, come from material balance requirements. The remaining equations come from assumptions of random distribution. For example, the relative number of primary amino groups that have secondary and tertiary amino groups as their nearest neighbors was assumed to be proportional to the relative number of bonds from secondary and tertiary amino groups that are available to form bonds (through ethylene groups) to primary amino groups. The resulting relationship (eq 9) reflects the fact that a

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$$\frac{Ps}{Pt} = \frac{Sx - Ps}{Tx} \quad (9)$$

secondary amino group that already has a primary as one nearest neighbor is not free to take another as a nearest neighbor, since the resulting P-E-S-E-P (diethylenetriamine) cannot be a part of the PEI's we are studying. In eq 9 Sx is the total of all the S-E bonds and Tx the total of the T-E bonds.

In order to subdivide the amino groups into additional useful categories on the basis of whether they or their neighbors would be protonated at pH 8.5, where the kinetic studies being discussed were carried out, we needed estimates of basicities. From the pK values for the conjugate acids of the ethylamines and of ethylenediamine and diethylenetriamine and their N-alkylated derivatives,[21] it was noted

(21) D. D. Perrin, "Dissociation Constants of Organic Bases in Aqueous Solution," Butterworths, London, 1965; Supplement, 1972.

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that replacement of a β-hydrogen by a β-amino substituent decreases the pK of a substituted ammonium ion by about 1.23 and that an ∈-amino substituent decreases the pK by about 0.17. Similarly, protonation of an amino substituent decreases the pK by about 2.55 in the β position and about 0.68 in the ∈ position. Since the nearest neighboring amino group is a β-substituent and the next-nearest neighboring amino group an ∈-substituent in a PEI, these generalizations were applied to the PEI's and the effect of more distant substituents ignored. Titrations of 1 *M* polymers with standard acid to pH 8.5 in the presence of 0.054 *M* isobutyraldehyde showed that 34.4, 32.1, 27.9, and 22.3% of the amino groups were protonated under these conditions in PEI-600, PEI-1200, PEI-1800, and PEI-50,000, respectively. The presence of protonated amino groups means that our categories of bonds must be expanded to include P^+t, Ts^+, sS^+p, etc., but our generalizations concerning basicity show that there should be no significant number of protonated tertiary amino groups nor of pairs of adjacent protonated amino groups. This permits the easy estimation of the basicity of the unprotonated secondary amino group associated with a pSs^+ bond, for example. This amino group has two nearest neighbor amino groups, of which one is protonated,

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and one next-nearest neighbor amino group, which must not be protonated (because it is adjacent to a protonated amino group). Correction of the pK value for diethylammonium ions (10.64)[21] for the effect of two β and one ∈ amino substituent and for protonation of one of the β substituents gives 5.46 as the pK that measures the basicity of the unprotonated secondary amino group in pSs^+. In other cases, such as that of the secondary amino group in pSt, we know how many next-nearest neighbor amino groups there are but not how many of them are protonated, and with the outside amino group in sSs, for example, we do not even know how many next-nearest neighbor amino groups there are. In such cases the number of next-nearest neighbors was taken to be half-way between the extreme possibilities (1 and 3 in the case of sSs), and unrestricted amino groups were assumed to be protonated to the same fractional extent as the polymer as a whole. Thus the correction for protonation of the two next-nearest neighbor amino groups of pSt in PEI-1800 is 2(0.68)(0.279). Combination of this correction with the pK value for diethylammonium ions and corrections for the nearest and next nearest neighbor amino groups gives a pK of 7.46 as a measure of the basicity of the secondary amino group in pSt. The fractions of the bonds to amino groups in the PEI's at pH 8.5 that are of the various types (pSt, Tp^+, etc.) were calculated by use of a set of simultaneous equations. A number of these were based on demands of symmetry and material balance as in the case of the equations used to solve for the similar fractions for the unprotonated polymer. Additional equations came from the definitions of the estimated pK values; one of the most simply estimated K values is equal to $[H^+]Pt/P^+t$. From the results it was possible to calculate the fraction of protonation of the PEI. The method described gave too small a calculated fraction of protonation for each PEI. Therefore the pK values were arbitrarily increased (by 0.62, 0.61, 0.29, and 0.01 in the cases of PEI-600, PEI-1200, PEI-1800, and PEI-50,000, respectively) until agreement was obtained.

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To estimate the relative reactivities of the various types of amino groups in the internal removal of deuterons from $Me_2CDCH{=}\overset{+}{N}H{-}$ groups their relative reactivities toward the N-methylisobutylidene-2-*d*-iminium ion were first estimated. The linearity of a plot (slope 0.84) of log *k* for attack of various bases on this ion *vs.* log *k* for their dedeuteration of isobutyraldehyde-2-*d* shows that isobutyraldehyde is a good model for its N-methyliminium ion in this reaction.[10] From the line in this plot, the value 93.4 M^{-1} for the equilibrium constant for the formation of N-isobutylidenemethylamine,[9,10] the value 3.57×10^{-11} *M* for the acidity constant of methylammonium ions,[10] and the value 1.32×10^{-7} *M* for the acidity constant of N-isobutylidenemethylammonium ions,[22]

(22) J. Hine, J. C. Craig, Jr., J. G. Underwood, II, and F. A. Via, *J. Amer. Chem. Soc.*, *92*, 5194 (1970).

we obtain eq 10, in which k_B is the rate constant for attack

$$\log k_B' = 0.84 \log k_B + 2.04 \quad (10)$$

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of a base on isobutyraldehyde-2-*d* and k_B' is the rate constant for attack of the same base on N-methylisobutylidene-2-*d*-iminium ions. From the observed values of k_B for methylamine,[23] dimethylamine,[6] trimethylamine,[6] diethylamine,

(23) The last part of the next to the last sentence of ref 10 should read "value of 1.55 or 2.52×10^{-8} M^{-1} sec^{-1}, depending on which C_a value is used." We used the average of these two values.

and triethylamine,[6] values of k_B' were calculated. The value for trimethylamine was 13 times that for triethylamine and the value for dimethylamine was twice that for diethylamine, presumably because of steric effects. We therefore assumed that k_B' for ethylamine is about 80% of that for methylamine and obtained a k_B' value of 0.49 M^{-1} sec^{-1}. Since Brønsted β values around 0.5 (0.49 for pyridines and 0.53 for phenoxide ions) have been observed for attack of bases on isobutyraldehyde-2-*d*,[6] the value for attack on the N-methyliminium ion was assumed to be 0.5 (0.84). We therefore assumed that the rate constants for all our primary amines would fall on a Brønsted line through the point for ethylamine, those for secondary amines on a line through the point for diethylamine, and those for tertiary amines on a line through the point for triethylamine, all these lines having slopes of 0.42. For each of the possible types of amino groups one of the Brønsted lines and the appropriate pK value, whose estimation has already been described, may be used to obtain a value of k_B'. From these results the average rate constant for the primary, secondary, and tertiary groups in each polymer

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were calculated. For example, we had five categories of unprotonated primary amino groups, those associated with Pt, pSs, pSt, pSs^+, and Ps^+ bonds. For these amino groups in PEI-600, k_B' values of 0.160, 0.296, 0.296, 0.353, and 0.0252 M^{-1} sec^{-1}, respectively, had been estimated. Since these five categories constitute 8.9, 1.3, 1.0, 0.3, and 1.3%, respectively, of the total primary amino groups in PEI-600, the average value of k_B' for all the primary amino groups (including the 87.2% that are protonated and therefore inactive) is 0.0217 M^{-1} sec^{-1}. The estimated average values of k_B' for the three kinds of amino groups in each of the four polymers are listed in Table VI. The differences in the estimated average reactivities of amino groups of a given type in the different polymers are seen to be much smaller than the differences in molecular weights. The values in Table VI refer to attack on the N-methyliminium ion, but we assumed that the *relative* values of k_B' will be the same for attack on any iminium ion

Table VI

Estimated Average Rate Constants for the Dedeuteration of $Me_2CDCH{=}\overset{+}{N}HMe$ by Amino Groups in PEI's[a]

Polyethylenimine	$10^5 k$, M^{-1} sec^{-1}		
	Primary	Secondary	Tertiary
PEI-600	21.7	24.5	3.83
PEI-1200	22.1	25.9	4.75
PEI-1800	28.7	23.8	4.46
PEI-50,000	34.0	22.9	4.23

[a] In water at 35°.

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derived from isobutyraldehyde-2-*d*. We then used the data on the effect of Dabco on rates of exchange in the presence of PEI's to correct for differences in the susceptibilities of complexed aldehyde to attack by bases as a function of the PEI to which the aldehyde is complexed.

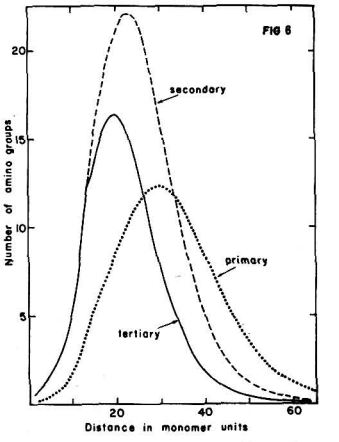

Figure 6.--Estimated numbers of primary, secondary, and tertiary amino groups at various distances from the average primary amino group in PEI-50,000.

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References and Notes

(1) (a) This investigation was supported in part by Public Health Service Grant GM 18593 from the National Institute of General Medical Sciences. Abstracted in part from the Ph.D. dissertation of R. L. Flachskam, Jr., 1973. Part XVI in the series Catalysis of α-Hydrogen Exchange; for part XV see (b) J.Hine, M. S. Cholod, and R. A. King, *J. Amer. Chem. Soc.*, **96**, 835 (1974). (c) National Science Foundation Trainee, 1968–1972.
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(3) J. Hine, E. F. Glod, R. E. Notari, F. E. Rogers, and F. C. Schmalstieg, *J. Amer. Chem. Soc.*, **95**, 2537 (1973).
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(14) Relative to the rate constant for attack by the average tertiary amino group.
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Tetracyclo[5.2.1.$0^{2,6}$.$0^{4,8}$]decane Ring System[1]

Irvin Rothberg,* James Fraser, Robert Garnick,[2] James C. King, Sheldon Kirsch, and Helene Skidanow[2]

Department of Chemistry, Rutgers University The State University of New Jersey, Newark, New Jersey 07102

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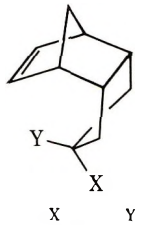
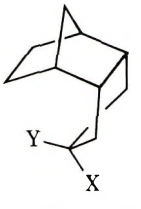
The tosylates of *endo*-5,6-trimethylene-2-norbornen-9-ol have been prepared and solvolyses carried out in acetic acid. This has led to *exo*-tetracyclo[5.2.1.$0^{2,6}$.$0^{4,8}$]decan-9-ol. Solvolysis of the tosylate of this compound leads to a degenerate rearrangement with migration of the C_4–C_8 bond.

Participation of π electrons in the solvolysis of norbornyl derivatives has led to new norbornyl-type ring systems in many cases.[3] We were interested in the solvolysis of *endo*-5,6-trimethylene-2-norbornen-9-yl tosylates (**2**, **4**) as a source of new ring systems.[4] Compound **3** was prepared by treatment of 4-hydroxycyclopentene with cyclopentadiene, oxidation of the product with chromium trioxide in pyridine, and reduction with lithium aluminum hydride.[5] Treatment of **4** with tetraethylammonium acetate and saponification of the resulting acetate yielded **1**. Hydrogenation of **1** and **3** led to the known saturated alcohols,[6] which served to prove the configuration at C_9 was well as confirm the structure of the ring skeleton. Rate data for the acetolysis of **2** and **4** are given in Table I.



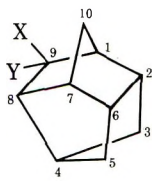


	X	Y
1	OH	H
2	OTos	H
3	H	OH
4	H	OTos
8	Cl	H

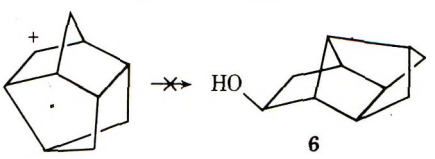
	X	Y
2a	OTos	H
4a	H	OTos

The exo/endo rate ratio of 27 at 25° is probably indicative of a small rate enhancement of the exo isomer due to participation of the π electrons. An alternate explanation of steric hindrance to ionization[6] of the endo isomer **4** seems unreasonable. The analogous saturated tosylates **2a** and **4a** exhibit an exo/endo acetolysis rate ratio of 0.62 at 25°.[6] It does not appear likely that introduction of the double bond would drastically change the relative rates for steric reasons. The rate for acetolysis of the saturated endo tosylate[6] **4a** is 7.19×10^{-7} sec^{-1}, while that of the unsaturated is 2.49×10^{-7} sec^{-1}. The decrease in rate of the unsaturated endo tosylate **4** compared to the saturated could be largely attributed to the electron-withdrawing character of the double bond. The exo-unsaturated tosylate **2** exhibits a rate of 66.4×10^{-7} sec^{-1}, while the saturated analog **2a** has a rate of 4.48×10^{-7} sec^{-1}. The fact that the unsaturated tosylate solvolyzes 15 times faster than the saturated is most reasonably explained by participation of the double bond.

Both exo and endo isomers gave excellent straight lines for first-order kinetics to over 80% of reaction. Examination of the products from acetolysis at 75° shows a 2:1 ratio of acetate to olefinic products from both **2** and **4**. Dicyclopentadiene was the only olefinic product. The acetate from **4** after saponification showed 70% of **1** and 30% of rearranged alcohol **5**. The product resulting from sapon-



	X	Y
5	OH	H
9	OTos	H
10	H	OH
11	H	OTos
13	D	OH

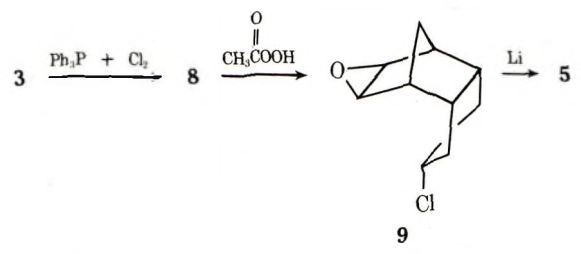


7 **6**

ification of the acetate derived from **2** was greater than 95% *exo*-tetracyclo[5.2.1.0^{2,6}.0^{4,8}]decan-9-ol (**5**). We did not find any of **6** which would have resulted from Wagner-Meerwein rearrangement of ion **7**.

Structure **5** was proven by an alternate synthesis and by its chemical and physical properties. The alternate synthesis is outlined in Chart I.

Chart I



Treatment of **3** with thionyl chloride led to a mixture of chlorides, which consisted of about 50% of rearranged chloride resulting from participation of the double bond. Reaction with triphenylphosphine and chlorine gave a very clean product with no signs of rearrangement. Treatment of epoxide **9** with lithium dispersion succeeded in closing the ring.[7]

The nmr spectrum of **5** is very suggestive of the structure. The methine proton of **5** shows a broadened singlet with a width at half-height of 4 Hz. The approximate dihedral angles that the methine proton makes with adjacent protons on C_1 and C_8 are 70 and 90°, respectively, leading to calculated[8] coupling constants of less than 1 Hz in both cases. This is very similar to the spectrum reported for *exo*-tricyclo[3.2.1.0^{3,6}]octan-2-ol.[7a] The epimeric alcohol **10** was prepared by chromic acid oxidation of **5** to ketone **12** and reduction with lithium aluminum hydride. The nmr spectrum of **10** and **11** showed a broadened doublet (J = 6.5 Hz) for the methine proton. The methine hydrogen makes approximate dihedral angles with the C_1 and C_8 protons of 60 and 27°, which would lead to calculated couplings of less than 2 and 6.5 Hz, respectively. One interesting feature of the nmr spectrum of **5** and **10** is the chemical shift for the methine protons. The endo methine proton of **5** is at δ 4.0 while the exo methine proton of **10** is at δ 3.67. This is the opposite of what is usually found in norbornyl systems; the exo proton is in the usual case downfield from the endo proton.[9] This same reversal of the relative positions of the exo and endo methine protons is also found in the tosylates and *p*-nitrobenzoates. This resembles the type of behavior found in the highly hindered half-cage and related compounds.[9]

Relative rates of chromic acid oxidation of **5** and **10** were also highly indicative of the structure. In 40% aqueous acetic acid at 25° (1.79×10^{-3} M in chromic acid and 2.68×10^{-3} M in alcohol) the rates of oxidation were 3.50×10^{-3} l. mol^{-1} sec^{-1} for **5** and 0.27 l. mol^{-1} sec^{-1} for **10**. The endo alcohol is being oxidized to ketone faster than the exo by a factor of 73, a $\Delta\Delta F^*$ difference of 2.5 kcal/mol. The rate ratio is reasonably similar to that found for the *endo*-5,6-trimethylene-2-norbornanols.[10] This is to be expected, since models show that the steric interactions of the endo alcohols seem to be approximately similar.

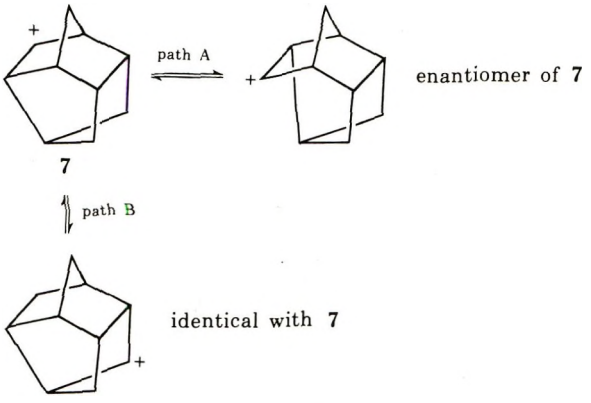
The kinetic results of acetolysis of tosylates **9** and **11** have previously[1] been reported, exhibiting an exo/endo rate ratio of 0.33 at 25°. The nmr spectrum of tosylate **9** shows essentially an identical pattern for the methine proton as was present for the alcohol precursor **5**, a broadened singlet with a width at half-height of 5 Hz. Alcohol, which showed no signs of skeletal rearrangement,[11] could be regenerated from **9** in 85% yield by treatment with sodium and naphthalene in tetrahydrofuran.[12,13]

Table I
Titrimetric Acetolysis Rates of Tosylates (Solutions 0.013 M in Tosylate and 0.015 M in Sodium Acetate)

Tosylate	Temp, °C	$k \times 10^7$, sec^{-1}	ΔH^*, kcal/mol	ΔS^*, eu (25°)
2	50.0	1640 ± 19	24.0	−1.8
	25.0	66.4 ± 1.3		
4	75.0	1700 ± 32	26.3	−0.80
	50.0	83.8 ± 1.2		
	25 (calcd)	2.49		
Cyclopentyl	25.0	17.9 ± 0.34		

The product of acetolyses from both **9** and **11** after saponification is largely **5**. The yield of **5** by vpc using dodecyl alcohol as an internal standard was 83% from **9** and 85% from **11** with less than 5% of **10** present in both cases. Samples collected by preparative vpc were identical with authentic alcohol. There were 8–10% of unidentified alcohols from both tosylate solvolyses.

The possibility of degenerate rearrangements exists. These could involve C_4–C_8 bond migration (path A), migration of endo 3-hydride to C_9 (path B), and possibly other more complex pathways.



These were investigated as follows. Ketone **12** was reduced with lithium aluminum deuteride to give **13**. Nmr spectroscopy showed a complete absence of methine proton and mass spectroscopy indicated a greater than 98.4% incorporation of deuterium at C_9. Solvolysis of the tosylate in acetic acid with sodium acetate and saponification led to exo alcohol whose nmr spectrum showed 0.25 ± 0.03 methine protons. Mass spectroscopy showed that all of the deuterium was still in the molecule. Preparation of tosylate from this sample of exo alcohol, acetolysis, and saponification led to exo alcohol which showed essentially no loss of deuterium by mass spectroscopy, but the methine proton by nmr was 0.48 ± 0.04. Preparation of tosylate from this alcohol, acetolysis, and saponification gave exo alcohol in which there was no further change. Treatment of the tosylate of **13** with tetraethylammonium acetate gave essentially the same result as acetolysis.

The data indicate that in the solvolysis of endo tosylate from **13** attack of nucleophile occurs before complete equilibration takes place. However, the exo isomer **9** solvolyzes with complete equilibration of **7** or formation of a delocalized ion from **7** before attack of nucleophile can occur. Clearly, **9** is solvolyzing with a degenerate rearrangement taking place by path A, path B, or some other pathway leading to the same results.

Oxidation of exo alcohol with 0.48 methine protons led to ketone that had lost 49.6% of its deuterium content

(mass spectroscopy). A combination of both path A and path B can be excluded at this point because less than 49.6% of deuterium would have been lost if both pathways were involved. Lithium aluminum hydride reduction of this ketone led to endo alcohol whose nmr spectrum permitted determination of the rearrangement path. If path A were the reaction process there should be approximately 50% of deuterium at C_8. The nmr spectrum should show a doublet for the methine hydrogen with a broadened singlet superimposed in the middle of the doublet. The doublet and singlet should be in a 1:1 ratio.

Path B should lead to product which should show a doublet for the methine hydrogen, since there should be no deuterium at C_8. Experimentally the nmr spectrum of the endo alcohol shows quite clearly a broadened singlet superimposed in the middle of a doublet estimated to be in a 1:1 ratio. Path A is the predominant process by which the degenerate rearrangement takes place.

Experimental Section

Melting points were determined in capillary tubes with a Thomas-Hoover apparatus and are uncorrected. Glpc was carried out on a Hewlett-Packard 5750 gas chromatograph with flame ionization detectors. Analytical measurements were on 10 ft × 0.125 in. columns and preparative work was on 10 ft × 0.25 in columns. The columns used were 10% of stationary phase on 60–80 mesh Chromosorb W. The stationary phases were UCW-98, Carbowax 20M, FFAP, and UCON LB-550X. Nmr spectra were recorded on a Varian A-60 instrument using deuteriochloroform as solvent and tetramethylsilane as internal standard. The spectra are reported in δ units as parts per million downfield from TMS. Ir spectra were measured with a Beckman IR-10 instrument.

All tosylates were prepared by treatment of alcohol with a 100% excess of *p*-toluenesulfonyl chloride in pyridine at 0° for 2 days and worked up in the usual way. Recrystallization was from ether–pentane.

Impure *endo*-5,6-Trimethylene-2-norbornen-*exo*-9-ol (1). The procedure of Webb[5] was followed. This involved heating of equimolar quantities of 4-hydroxycyclopentene[14] and freshly cracked cyclopentadiene at 180° for 18 hr. This procedure in our hands gave after distillation [82–94° (2 mm)] material with about 50% of impurities resulting from higher molecular weight Diels–Alder reaction products of cyclopentadiene, as well as *exo*-5,6-trimethylene-2-norbornen-9-ol as an impurity. Glpc (FFAP) showed 45% of **1**, 8% of *exo*-5,6-trimethylene-2-norbornen-9-ol, and 47% of cyclopentadiene adducts. This material proved to be intractable in further synthetic work and required purification. A crude distilled mixture (15.0 g) was dissolved in 200 ml of ether and extracted with 50-ml portions of 10% silver nitrate solution until glpc showed essentially no alcohol in the ether (eight extractions). To the aqueous silver nitrate at 0° was added 100 ml of ammonium hydroxide. The ammonia solution was extracted with ether, and the ether was dried (magnesium sulfate) and evaporated to give 7.0 g of product, which by glpc consisted of 81% of **1**, 17% of its isomer, and 2% of cyclopentadiene adducts.

***endo*-5,6-Trimethylene-2-norbornen-*endo*-9-ol (3).** Impure **1** (containing only **1** and its isomer) was oxidized to ketone with chromium trioxide in pyridine and reduced with lithium aluminum hydride, according to the procedure of Webb,[5] to give **3**: mp 64–65° (lit.[5] mp 65.5–66.5°); ir 3650, 3350 (broad), 3060 cm^{-1}; nmr δ 6.18 (2, t, J = 2 Hz), 4.02 (1, m), 2.7 (2, m), 2.3 (2, broad m), 2.0–0.97 (6, complex m).

Anal. Calcd for $C_{10}H_{14}O$: C, 79.96; H, 9.39. Found: C, 79.72; H, 9.30.

Hydrogenation of 3. Compound **3** (50 mg) was hydrogenated in ethanol using 5% p[illegible]n on charcoal to give after work-up 40 mg (79%) of *endo*-[illegible]ethylene-*endo*-9-norbornanol identical after recrystallizati[illegible]ther–pentane) with authentic material (ir, glpc, melting poi[illegible]ixture melting point).

Tosylate 4 had mp 83–85°.

Anal. Calcd for $C_{17}H_{20}SO_3$: C, 67.08; H, 6.62; S, 10.53. Found: C, 67.38; H, 6.42; S, 10.33.

***endo*-5,6-Trimethylene-2-norbornen-*exo*-9-ol (1).** Tosylate **4** (1.6 g, 5.3 mmol) and 3.0 g of tetraethylammonium acetate[15] were dissolved in 30 ml of acetone and refluxed for 24 hr. The acetone distilled off and the residue was added to 100 ml of water and extracted with ether. The ether was dried (magnesium sulfate) and evaporated, and the residue was refluxed for 1 hr with 1 g of potassium hydroxide in methanol. The reaction mixture was worked up in the usual way to give 450 mg (57%) of alcohol **1**. Glpc (FFAP) showed a purity of 98%. An analytical sample was obtained by recrystallization from ether–pentane: mp 69.5–70.0°; ir 3650, 3350 (broad), 3075, 1660 cm^{-1}; nmr δ 6.10 (2, t, J = 2 Hz), 4.25 (1, broad m), 2.7 (4, broad m), 1.8–0.8 (6, complex m).

Anal. Calcd for $C_{10}H_{14}O$: C, 79.96; H, 9.39. Found: C, 79.80; H, 9.28.

Tosylate 2 had mp 59–61°.

Anal. Calcd for $C_{17}H_{20}SO_3$: C, 67.08; H, 6.62; S, 10.53. Found: C, 67.25; H, 6.61; S, 10.38.

Hydrogenation of 1. Compound **1** (40 mg) was hydrogenated in 81% yield in the same way as described for **3** to give *endo*-5,6-trimethylene-*exo*-9-norbornanol identical with authentic material.

***exo*-Tetracyclo[5.2.1.$0^{2,6}$.$0^{4,8}$]decan-9-ol (5) (Preparative Scale).** Tosylate (21.1 g) from impure **1** (containing 80% **1** and 20% of *exo*-5,6-trimethylene-2-norbornen-9-ol) was made 0.5 *M* in acetic acid which was 1.0 *M* in sodium acetate. The reaction mixture was heated at 50° for 24 hr, then poured into water and extracted with pentane. The pentane was washed with sodium carbonate solution, dried, and evaporated. The residue was dissolved in 100 ml of methanol (3 g of potassium hydroxide added), refluxed for 1 hour, and worked up in the usual way. An ether solution showed 80% of **5** and 20% of *exo*-5,6-trimethylene-2-norbornen-9-ol. The ether solution was extracted with 10% aqueous silver nitrate until glpc showed greater than 95% of **5**. The ether solution was then dried and evaporated, and the residue was chromatographed on alumina using gradient elution (pentane–ether) to give 4.0 g of product. An analytical sample was prepared by recrystallization from ether–pentane: mp 179–180°; ir (CCl_4) 3650, 3400 (broad), 1080 cm^{-1}; nmr δ 4.00 (1, s, CH methine), 2.2 (6, m, CH tertiary), 1.9–0.8 (6, m, CH_2); mass spectrum mol wt calcd 150, found 150.

Anal. Calcd for $C_{10}H_{14}O$: C, 79.96; H, 9.39. Found: C, 79.90; H, 9.25.

***p*-Nitrobenzoate Derivative of 5** had mp 102–103°.

Anal. Calcd for $C_{17}H_{17}NO_4$: C, 68.20; H, 5.72; N, 4.68. Found: C, 68.07; H, 5.80; N, 4.86.

***exo*-Tetracyclo[5.2.1.$0^{2,6}$.$0^{4,8}$]dec-9-yl Tosylate (9)** had mp 80–81°; ir 1170, 1360 cm^{-1}; nmr δ 7.6 (4, q, center of an AB pattern, CH aromatic), 4.80 (1, s, CH methine), 2.46 (3, s, CH_3), 2.3 (6, m, CH tertiary), 2.0–0.8 (6, m, CH_2).

Anal. Calcd for $C_{17}H_{20}O_3S$: C, 67.08; H, 6.62; S, 10.53. Found: C, 67.38; H, 6.88; S, 10.53.

Reaction of Tosylate 9 with Sodium. Sodium (46 mg, 2.0 mmol) was added, with stirring, to 270 mg (21 mmol) of naphthalene in 7 ml of tetrahydrofuran which had been flushed with nitrogen and then kept under a static pressure of nitrogen. After the solution had become dark green and all traces of sodium had disappeared (1 hr), it was cooled to −78° and 100 mg of tosylate **9** in 5 ml of tetrahydrofuran was added. The solution immediately became colorless and was stirred for an additional 10 min. Water was added and the solution was poured into saturated sodium chloride. The layers were separated and the aqueous portion was extracted with ether. Examination by glpc (UCW-98) with an external standard showed an 85% yield of tetracyclo-[5.2.1.$0^{2,6}$.$0^{4,8}$]decan-9-ols. A sample collected by preparative glpc showed by ir spectroscopy 85% of **5** and 15% of **10**. Compound **10** had an absorption at 1110 cm^{-1} that was completely absent in **5**. With the use of standards, a quantitative evaluation of the relative amounts of **5** and **10** could be made. Glpc on five columns would not separate the isomers.

Tetracyclo[5.2.1.$0^{2,6}$.$0^{4,8}$]decan-9-one (12). Alcohol **5** was oxidized essentially according to the procedure of Brown, Garg, and Liu[16] to give a 96% yield of ketone, 94% pure by glpc. Chromatography on alumina, using gradient elution (pentane–ether), and recrystallization (pentane) gave an analytical sample >99% pure, mp 184–185°, ir 1753 cm^{-1}.

Anal. Calcd for $C_{10}H_{12}O$: C, 81.04; H, 8.16. Found: C, 80.82; H, 7.95.

***endo*-Tetracyclo[5.2.1.$0^{2,6}$.$0^{4,8}$]decan-9-ol (10).** Ketone **12** was reduced with lithium aluminum hydride in the usual way to give a 98% yield of alcohol, 97% pure. Recrystallization (ether–pentane) gave an analytical sample: mp 209–210°; ir (CCl_4) 3650, 3500 (broad), 1110, 1080 cm^{-1}; nmr δ 3.67 (1, d, J = 6.5 Hz, CH methine), 2.55 (1, d, J = 11 Hz, CH endo C_3), 2.17 (6, m, CH tertiary), 1.6–0.85 (5, complex m, CH_2).

Anal. Calcd for $C_{10}H_{14}O$: C, 79.96; H, 9.39. Found: C, 80.19; H, 9.22.

p-**Nitrobenzoate Derivative of 10** had mp 125–126°.

Anal. Calcd for $C_{17}H_{17}NO_4$: C, 68.20; H, 5.72; N, 4.68. Found: C, 68.02; H, 5.87; N, 4.95.

Tosylate 11 had mp 59–61°; nmr δ 7.69 (4, center AB quartet, J = 8 Hz), 4.30 (1, d, J = 6 Hz, CH methine), 2.50 (3, s, CH_3), 2.22 (7, complex m, CH tertiary and endo C_3 H), 1.8–0.9 (5, complex m, CH_2).

Anal. Calcd for $C_{17}H_{20}O_3S$: C, 67.08; H, 6.62; S, 10.53. Found: C, 67.48; H, 6.88; S, 10.33.

endo-**5,6-Trimethylene-***exo*-**9-chloro-2-norbornene (8).** Triphenylphosphine (3.74 g, 14.3 mmol) was dissolved in 10 ml of carbon tetrachloride and chlorine was bubbled in with stirring. A solid immediately precipitated. This became an oil as addition of chlorine continued. The solvent was removed by rotary evaporation and the residue was dissolved in 10 ml of acetonitrile (distilled from phosphorus pentoxide). The solvent was again evaporated off to remove chlorine. The residue was triturated with anhydrous ether, the ether was poured off, and the residue was dried at 2 mm for 30 min. The residue was dissolved in 10 ml of acetonitrile and a solution of 1.0 g (6.65 mmol) of **3** and 0.55 ml (6.65 mmol) of pyridine in 5 ml of acetonitrile was added at 0°. After addition the reaction was stirred for 10 min, allowed to warm to room temperature, and stirred for 1 hr. The solvent was removed at reduced pressure and the residue was triturated well with pentane. The pentane was washed with water, dried, and evaporated, and the residue was distilled to give 0.45 g (2.7 mmol, 40%) of oily product: bp 50–53° (0.3 mm); n^{29}D 1.5174; ir 3060, 1650, 730 cm^{-1}; nmr δ 6.18 (2, t, J = 1.5 Hz, CH vinyl), 4.47 (1, m, CH methine), 3.0–2.82 (4, m, CH tertiary), 2.6–1.3 (6, m, CH_2).

Anal. Calcd for $C_{10}H_{13}Cl$: C, 71.20; H, 7.77; Cl, 21.02. Found: C, 71.04; H, 7.95; Cl, 21.30.

exo-**4-Chloro-9-oxatetracyclo[5.3.1.$0^{2,6}$.$0^{8,10}$]undecane (9).** Chloride **8** (0.330 g, 1.97 mmol) was dissolved in 7 ml of chloroform and cooled to −5°, and 1.60 ml of 40% peracetic acid buffered with 0.30 g of sodium acetate was added over 2 min. The solution was kept at 0°, stirred for 3 hr, and then worked up in the usual way to give 0.30 g of white solid. Recrystallization (pentane) gave 170 mg of analytical material: mp 76–77°; ir 3040, 1270, 910, 840 cm^{-1}; nmr δ 4.56 (1, m, CH methine), 3.20 (2, s, CH epoxide), 2.87–2.51 (4, m, CH tertiary), 2.05–0.85 (6, m, CH_2).

Anal. Calcd for $C_{10}H_{13}OCl$: C, 65.03; H, 7.09; Cl, 19.20. Found: C, 65.35; H, 7.35; Cl, 19.34.

Reaction of Epoxide 9 with Lithium.[7] A three-neck flask was fitted with a gas inlet tube, a condenser, and an injection port covered with a serum stopple and connected to a mercury bubbler. The apparatus was flame dried with a helium stream and to the flask was added 0.40 g (0.036 mol) of lithium dispersion (50% dispersion in hexane) and 5 ml of tetrahydrofuran. A solution of 80 mg (0.43 mmol) of chloro epoxide **9** in 5 ml of tetrahydrofuran was added and the mixture was stirred and refluxed for 45 hr under a static pressure of helium. The work-up was carried out, essentially as described by Sauers,[7] to give a 64% yield of product (glpc with an external standard). Preparative glpc (UCW-98) yielded a sample that was identical with authentic material (ir, melting point, mixture melting point, nmr, glpc).

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Registry No.—**1**, 50506-62-2; **2**, 50506-63-3; **3**, 50506-64-4; **4**, 50506-65-5; **5**, 28029-30-3; **5** *p*-nitrobenzoate, 50506-67-7; **8**, 50506-68-8; **9**, 27743-80-2; **10**, 27786-03-4; **10** *p*-nitrobenzoate, 50506-71-3; **11**, 27743-81-3; **12**, 27852-55-7; *exo*-4-chloro-9-oxatetracyclo[5.3.1.$0^{2,6}$.$0^{8,10}$]undecane, 50506-74-6; *p*-toluenesulfonyl chloride, 98-59-9; 4-hydroxycyclopentene, 14320-38-8; cyclopentadiene, 542-92-7.

References and Notes

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Critical Dependence of the Stability of an Overcrowded Benzylic Carbocation on the Aromatic Ring Substituent. Substituent and Solvent Effects on the Ring Opening of 1-Aryl-Substituted Epoxides. 1-(*p*-Methoxyphenyl)-2,2-dimethyl-7-oxabicyclo[4.1.0]heptane

Aldo Balsamo, Paolo Crotti, Bruno Macchia, and Franco Macchia*

Istituti di Chimica Organica e Chimica Farmaceutica, Università di Pisa, 56100 Pisa, Italy

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The reactions of 1-(*p*-methoxyphenyl)-2,2-dimethyl-7-oxabicyclo[4.1.0]heptane (**5**) under acidic conditions have been studied and compared with the analogous ones of the corresponding nonmethylated epoxide **12** and of the parent epoxide without substituent on the aryl group **13**. Relevant differences appear both in regio- and stereoselectivity and in the amount of rearranged products. The results can be explained on the basis of the primary steric effect of the two methyl groups and of the balance between the electronic effect of the strongly electron-donating aryl group and the secondary steric effect of the methyl groups which prevents coplanarity of the aryl group and the intermediate benzylic carbenium ion. The reactions of epoxide **5** with trichloroacetic acid in low polarity aprotic solvents showed a marked dependence on solvent which can be ascribed to a nucleophilic assistance in the development of the positive charge on the benzylic carbon.

The ring opening of aryl-substituted oxiranes under acidic conditions proceeds through an intermediate or a transition state with a high degree of development of positive charge on carbon. The regio- and stereoselectivity of these ring openings and the amount of rearranged products are strictly related not only to the reaction conditions, but also to the capability of the π system to stabilize the electron-deficient center.[1] It has, in fact, been shown[1a,d,2] that the syn stereoselectivity in the acid-catalyzed hydrolysis of 1-aryl-1,2-epoxycyclohexanes almost parallels the rate of solvolysis of the corresponding 1-aryldimethylcarbinyl chlorides[3] (SN1 reaction type), that is the stabilities of the related carbocations. Furthermore, in the reactions with acids an electron-donating substituent on the aryl moiety of aryloxiranes increases the percentage of rearranged products.[1d] The steric effects of the two methyl groups in 6,6-dimethyl-1-phenylcyclohexene oxide (**13**) prevents coplanarity of the phenyl group with the carbenium ion arising from the protonated epoxide, thus reducing in a striking way the tendency of this epoxide towards syn opening and causing a lower regioselectivity in the ring opening with respect to the nonmethylated epoxide.[1c]

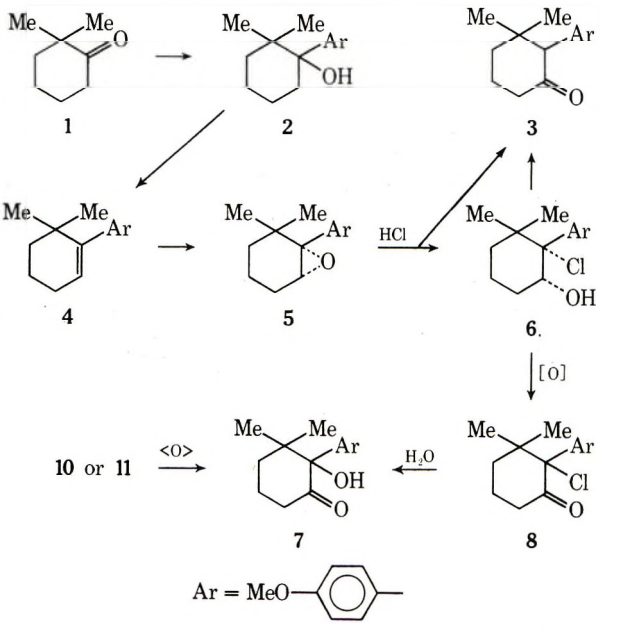
All these results imply that the syn addition products involve a benzylic carbocation in a tight ion pair which collapses to give the adduct.[1,2] Therefore aryl-substituted epoxides offer a useful tool for a study of the reactivities of carbocations by examining the stereo- and regiochemistry of their reactions with different acids under different conditions.

We have now extended our work on oxiranes to 1-(*p*-methoxyphenyl)-2,2-dimethyl-7-oxabicyclo[4.1.0]heptane (**5**) in order to get more information on the transmission of electronic effects of a strongly donating aryl group to a carbocation through a single bond in a case where the geometry is such as to severely hinder coplanarity.

Results

Reaction of 2,2-dimethylcyclohexanone (**1**) with *p*-methoxyphenyllithium gave good yield of alcohol **2**, which was dehydrated to olefin **4** (Scheme I). Epoxidation of **4** yielded **5**. The reaction of **5** with anhydrous HCl in benzene gave a mixture of the ketone **3** and of the cis chlorohydrin **6**. No evidence for the formation of trans halohydrins was found. Treatment with alkali transformed **6** into the ketone **3**. Chlorohydrin **6** on chromic oxidation in the two-phase benzene–water system gave the chloro ketone **8**. However oxidation of **6**, under the usual homogeneous Jones conditions,[4] gave, after short reaction times, a mixture of **6** and of the ketol **7**; longer reaction times produced practically pure **7**. The ketol **7** was also formed by oxidation of the diols **10** and **11** with Jones reagent in acetone. Separate experiments indicated that the replacement of chlorine by hydroxyl takes place at the chloro ketone **8** rather than at the chlorohydrin **6** stage.

Scheme I



The reaction of **5** with trichloroacetic acid in benzene afforded a mixture of **3** and of the cis trichloroacetate **9** which was hydrolyzed to the cis diol **11** (Scheme II). The secondary ester **9** is very probably not the primary product of the reaction, the tertiary ester being initially formed and rapidly transformed into the more stable secondary one **9** through an acyl shift.[1a,5] The reaction of **5** with aqueous sulfuric acid gave a mixture of the ketone **3** and of the diols **10** and **11**. Table I reports the percentages of products resulting from the acid hydrolysis of **5** and of the diols **10** and **11**. Table I reports the percentained from the reaction of **5** with trichloroacetic acid in different solvents.

Table I
Products of Trichloroacetolysis and Hydrolysis of 5

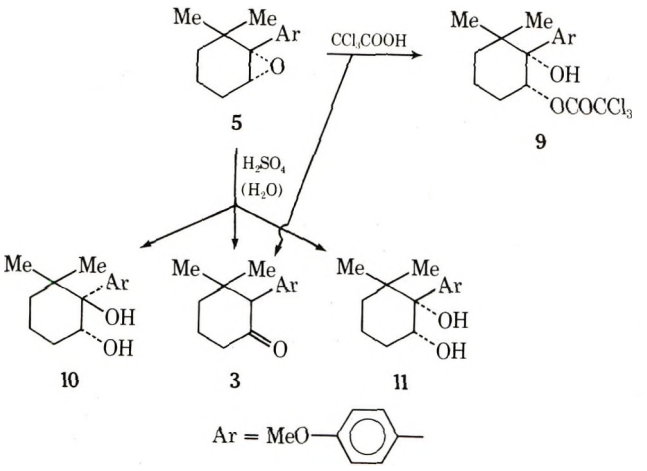
Solvent	Acid	% 3	% 11	% 10
Cyclohexane	CCl_3COOH	54.5	44	1.5
CCl_4	CCl_3COOH	55	44	1
Benzene	CCl_3COOH	63.5	35.5	<1
$CHCl_3$	CCl_3COOH	76.5	23	<0.5
CH_2Cl_2	CCl_3COOH	93.9	6	<0.1
H_2O	H_2SO_4	17.5	35	47.5

Table II
Nmr Data and Wavenumber of OH Protons

	Nmr δ, ppm			Ir, cm^{-1}	
Compd	CHX ($W_{1/2}$, Hz)	CH_3		OH free	OH···X
6	4.53 (16.5)[a]	1.01	0.82		3581[c]
9	5.77 (17.0)[b]	0.88	0.85		3596[b]
10	3.95 (17)[a,d]	1.12	0.66	3625[e]	3576[a,f]
11	4.38 (16.0)[a]	0.80		3620[e]	3583[f] 3558[a]

[a] X = OH. [b] X = $OCOCCl_3$. [c] X = Cl. [d] Approximate values due to the partial overlapping of the signal with that one of the methoxy group. [e] Weak band. [f] X = aryl.

Scheme II



While the structure and configuration of the chlorohydrin **6** can be defined by its reactions (conversion into **3** by treatment with alkali and oxidation to the chloro ketone **8**), those of compounds **9**, **10**, and **11** have been demonstrated, and that of **6** confirmed by nmr spectroscopy and by ir studies in 3-μ range (Table II). The chemical shifts and the half-bandwidths of the methinyl protons β to the *p*-methoxyphenyl group[1a,c,d,5-7] of the cis compounds **6**, **9**, and **11** are consistent, respectively, with their natures and with their axial positions. Furthermore the ir spectra of these compounds show the presence of strong OH···X hydrogen bonds,[1c,d,8] in accordance with their structures and configurations. These data indicate for the cis compounds a configuration with the aryl group in equatorial position. The presence in the ir spectrum of the trans diol **10** of OH···O interactions[1c,8] and the half-bandwidth of the proton α to the hydroxyl group[1a,c,5,7] suggests for this compound a twist conformation or one in which the aryl group occupies an axial position.[1c] Moreover, the ir and nmr spectra of these compounds are fully consistent with the corresponding spectra of the analogous derivatives without substituent on the phenyl group.[1c]

Discussion

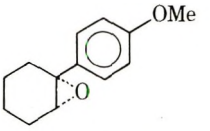
The results obtained in the ring opening of the epoxide **5** with acid appear quite interesting when compared with the ones relative to the analogous reactions of the non-6-methylated epoxide **12**[1d] and of the parent epoxide **13**

Table III
Product Compositions for the Trichloroacetolysis and Hydrolysis of Epoxides 5, 12, and 13

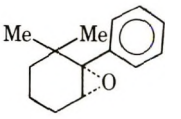
Epoxide	Acid	Solvent	Syn adduct	Anti adduct	Rearrt products
5	H_2SO_4	H_2O	35	47.5	17.5
12[a]	H_2SO_4	H_2O	93	3.8	3.2
13[b]	H_2SO_4	H_2O	0.7	99	0.3
5	CCl_3COOH	Benzene	35.5	<1	63.5
12[a]	CCl_3COOH	Benzene	68	0	32
13[b]	CCl_3COOH	Benzene	6	78	16

[a] Reference 1d. [b] Reference 1c.

without substituent on the aryl group[1] (Table III). Previous results[1c] clearly indicated that in **13** the secondary steric effect of the methyl groups, preventing overlap between the aryl π system with the developing p orbital on the benzylic carbon atom, strongly reduced the carbocationic character of the intermediate stage, as shown by the high percentages of anti adducts, and particularly by the fact that the reaction of **13** with HCl gave 50% of the anti-Markovnikov anti adduct, which can arise only from a reaction with a high degree of A-2 character. On the other hand, in the case of epoxide **12**[1d] the unhindered nature of the aryl group and its strongly electron-donating properties favor the development of the benzylic carbocation and cause practically exclusive formation of the syn adducts through an ion-pair intermediate.



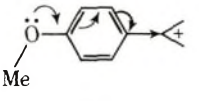
12



13

The epoxide **5** presents an intermediate situation since it possesses both features, having a hindered, but strongly activating aryl group. These features are clearly evident in the results of its ring-opening reactions. The addition of HCl (and presumably also of CCl_3COOH and of H_2O) is entirely regioselective in the Markovnikov sense. A high syn stereoselectivity is observed in the reactions of **5** with HCl and CCl_3COOH, but not in the hydrolytic opening.

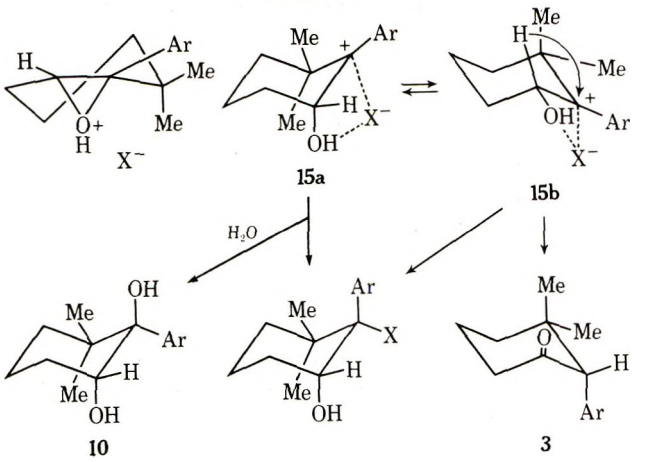
These results can be explained by assuming that the electronic effect of the *p*-methoxy substituent in **5** counterbalances the reduced stabilization of the intermediate benzylic carbocation and the primary steric effects of the two methyl groups[1c] making the attack of the nucleophile on the benzylic carbon of **5** exclusive. Furthermore the high syn stereoselectivity in the ring opening of **5** with CCl_3COOH shows that a discrete cationic charge has developed on the benzylic carbon atom in such a way as to permit the ion-pair mechanism (**15a,b**) to operate in an efficient manner.[1,2,5,6] Evidently the mesomeric electron-releasing effects of the methoxy substituent prevail over the opposite inductive effect and can be transmitted to the benzylic carbon atom notwithstanding the undoubtedly serious inhibition of coplanarity of the benzylic carbocation with the aryl group. The stabilization of the cationic intermediate could result from a residual overlapping of the orbitals, or from an inductomeric electron release,[1c] as shown in **14**.



14

The lack of stereoselectivity in the reaction of **5** with water is probably due to the fact that the collapse of the

Scheme III



intimate ion pair **15a** is hindered by the primary steric effect of the axial OH and methyl, and in the presence of large excess of water molecules attack by H_2O rather than by X^- takes place; this attack occurs preferentially on the trans side because the mentioned steric effect (Scheme III).

The fact that **5** gives higher amounts of rearranged products than **12** and **13** can also be taken as a proof of this mechanistic proposal. It is known that the conversion of epoxides into carbonylic compounds involves transition states with a high carbocation character.[1b,9,10] As a matter of fact **5** affords more rearranged products than epoxide **13** which gives the least stable benzylic carbocation, but also more than **12** which should give the most stable cation, in apparent contrast with the premise. However, the primary steric effect of the two methyl groups in **5** retards the attack by an external nucleophile rendering the nucleophilic rearrangement more competitive. It can also be assumed that the syn interaction between OH and methyl in the ion **15a** facilitates conversion into the conformer **15b**, which is ideally disposed for the 1,2-hydride shift giving the ketone **3** (see Scheme III). The much lower amount of ketone **3** obtained in the hydrolytic reaction can again be explained on the basis of the large availability of nucleophilic molecules that can attack the ion **15a** before it passes to **15b** or, in any case, before the rearrangement stage.

A further point of interest is given by the reactions of **5** with trichloroacetic acid in several aprotic solvents (Table I). While the syn stereoselectivity of the ring opening of **5** is practically complete in all solvents, the amount of ketone **3** varies considerably. This solvent effect can be explained by assuming[1a,c] that the intermediate positive charge can be stabilized through a nucleophilic assistance by the nonprotic solvent. In fact the amount of ketone **3** is low in a solvent like cyclohexane which has very little solvating power. In chlorinated solvents the center of charge can be solvated by the external electrons of the chlorine atoms;[1a,c] the solvation effect will depend in a stringent way on the electron density on the chlorine and therefore on the order of polarization of the C–Cl bond in the solvent which is $CH_2Cl_2 > CHCl_3 > CCl_4$, and this is in accordance with the results. Also benzene can provide such an assistance by its π-electron system[1a,c,11,12] thus facilitating the formation of ketone **3**.

Experimental Section

Melting points were determined on a Kofler apparatus and are uncorrected. Ir spectra for comparison between compounds were taken on paraffin oil mulls on a Perkin-Elmer Infracord Model 137 and those for the determination of OH stretching bands with a Perkin-Elmer Model 257 double beam grating spectrophotometer in dried (P_2O_5) CCl_4, using the indene band at 3110 cm^{-1} as a calibration standard; a quartz cell of 2-cm optical length was employed, and the concentration of the solutions was 5×10^{-3} *M* or lower to prevent intramolecular association. Nmr spectra were determined in an ~10% $CDCl_3$ solution with a JEOL C 60 HL spectrometer using TMS as an internal standard. Glpc were run on a Carlo Erba Fractovap GV apparatus with a flame ionization detector, using a dual column system with glass columns (3 mm × 2 m) packed with 1% neopentyl glycol succinate on 80–100 mesh silanized Chromosorb W; column temperature 165°, evaporator temperature 200°, detector temperature 200°; nitrogen flow 40 ml/min; retention time for **3**, 5 min, **11**, 10 min, **10**, 17 min. The ratio of chlorohydrin **6** and ketone **3** was roughly estimated through the nmr signals of the two methyl groups adjacent the phenyl group. Analytical (0.25-mm layer) and preparative (2-mm layer) tlc were performed on silica gel F 254 plates containing a fluorescent indicator; spots were detected under uv light (245 nm). A 6:4 mixture of petroleum ether and ether was always used as the eluent. All comparison between compounds were made on the basis of ir and nmr spectra, tlc, and glpc. Magnesium sulfate was always used as drying agent. Evaporations were made *in vacuo* (rotating evaporator). Petroleum ether refers to the fraction boiling at 30–50°; cyclohexane, CCl_4, $CHCl_3$, and CH_2Cl_2 were refluxed over P_2O_5 and rectified; benzene was washed with concentrated sulfuric acid, refluxed over sodium, and rectified.

2,2-Dimethylcyclohexanone (**1**) was prepared as described before:[13] bp 170–172° (760 mm), $n^{20}D$ 1.4485.

2,2-Dimethyl-1-(*p*-methoxyphenyl)cyclohexanol (**2**). A solution of *p*-methoxybromobenzene (16.5 g, 88 mmol) in anhydrous *n*-pentane (100 ml) was treated under N_2 with 2.3 *M* solution of *n*-butyllithium in *n*-heptane (38 ml, 88 mmol) and stirred 6 hr at room temperature. The reaction mixture was added to a solution of **1** (10.0 g, 79 mmol) in anhydrous *n*-pentane (40 ml) and anhydrous ether (20 ml), stirred at room temperature 14 hr, and refluxed for 3 hr and then treated with saturated aqueous NH_4Cl and ice. The organic layer was washed with 10% aqueous Na_2CO_3 and water, dried, and evaporated to yield a residue which on crystallization from petroleum ether gave pure **2** (11.5 g): mp 72–73.5°; ir λ_{OH} 2.82 μ; nmr δ 7.35 and 6.77 ppm (2 H each, d, J = 9 Hz, C_6H_4–). *Anal.* Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.70; H, 9.37.

6,6-Dimethyl-1-(*p*-methoxyphenyl)cyclohexene (**4**). **2** (3.0 g) was added to 15 ml of a freshly prepared solution of sulfuric acid and acetic acid (2:8 v/v). The mixture was shaken 10 min at room temperature and then poured into a separatory funnel containing ether (100 ml) and water (100 ml). The ether layer was washed with water, 10% aqueous Na_2CO_3, and water, dried, and evaporated to yield crude **4** (2.7 g) which was chromatographed through a 1.5 × 27 cm column of neutral Al_2O_3 (activity II). Elution with petroleum ether (250 ml) gave pure **4** (2.6 g): nmr δ 5.32 (1 H, m, HC=), 1.03 ppm (6 H, s, CH_3). *Anal.* Calcd for $C_{15}H_{20}O$: C, 83.28; H, 9.32. Found: C, 83.45; H, 9.17.

2,2-Dimethyl-1-(*p*-methoxyphenyl)-7-oxabicyclo[4.1.0]heptane (**5**). A solution of **4** (2.05 g, 9.50 mmol) in $CHCl_3$ (20 ml) was treated dropwise under stirring with a 0.245 *M* solution of peroxybenzoic acid[14] in $CHCl_3$ (43 ml, 10.5 mmol), while keeping the temperature below −6°, stirred 45 min at −6°, and then left 3 days at 5°. The reaction mixture was washed with 10% aqueous Na_2CO_3 and water, dried, and evaporated to yield a crude residue (2.1 g) which on crystallization from ethanol–water (8:2, v/v) containing a trace of KOH gave pure **5** (1.92 g). An analytical sample was obtained from petroleum ether: mp 47–49°; nmr δ 3.12 ppm (1 H, m, CHO). *Anal.* Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.81; H, 8.70.

6,6-Dimethyl-1-phenyl-*c*-2-trichloroacetoxy-*r*-1-cyclohexanol (**9**). A solution of **5** (0.250 g, 1.08 mmol) in anhydrous benzene was treated with a 1.0 *M* solution of trichloroacetic acid in anhydrous benzene (1.19 ml, 1.19 mmol), left 4 days at room temperature, washed with saturated aqueous $NaHCO_3$ and water, and evaporated to give a solid mixture (0.27 g) of **3** and **9** (ir). Extraction of the mixture with petroleum ether at room temperature yielded a residue (0.050 g) consisting of **3**. Crystallization of the extracts at −7° from petroleum ether afforded pure **9**: mp 104–105.5°; ir λ_{CO} 5.74 μ. *Anal.* Calcd for $C_{17}H_{21}Cl_3O_4$: C, 51.60; H, 5.35. Found: C, 51.90; H, 5.31.

Compound **9** was recovered unchanged after treatment of its acetone solution with Jones reagent[4] for 15 min.

6,6-Dimethyl-1-(*p*-methoxyphenyl)-*r*-1,*c*-2-cyclohexanediol (**11**). A solution of **9** (0.030 g) in THF (3 ml) was treated with a 1 *M* solution of KOH in ethanol (1 ml). After 5 hr at room temper-

ature the solution was diluted with water and extracted with ether. Evaporation of the washed and dried ether extracts yielded **9** (0.017 g), which after crystallization from petroleum ether (bp 40–70°) had mp 114–116°. *Anal.* Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.13; H, 8.72.

Reaction of 5 with Sulfuric Acid in Water. A suspension of **5** (0.500 g) in water (45 ml) and 2 *N* aqueous sulfuric acid (5 ml) was stirred 2 days at room temperature and then extracted with ether. Evaporation of the washed (water) and dried extracts yielded a solid (0.490 g) consisting of ketone **3**, diols **10** and **11** (Table I), and starting epoxide **5**. The crude reaction mixture was subjected to preparative tlc. Elution was repeated four times. Extraction of the four bands (the relative R_f were **5** > **3** > **11** > **10**) yielded **5** (0.050 g), **3,3-dimethyl-2-(*p*-methoxyphenyl)cyclohexanone (3)** (0.060 g), **11** (0.100 g), and **6,6-dimethyl-1-(*p*-methoxyphenyl)-*r*-1,*t*-2-cyclohexanediol (10)** (0.180 g).

3: mp 97–98° [from petroleum ether (bp 40–70°)]; ir λ_{CO} 5.88 μ; nmr δ 3.43 (1 H, s, CHAr), 0.83 and 0.87 ppm (3 H each, s, CH_3). *Anal.* Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.60; H, 8.46.

10: mp 90–92° [from petroleum ether (bp 60–80°)]. *Anal.* Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.18; H, 8.67.

Reaction of 5 with Trichloroacetic Acid in Several Solvents. The reactions were carried out in anhydrous benzene, cyclohexane, CCl_4, $CHCl_3$, and CH_2Cl_2 in the following way. To a solution of **5** (0.100 g, 0.430 mmol) in the solvent was added trichloroacetic acid (0.480 mmol) using a *ca.* 1 *M* solution of the acid in the same solvent. The reaction mixture was allowed to stand 4 days at room temperature, then washed with saturated aqueous $NaHCO_3$ and water, dried, and evaporated to dryness. The crude residue was dissolved in THF (10 ml), treated with 1 *M* KOH in ethanol (4 ml), and left 4 hr at room temperature. Dilution with water, extraction with ether, and evaporation of the washed (water) and dried ether extracts gave a residue consisting of a mixture of **3**, **10**, and **11** which was analyzed by glpc (Table I).

Reaction of 5 with HCl in Benzene. Dry gaseous HCl was bubbled through a solution of **5** (0.300 g) in anhydrous benzene (30 ml) to saturation. After 1 hr at room temperature the solution was washed with water, saturated aqueous $NaHCO_3$, and water, dried, and evaporated to give a residue (0.315 g) consisting of ketone **3** and chlorohydrin **6** in a ratio of 36:64 (nmr). The crude reaction mixture was subjected to preparative tlc. Extraction of the two bands (the faster moving band contains the ketone **3**) yielded **3** (0.040 g) and **3,3-dimethyl-*c*-2-chloro-2-(*p*-methoxyphenyl)-*r*-cyclohexanol (6)** (0.180 g) which on crystallization from petroleum ether gave pure **6** (0.140 g), mp 78–80°. *Anal.* Calcd for $C_{15}H_{21}ClO_2$: C, 67.03; H, 7.88. Found: C, 67.02; H, 7.81.

Treatment of Chlorohydrin 6 with Aqueous Potassium Hydroxyde. A solution of **6** (0.020 g) in 2-propanol (6 ml) was treated with KOH (0.120 g), then refluxed for 25 min, diluted with water, and extracted with ether. Evaporation of the washed (water) and dried extracts yielded a solid residue (0.015 g) which on crystallization from petroleum ether gave pure **3** (0.010 g).

3,3-Dimethyl-2-chloro-2-(*p*-methoxyphenyl)cyclohexanone (8). A solution of **6** (0.120 g, 0.45 mmol) in anhydrous benzene (10 ml) was treated with 8 *N* chromic acid in aqueous sulfuric acid[4] (0.22 ml), stirred at room temperature for 4 hr, and then washed (water) and evaporated to give a residue (0.110 g) which on crystallization from petroleum ether at −5° yielded **8** (0.060 g): mp 58–60°; ir λ_{CO} 5.82 μ; nmr δ 0.82 and 0.89 ppm (3 H each, s, CH_3). *Anal.* Calcd for $C_{15}H_{19}ClO_2$: C, 67.53; H, 7.18. Found: C, 67.34; H, 7.23.

3,3-Dimethyl-2-hydroxy-2-(*p*-methoxyphenyl)cyclohexanone (7). A solution of **11** (0.040 g, 0.16 mmol) in acetone (4 ml) was treated with 8 *N* chromic acid in aqueous sulfuric acid[4] (0.1 ml), left 1 min at room temperature, diluted with water, and extracted with ether. Evaporation of the washed (10% aqueous Na_2CO_3, water) ether yielded a residue which on crystallization from petroleum ether yielded pure **7** (0.030 g): mp 132–136°; ir λ_{OH} 2.91, λ_{CO} 5.89 μ; nmr δ 4.15 (1 H, OH), 0.86 and 0.77 ppm (3 H each, s, CH_3). *Anal.* Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.73; H, 7.98.

Similar oxidation of **10** (0.040 g) yielded **7** (0.020 g).

Treatment of Chlorohydrin 6 with Jones Reagent. A solution of **6** (0.130 g, 0.49 mmol) in acetone (13 ml) was treated with 8 *N* chromic acid in aqueous sulfuric acid[4] (0.13 ml), left 4 min at room temperature, diluted with water, and extracted with ether. Evaporation of the washed (saturated aqueous $NaHCO_3$ and water) and dried extracts yielded a residue (0.120 g) consisting of an almost equimolar mixture of **7** and **8** (tlc). When the reaction time was longer (60 min), practically pure **7** was obtained.

Chlorohydrin **6** (0.015 g, 0.06 mmol) was recovered almost unchanged by treatment of its solution in acetone (1.5 ml) with 8 *N* aqueous sulfuric acid (0.06 ml) for 20 min; just traces of diols **10** and **11** were revealed (tlc).

When a solution of chloro ketone **8** (0.010 g, 0.04 mmol) in acetone (1 ml) was treated with 8 *N* chromic acid in aqueous sulfuric acid[4] (0.1 ml) for 1 min, an almost equimolar mixture of **7** and **8** was recovered.

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Registry No.—**1**, 1193-47-1; **2**, 50562-44-2; **3**, 50562-45-3; **4**, 50562-46-4; **5**, 50562-47-5; **6**, 50562-48-6; **7**, 50562-49-7; **8**, 50562-50-0; **9**, 50562-51-1; **10**, 50562-52-2; **11**, 50562-53-3; **12**, 43050-16-4; **13**, 40358-13-2.

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Electronic Effects in Elimination Reactions. VIII. E2 Reaction of 2-Arylethyl Fluorides

Charles H. DePuy* and Arnold L. Schultz

Department of Chemistry, University of Colorado, Boulder, Colorado 80302

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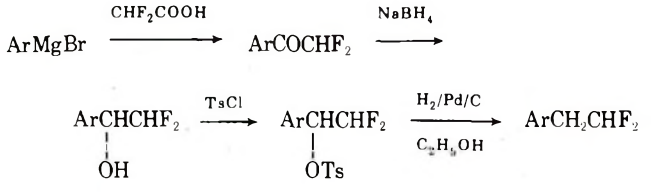
The rates of bimolecular elimination from a series of 1-fluoro-2-arylethanes, 1,1-difluoro-2-arylethanes, and 1,1,1-trifluoro-2-arylethanes have been measured in *tert*-butyl alcohol using potassium *tert*-butoxide as the base. The absolute rate of the reaction and the Hammett ρ value for the elimination both increase with the number of fluorines. Values for the latter are +3.24 for the fluoride, +3.56 for the difluoride, and +4.04 for the trifluoride, indicating that the transition state is highly carbanionic in character, as is also indicated by a relatively low value of k_H/k_D.

Only a relatively few kinetic and mechanistic studies have been performed on organofluorine compounds. Some years ago we measured the rates of elimination of hydrogen fluoride from a series of substituted 2-arylethyl fluorides in sodium ethoxide–ethanol solution.[1] These compounds react slowly as compared to analogs with other halide leaving groups (the relative rates of elimination of 2-phenylethyl halides in sodium ethoxide–ethanol are F:Cl:Br:I = 1:70:4100:26,600), and the elimination reaction of the fluorides has a higher Hammett ρ value (+3.1) as compared to the chlorides (+2.6), bromides (+2.1), or iodides (+2.1). We were interested in investigating elimination reactions of fluorides further, and in this paper we present the results of a study on the elimination of hydrogen fluoride from a series of 1-fluoro-, 1,1-difluoro-, and 1,1,1-trifluoro-2-arylethanes in *tert*-butyl alcohol with potassium *tert*-butoxide as the reacting base.

The synthesis of the requisite fluorides proceeded along straightforward lines. The 1-fluoro-2-arylethanes were prepared as reported previously[1] from the arylacetic acids by reduction to the alcohols, tosylation, and displacement by potassium fluoride in diethylene glycol solution.[2] The 1,1-difluoro-2-arylethanes were prepared as shown in Scheme I, and the 1,1,1-trifluoro-2-arylethanes were prepared analogously using trifluoroacetic acid. The elimination reactions were carried out at 50° in *tert*-butyl alcohol solution containing 0.1 *N* potassium *tert*-butoxide, and the rate of disappearance of base was followed by titration with standard hydrochloric acid solution. The 1-fluoro- and 1,1-difluoroethanes each consumed 1 equiv of base and produced styrenes and a mixture of *cis*- and *trans*-β-fluorostyrenes, respectively. In the case of the 1,1,1-trifluoro-2-arylethanes the elimination reaction was found to occur with the consumption of 2 mol of potassium *tert*-butoxide. If the reaction was carried out in an nmr tube with less than 1 equiv of base, we were able to detect some β,β-difluorostyrene[3] among the products. This initially formed olefin apparently undergoes an addition–elimination reaction analogous to that of trifluorostyrene[4] forming ultimately a cis,trans mixture of 1-(*tert*-butoxy)-1-fluoro-2-arylethylenes (eq 1). The second reaction in this sequence appears to be faster than the first, because initial rate constants were identical with those calculated on the basis of the consumption of 2 mol of *tert*-butoxide for each trifluoroethyl molecule.

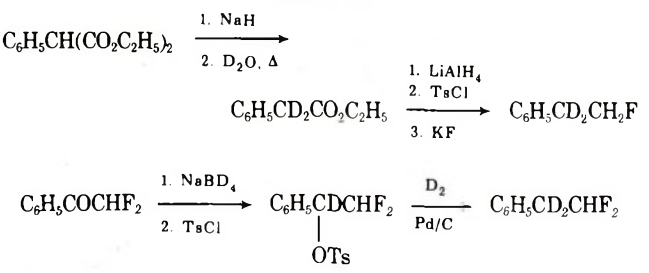
Scheme I



$$ArCH_2CF_3 \xrightarrow{t\text{-}BuO^-} ArCH{=}CF_2 \xrightarrow[t\text{-}BuO^-]{t\text{-}BuOH} ArCH{=}CF(O\text{-}t\text{-}Bu) \quad (1)$$

In order to determine kinetic isotope effects and to investigate the possibility of deuterium–hydrogen exchange, 1-fluoro-2-phenylethane-2,2-d_2 and 1,1-difluoro-2-phenylethane-2,2-d_2 were prepared by the methods outlined in Scheme II. The rate constants for these compounds did not increase with time, as they would be expected to do if extensive hydrogen–deuterium exchange were occurring before elimination. As a more sensitive check, one reaction of each deuterium compound was quenched after approximately 1 half-life, and the mass spectrum of the recovered starting material was compared with that of authentic deuterated material. This indicated that no detectable hydrogen deuterium exchange had occurred.

Scheme II



The rate constants that we have determined for the compounds prepared in this study are given in Table I.

In determining Hammett ρ values for these elimination reactions, we found that the σ value for fluorine derived from the acidity of *p*-fluorobenzoic acid would not correlate with that of other substitutents, but that the σ^- value derived from the acidity of *p*-fluorophenol would do so, although less well in the case of the 2-arylethyl fluorides than with the di- and trifluorides. It has previously been observed that the *p*-nitro group also requires the use of a σ^- value for correlation in the elimination reaction of other 2-arylethyl derivatives.[5]

The ρ values found were +3.24 ± 0.05 for the fluoride, +3.56 ± 0.07 for the difluoride, and +4.04 ± 0.30 for the trifluoride.

The results of these measurements indicate that, as might be expected, the eliminations are highly carbanionic. Koch[6] has postulated recently that eliminations of HF from $C_6H_5CHClCF_3$ occurs with reversible formation of the hydrogen-bonded carbanion, a carbanion which has an activation energy for exchange with solvent because of

Table I
Rates of the Elimination Reaction of 2-Arylethyl Fluorides by Potassium *tert*-Butoxide in *tert*-Butyl Alcohol at 50°

Y	Registry no.	$k_{E2} \times 10^4$, l. mol^{-1} sec^{-1}	k_H/k_D
		$YC_6H_4CH_2CH_2F$	
m-CF_3	50512-33-9	46.6 ± 0.36	
H	458-87-7	1.88 ± 0.01	
m-CH_3	50561-90-5	1.21 ± 0.01	
p-F	2343-30-8	1.10 ± 0.01	
p-CH_3	50561-92-7	0.513 ± 0.007	
		$YC_6H_4CD_2CH_2F$	
H	50561-93-8	0.418 ± 0.009	4.50
		$YC_6H_4CH_2CHF_2$	
H	10541-59-0	11.8 ± 0.09	
p-F	50561-95-0	9.62 ± 0.05	
m-CH_3	50561-96-1	6.47 ± 0.03	
p-CH_3	50561-97-2	2.88 ± 0.00	
		$YC_6H_4CD_2CHF_2$	
H	50561-98-3	4.26 ± 0.03	2.77
		$YC_6H_4CH_2CF_3$	
H	21249-93-4	22.8 ± 0.45	
p-F	50561-99-4	16.8 ± 0.30	
m-CH_3	50562-00-0	12.7 ± 0.50	
p-CH_3	50562-01-1	4.45 ± 0.09	

this hydrogen bonding. The ρ value found in that study is, within experimental error, the same as we find for the trifluoro compound. Koch has also suggested that fluoride is a poorer leaving group when it comes from a trifluoromethyl group rather than from a less highly fluorinated group. Our results are thus in agreement with the view that the addition of each fluorine to the methyl group has two effects. On the one hand, it acidifies the hydrogens on the adjacent carbon but at the same time it reduces the leaving ability of the fluorines. As a consequence a larger negative charge is required in the transition state for the elimination from the trifluoro compound than from the di- and monofluoro compounds. We cannot say from our data whether a carbanion is an actual intermediate or not; it may be formed reversibly without exchange in the trifluoro case at least. The low k_H/k_D values also are in agreement with a transition state with a great deal of carbon–hydrogen bond breaking so that the hydrogen is more than half transferred to base.

Experimental Section

Melting points are uncorrected and were taken on a Fisher-Johns melting point apparats. Ir absorption spectra were determined on a Beckman IR-10 spectrometer. All proton nmr spectra were determined on a Varian A-60A spectrometer using TMS as an internal standard. All fluorine nmr spectra were recorded on a Varian HA-100 spectrometer using $FCCl_3$ as an internal standard. Chemical shifts are reported in ppm relative to this standard. Mass spectra were recorded on either a Varian MAT CH-5 or CH-7 spectrometer at 70 eV. Microanalyses were performed by Dr. Alfred Bernhardt Mickroanalytisches Laboratorium, Mülheim, West Germany.

Preparation of 2-Arylethyl Fluorides. All of the 2-arylethanols, with the exception of 2-phenylethanol which is commercially available, were prepared by the reduction of the corresponding arylacetic acid with diborane using the general procedure of Brown and Rao.[7] The arylacetic acids, with the exception of the *m*-trifluoromethylphenylacetic acid, were commercially available. The latter was prepared from *m*-trifluoromethylbenzyl chloride by reaction with magnesium and CO_2.[8] The alcohols were converted into their tosylates by the method of Tipson,[9] and these in turn converted into fluorides by the procedure of Bergman and Shahak.[1,2] **2-*p*-Tolylethanol:** bp 69–74° (0.8–0.6 mm) [lit.[10] bp 117–118° (14 mm)], 85% yield. **2-*m*-Tolylethanol:** bp 69–74° (0.8–0.6 mm) [lit.[11] bp 112° (10 mm)], 86% yield. **2-(*p*-Fluorophenyl)ethanol:** bp 59–61° (0.5 mm) [lit.[12] bp 110° (20 mm)], 87% yield. **2-(*m*-Trifluoromethylphenyl)ethanol:** bp 58–62° (0.5 mm) [lit.[13] bp 85–90° (4 mm)], 72% yield. **2-Phenylethyl *p*-toluenesulfonate:** mp 38.5–39.5° (lit.[14] mp 38.5–39°), 65% yield. **2-*p*-Tolylethyl *p*-toluenesulfonate:** mp 67–68°, 89% yield. **2-*m*-Tolylethyl *p*-toluenesulfonate:** oil, 89% yield. **2-(*p*-Fluorophenyl)ethyl *p*-toluenesulfonate:** mp 35.7–36.2°, 88% yield. **2-(*m*-Trifluoromethylphenyl)ethyl *p*-toluenesulfonate:** oil, 91% yield. **2-Phenylethyl fluoride:** bp 50–51° (9 hm) [lit.[1] bp 55–56° (12 mm)]; 53% yield; ^1H nmr (CCl_4) δ 2.80 (dt, 2 H, $J_{HF,vic}$ = 22.7 Hz, $J_{HH,vic}$ = 6.6 Hz), 4.41 (dt, 2 H, $J_{HF,gem}$ = 47.4 Hz), 7.13 (s, 5 H); ^{19}F nmr ($FCCl_3$) 215.3 ppm (tt). **2-*p*-Tolylethyl fluoride:** bp 74–76° (18 mm), 61% yield. *Anal.* Calcd for $C_9H_{11}F$: C, 78.23; H, 8.02; F, 13.75. Found: C, 78.12; H, 7.86; F, 13.90. **2-*m*-Tolylethyl fluoride:** bp 74–78° (18 mm), 63% yield. *Anal.* Calcd for $C_9H_{11}F$: C, 78.23; H, 8.02; F, 13.75. Found: C, 78.11; H, 7.90; F, 13.94. **2-(*p*-Fluorophenyl)ethyl fluoride:** bp 53.5–54° (10 mm), 63% yield. *Anal.* Calcd for $C_8H_8F_2$: C, 67.60; H, 5.67; F, 26.73. Found: C, 67.79; H, 5.81; F, 26.68. **2-(*m*-Trifluoromethylphenyl)ethyl fluoride:** bp 56–58° (10 mm), 50% yield. *Anal.* Calcd for $C_9H_8F_4$: C, 56.26; H, 4.21; F, 39.55. Found: C, 56.32; H, 4.34; F, 39.76.

Preparation of α,α-Difluoroacetophenones. The ketones were prepared by reaction of the appropriate aryl Grignard reagent with difluoroacetic acid according to the procedure of Dishart and Levine[15] using the modification described by Bergmann, Pelchowicz, and Shani.[16] **α,α-Difluoroacetophenone:** bp 60–62° (10 mm) [lit.[17] bp 83–85° (20 mm)]; 51% yield; nmr (CCl_4) δ 6.18 (t, 1 H, $J_{HF,gem}$ = 53.8 Hz), 7.53 (m, 3 H), 8.03 (m, 2 H). ***p*-Methyl-α,α-difluoroacetophenone:** bp 80–82° (13–14 mm), mp 47–49°, 51% yield. ***m*-Methyl-α,α-difluoroacetophenone:** bp 78–79° (11 mm), 44% yield. ***p*-Fluoro-α,α-difluoroacetophenone:** bp 62–64° (13 mm), 55.5% yield. ***m*-Trifluoromethyl-α,α-difluoroacetophenone:** bp 61–64° (10 mm), 67% yield.

Preparation of 1-Aryl-2,2-difluoroethanols and Their Tosylates. The alcohols were prepared by reduction of the acetophenones with sodium borohydride in 90% aqueous dioxane. To a solution of 0.15 mol of the α,α-difluoroacetophenone in 80 ml of 90% aqueous dioxane contained in a 250-ml erlenmeyer flask equipped with a magnetic stirrer was added in small portions with stirring 1.81 g (0.048 mol) of sodium borohydride. Gas evolution was observed with each addition, being more vigorous with the initial ones. Intermittent cooling of the reaction mixture was necessary. After stirring overnight, the reaction mixture was cooled in an ice bath and the excess borohydride was destroyed by the cautious addition of cold, 3 *N* hydrochloric acid. The solution was extracted with ether (4 × 50 ml); the combined extracts were washed with water until the washings were neutral to indicator paper and then dried over anhydrous magnesium sulfate. The solvent was removed and the product distilled. The tosylate was prepared in the usual way, but rather long reaction times (several days in some cases) were required for reaction. **1-Phenyl-2,2-difluoroethanol:** bp 58–61° (1 mm) [lit.[18] bp 107–108° (20 mm)]; 87% yield; nmr (CCl_4) δ 3.45 (s, 1 H), 4.57 (m, 1 H), 5.57 (td, 1 H, $J_{HF,gem}$ = 55.5 Hz, $J_{HH,vic}$ = 4.5 Hz), 7.28 (s, 5 H). **Tosylate:** mp 96.0–96.5°; 77% yield; nmr ($CDCl_3$) δ 2.35 (s, 3 H), 5.55 (td, 1 H, $J_{HF,vic}$ = 10.2 Hz, $J_{HH,vic}$ = 4.0 Hz), 5.91 (td, 1 H, $J_{HF,gem}$ = 55.0 Hz), 7.18 (d, 2 H), 7.30 (s, 5 H), 7.85 (d, 2 H). **1-(*p*-Tolyl)-2,2-difluoroethanol:** bp 60–62° (0.5–0.6 mm), 87% yield. **Tosylate:** mp 65.0–65.5°, 66% yield. **1-(*m*-Tolyl)-2,2-difluoroethanol:** bp 58–61° (0.5 mm), 78% yield. **1-(*p*-Fluorophenyl)-2,2-difluoroethanol:** bp 92–96° (11 mm), 78% yield. **Tosylate:** mp 54–57°, 73% yield. **1-(*m*-Trifluoromethylphenyl)-2,2-difluoroethanol:** bp 50–52° (0.4–0.5 mm), 90% yield. **Tosylate:** mp 42–43°, 58% yield.

Preparation of 1,1-Difluoro-2-arylethanes. Hydrogenolysis of the corresponding tosylates over 5% palladium-on-carbon catalyst in 95% ethanol, at room temperature and atmospheric pressure, gave rise to the desired 1,1-difluoro-2-arylethanes. The hydrogenations were conducted in an apparatus essentially the same as that described by Wiberg.[19] The products were distilled through a 7 × 5/8 in. column packed with glass beads, and the distillation was monitored by glpc. Fractions of the highest purity, usually greater than 99% pure, were used in the kinetic runs. **1,1-Difluoro-2-phenylethane:** bp 68–69° (32 mm); 79% yield; nuclear magnetic resonance (CCl_4) δ 2.85 (td, 2 H, $J_{HF,vic}$ = 17.0 Hz, $J_{HH,vic}$ = 4.5 Hz), 5.75 (tt, 1 H, $J_{HF,gem}$ = 56.5 Hz), 7.20 (s, 5 H). *Anal.* Calcd for $C_8H_8F_2$: C, 67.60; H, 5.67; F, 26.73. Found: C, 67.76; H, 5.74; F, 26.75. **1-Difluoro-2-(*p*-tolyl)ethane:** bp 69° (13 mm), 81% yield. *Anal.* Calcd for $C_9H_{10}F_2$: C, 69.22; H, 6.45; F, 24.33. Found: C, 69.12; H, 6.56; F, 24.29. **1,1-Difluoro-2-(*m*-tolyl)ethane:** bp 61–62° (10 mm), 78% yield. *Anal.* Calcd for

$C_9H_{10}F_2$: C, 69.22; H, 6.45; F, 24.33. Found: C, 69.04; H, 6.27; F, 24.18. **1,1-Difluoro-2-(*p*-fluorophenyl)ethane:** bp 77° (37 mm), 82% yield. *Anal.* Calcd for $C_8H_7F_3$: C, 60.00; H, 4.41; F, 35.59. Found: C, 59.86; H, 4.34; F, 35.32. **1,1-Difluoro-2-(*m*-trifluoromethylphenyl)ethane:** bp 80–81° (30 mm), 81% yield. *Anal.* Calcd for $C_9H_7F_5$: C, 51.44; H, 3.36; F, 45.20. Found: C, 51.24; H, 3.19; F, 45.51.

Preparation of α,α,α-Trifluoroacetophenones. All of α,α,α-trifluoroacetophenones were prepared by reaction of the appropriate aryl Grignard reagent with trifluoroacetic acid in a manner analogous to that described above for the preparation of the α,α-difluoroacetophenones. **α,α,α-Trifluoroacetophenone:** bp 143.5–144° (lit.[20] bp 152°), 71% yield. ***p*-Methyl-α,α,α-trifluoroacetophenone:** bp 66–68° (13 mm) [lit.[21] bp 81–82.5° (22 mm)], 67% yield, ***m*-Methyl-α,α,α-trifluoroacetophenone:** bp 62–64° (14–20 mm) [lit.[22] bp 79° (24 mm)]; 61% yield; nmr (CCl_4) δ 2.38 (s, 3 H), 7.42 (m, 2 H), 7.83 (m, 2 H). ***p*-Fluoro-α,α,α-trifluoroacetophenone:** bp 58–60° (24 mm) [lit.[23] bp 66–67° (34 mm)]; 69% yield; nmr (CCl_4) δ 7.23 (m, 2 H), 8.13 (m, 2 H). ***m*-Trifluoromethyl-α,α,α-trifluoroacetophenone:** bp 52–54° (14 mm) [lit.[24] bp 65.0–67.5° (24 mm)], 75% yield.

Preparation of 1-Aryl-2,2,2-trifluoroethanols and Their Tosylates. The 1-aryl-2,2,2-trifluoroethanols were prepared by reduction of the corresponding α,α,α-trifluoroacetophonones in a manner analogous to that described above for the preparation of the 1-aryl-2,2-difluoroethanols. The tosylates were prepared in an analogous manner to that described above for the preparation of the 1-aryl-2,2-difluoroethyl *p*-tolunenesulfonates. **1-Phenyl-2,2,2-trifluoroethanol:** bp 90–91° (18 mm) [lit.[25] bp 64–65° (5 mm)]; ^1H nmr (CCl_4) δ 3.86 (s, 1 H), 4.73 (q, 1 H, $J_{HF,vic}$ = 6.8 Hz), 7.27 (s, 5 H); ^{19}F nmr ($FCCl_3$) 78.5 ppm (d, $J_{HF,vic}$ = 6.9 Hz). **Tosylate:** mp 115–116°; 63% yield; ^1H nmr ($CDCl_3$) δ 2.37 (s, 3 H), 5.68 (q, 1 H), 7.27 (d, 2 H), 7.32 (s, 5 H), 7.63 (d, 2 H); ^{19}F nmr ($FCCl_3$) 76.8 ppm (d, $J_{HF,vic}$ = 6.4 Hz). **1-(*p*-Tolyl)-2,2,2-trifluoroethanol:** bp 50° (0.75 mm) [lit.[24] bp 74.5–75° (2.5 mm)], 90% yield. **1-(*m*-Tolyl)-2,2,2-trifluoroethanol:** bp 54° (0.55 mm) [lit.[22] bp 95–97° (24 mm)], 90% yield. **Tosylate:** mp 75–78°, 82% yield. **1-(*p*-Fluorophenyl)-2,2,2-trifluoroethanol:** bp 88–90° (17 mm), 92% yield. **Tosylate:** mp 78.0–78.5°, 80% yield. **1-(*m*-Trifluoromethylphenyl)-2,2,2-trifluoroethanol:** bp 76–78° (10 mm) [lit.[24] bp 95–97° (24 mm)], 93% yield. **Tosylate:** mp 51.5–52.5°, 68% yield.

Preparation of 1,1,1-Trifluoro-2-arylethanes. The 1,1,1-trifluoro-2-arylethanes were prepared by the hydrogenolysis of the corresponding 1-aryl-2,2,2-trifluoroethyl *p*-toluenesulfonates in a manner analogous to that described above for the preparation of the 1,1-difluoro-2-arylethanes. **1,1,1-Trifluoro-2-phenylethane:** bp 124–126°; 81% yield; nmr (CCl_4) δ 3.17 (q, 2 H, $J_{HF,vic}$ = 11.0 Hz), 7.18 (s, 5 H). *Anal.* Calcd for $C_8H_7F_3$: C, 60.00; H, 4.41; F, 35.59. Found: C, 60.20; H, 4.45; F, 35.83. **1,1,1-Trifluoro-2-(*p*-tolyl)ethane:** mp 43.5–43.7° (sublimed), 84% yield. *Anal.* Calcd for $C_9H_9F_3$: C, 62.07; H, 5.21; F, 32.72. Found: C, 61.99; H, 5.10; F, 32.88. **1,1,1-Trifluoro-2-(*m*-tolyl)ethane:** bp 45.0–45.7° (11 mm), 88% yield. *Anal.* Calcd for $C_9H_9F_3$: C, 62.07; H, 5.21; F, 32.72. Found: C, 62.22; H, 5.24; F, 32.81. **1,1,1-Trifluoro-2-(*p*-fluorophenyl)ethane:** bp 58° (34 mm), 78% yield. *Anal.* Calcd for $C_8H_6F_4$: C, 53.94; H, 3.40; F, 42.66. Found: C, 54.23; H, 3.16; F, 42.74. **1,1,1-Trifluoro-2-(*m*-trifluoromethylphenyl)ethane:** bp 37–38° (8 mm), 82% yield. *Anal.* Calcd for $C_9H_6F_6$: C, 47.38; H, 2.65; F, 49.97. Found: C, 47.48; H, 2.81; F, 49.83.

Preparation of Deuterio Compounds. 2-Phenylethyl-2,2-d_2 fluoride was prepared by a scheme analogous to that used to prepare 2-phenylethyl fluoride with the exception that 2-phenylethanol-2,2-d_2, which was prepared from ethyl phenylacetate-2,2-d_2, was the starting material in this sequence. **Ethyl phenylacetate-2,2-d_2:** bp 45–46° (0.1 mm) [lit.[26] bp 73–74° (0.5 mm)]; 11% yield; nmr (CCl_4) δ 2.13 (t, 3 H), 4.08 (q, 2 H), 7.25 (s, 5 H). **2-Phenylethanol-2,2-d_2:** bp 73–74° (2.0 mm) [lit.[26] bp 110° (20 mm)], 82% yield. **2-Phenylethyl-2,2-d_2 *p*-toluenesulfonate:** oil (lit.[27] mp 37.5–38.2°), 90% yield. **2-Phenylethyl-2,2-d_2 fluoride:** bp 51° (2 mm); 38% yield; nmr (CCl_4) δ 4.45 (dd, 2 H, $J_{HF,gem}$ = 47.8 Hz), 7.15 (s, 2 H). (Comparison of *m/e* 92 and 91 in the deuterio compound with 90 and 89 in the undeuterated compound indicated a minimum of 1.87 atoms of D/molecule in the former.)

Reduction of α,α-difluoroacetophenone with sodium borodeuteride in deuterium oxide–dioxane in a manner analogous to that described above for the preparation of the 2,2-difluoro-1-arylethanols gave rise to 2,2-difluoro-1-phenylethanol-1-d_1. Hydrogenolysis of the tosylate, prepared from this alcohol in the usual manner, with deuterium following the procedure described above for the preparation of 2,2-difluoro-1-arylethanes, with the exception that the catalyst was prereduced with deuterium before the tosylate was introduced, yielded 2,2-difluoro-1-phenylethane-1,1-d_2. **2,2-Difluoro-1-phenylethanol-1-d_1:** bp 63–64° (0.3 mm); 86% yield; nmr (CCl_4) δ 3.42 (s, 1 H), 5.57 (t, 1 H, $J_{HF,gem}$ = 56.0 Hz), 7.27 (s, 5 H). **Tosylate:** mp 93–95°; 85% yield; nmr ($CDCl_3$) δ 2.37 (s, 3 H), 5.92 (t, 1 H, $J_{HF,gem}$ = 55.0 Hz), 7.20 (d, 2 H), 7.30 (s, 5 H), 7.85 (d, 2 H). **2,2-Difluoro-1-phenylethane-1,1-d_2:** bp 69.5–70.0° (33 mm); 73% yield; nmr (CCl_4) δ 5.75 (t, 1 H, $J_{HF,gem}$ = 57.0 Hz), 7.18 (s, 5 H). (Comparison of *m/e* 144 and 143 in the deuterio compound with 142 and 141 in the undeuterated compound indicated a minimum of 1.93 atoms of D/molecule in the former.)

Kinetic Procedures. Anhydrous *tert*-Butyl Alcohol. Reagent grade *tert*-butyl alcohol was distilled from Na (5 g of sodium/l. of alcohol) three times and then from potassium once. The purified alcohol was stored under nitrogen.

0.2 *N* Potassium *tert*-Butoxide. A clean, dry 5-g ampoule of pure potassium metal (99.95%, Alfa Inorganics) was broken into 640 ml of anhydrous *tert*-butyl alcohol under a nitrogen atmosphere. The flask was protected from moisture and carbon dioxide by means of a drying tube containing anhydrous calcium sulfate and Ascarite until the metal had all reacted. The flask was then fitted with a siphon device which allowed removal of portions of the solution under a slight positive pressure of nitrogen.

Kinetic Runs. All kinetic runs were preformed at 50.00 ± 0.03°. Reactions for which the second-order rate constant for elimination was less than 10^{-3} l. mol^{-1} sec^{-1} were run in sealed ampoules. The fluoride sample, approximately 2.5 mmol, was accurately weighed into a 50-ml volumetric flask and diluted with 25 ml of anhydrous *tert*-butyl alcohol. The flask was then filled to the mark with 0.2 *N* potassium *tert*-butoxide, and the reagents were mixed thoroughly. Nine 5-ml aliquots were pipetted, from automatic zeroing pipets that had been calibrated at 26° with *tert*-butyl alcohol [density (at 26°) 0.779 g/ml], into 15 × 125 mm test tubes which were then sealed and placed in the reaction bath. When the ampoules had equilibrated at the reaction temperature, one was withdrawn and the timer started. The ampoule was opened and the reaction quenched in 50 ml of distilled water. The ampoule was washed out with a 1:1 solution of *tert*-butyl alcohol–distilled water. Two drops of 0.25% phenolphthalein solution in 1:1 ethyl alcohol–water were added, and the sample was titrated with standard hydrochloric acid. The ampoules were withdrawn at appropriate intervals and the samples titrated.

Reactions for which the second-order rate constant for elimination was greater than 10^{-3} l. mol^{-1} sec^{-1} were run directly in the volumetric flask. The fluoride sample was accurately weighed into a 50-ml volumetric flask and diluted with 25 ml of anhydrous *tert*-butyl alcohol. The flask was stoppered and placed in the reaction bath. When the solution had equilibrated at the reaction temperature 0.2 *N* potassium *tert*-butoxide that had been equilibrated at the reaction temperature was added to the mark, and the reagents were thoroughly mixed. A 5-ml aliquot was pipetted directly from the volumetric flask and the timer started as the reaction mixture started to drain. The sample was quenched and titrated. Aliquots were withdrawn and titrated at appropriate intervals.

The second-order rate constant, k_2, was calculated for each kinetic point. An average rate constant was calculated for each run. For reactions run in sealed ampoules a correction factor of a 3% increase in measured rate constant was made to account for the thermal expansion of the solvent.[28]

Measured infinity points were generally less than, but within 3% of, those calculated because some substrate reacted before the zero point could be taken.

An unweighted least-squares statistical analysis computer program was employed to calculate the rate constants. The computer rate constants varied slightly from the numerical average due to the emphasis on the zero and infinity points in calculating the best least-squares slope.

Registry No.—Deuterium, 7782-39-0; 2-*p*-tolylethyl *p*-toluenesulfonate, 14503-40-3; 2-(*p*-fluorophenyl)ethyl *p*-toluenesulfonate, 50562-02-2; α,α-difluoroacetophenone, 395-01-7; *p*-methyl-α,α-difluoroacetophenone, 704-36-9; *m*-methyl-α,α-difluoroacetophenone, 50562-05-5; *p*-fluoro-α,α-difluoroacetophenone, 50562-06-6; *m*-trifluoromethyl-α,α-difluoroacetophenone, 50562-07-7; 1-phenyl-2,2-difluoroethanol, 345-64-2, 50562-09-9 (tosylate); 1-(*p*-tolyl)-2,2-difluoroethanol, 50562-10-2, 50562-11-3 (tosylate); 1-(*m*-tolyl)-2,2-difluoroethanol, 50562-12-4; 1-(*p*-fluorophenyl)-2,2-difluoroethanol, 2546-44-3, 50562-14-6 (tosylate); 1-(*m*-trifluoromethylphenyl)-2,2-difluoroethanol, 50562-15-7, 50562-16-8 (tosylate);

1,1-difluoro-2-(*m*-trifluoromethylphenyl)ethane, 50562-17-9; *p*-fluoro-α,α,α-trifluoroacetophenone, 655-32-3; 1-phenyl-2,2,2-trifluoroethanol, 340-04-5; 1-(*m*-tolyl)-2,2,2-trifluoroethanol tosylate, 655-32-3; 1-(*p*-fluorophenyl)-2,2,2-trifluoroethanol, 50562-19-1, 50562-20-4 (tosylate); 1-(*m*-trifluoromethylphenyl)-2,2,2-trifluoroethanol tosylate, 50562-21-5; 1,1,1-trifluoro-2-(*m*-trifluoromethylphenyl)ethane, 50562-22-6; 2,2-difluoro-1-phenylethanol-*1*-d_1, 50562-23-7, 50562-24-8 (tosylate).

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Steric and Electronic Factors Which Effect the Thermal Cyclization of Meta-Substituted Aryl Propargyl Ethers. Synthesis of 5- and 7-Substituted 3-Chromenes[1]

Wayne K. Anderson,* Edmond J. LaVoie, and Peter G. Whitkop

Department of Medicinal Chemistry, School of Pharmacy, State University of New York at Buffalo, Buffalo, New York 14214

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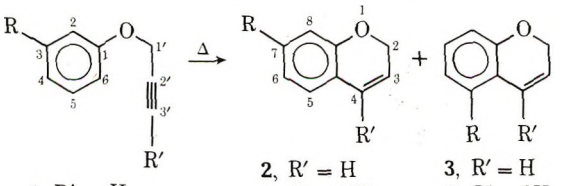
The thermal cyclization of meta-substituted phenyl propargyl ethers (**1** and **4**) proceeded to yield a mixture of 5- and 7-substituted 3-chromenes. The ratio of chromene isomers was somewhat dependent upon the nature of the starting materials. Thus, terminal acetylenes (**1**) gave a mixture of **2** and **3** (resulting from para and ortho cyclization, respectively) with the latter product usually in slight excess. Nonterminal acetylenes (**4**) also gave a mixture of ortho- and para-cyclized products (**6** and **5**, respectively); however, para cyclization was found to be favored. Regioselective cyclization was greatest for **4d**, which gave a mixture of 4,7- and 4,5-dimethyl-3-chromene in a ratio of 2:1. The cyclization of 3-(3-methoxyphenyloxy)-3-methylbutyne (**16**) also proceeded with little regioselectivity to give a mixture of **17** and **18**. The effects of electron-donating and electron-withdrawing meta substituents were also studied.

In our initial studies[2] on the thermal cyclization of aryl propargyl ethers we found that the cyclization of **1a** did not proceed in the regioselective manner previously reported.[3] Instead, the cyclization of **1a** led to the formation of both **2a** and **3a** where, in fact, the previously unreported 5-methoxy isomer (**3a**) was the more abundant product. Our interest in the use of certain substituted chromenes as intermediates in the synthesis of tumor-inhibitory trichothecan mycotoxins[4] prompted us to further examine those factors which influence regioselectivity in this reaction and to study the effects of various substituents on the aromatic ring.



1, R′ = H
4, R′ = CH_3

2, R′ = H
5, R′ = CH_3

3, R′ = H
6, R′ = CH_3

a, R = OCH_3
b, R = $COCH_3$
c, R = $N(C_2H_5)_2$
d, R = CH_3
e, R = $OCOCH_3$

The aryl propargyl ethers used in this study were synthesized by a Williamson reaction using the appropriately substituted phenols and propargyl bromides.[2] The cyclization of the aryl propargyl ethers was carried out in *N,N*-diethylaniline at 210–215°;[2] the isolated yield of the cyclized products, boiling points, reaction times, and product ratios are given in Table I.

The structures of the various chromene isomers were determined by comparison of nmr spectra. Typical 1,2,3- and 1,2,4-trisubstituted benzene patterns were generally evident in the nmr spectra of the 5 and 7 isomers ($J_o \cong 8$ and $J_m \cong 2$ Hz).

In the nmr spectra of the various chromenes the C-2 protons always appeared at slightly higher field in the 5-substituted isomer compared to the 7-substituted isomer. Similarly, the C-3 proton appeared at slightly lower field in the 5 isomer compared to the 7 isomer. The C-4 proton (or the C-4′ methyl protons) generally appeared at lower field in the nmr spectra of the 5-substituted compound compared to the 7 isomer. One exception to this latter

Table I
Thermal Cyclization of Meta-Substituted Aryl Propargyl Ethers (1 or 4)

Compd	R	Reaction time, hr	Yield, %	Bp, °C (mm)	Ortho:para[a] ratio
1a[2]	OCH_3	18.5	51	54 (0.6)	54:46
4a	OCH_3	30	86	93.5 (0.4)	47:53
1b[b]	$COCH_3$	*15*	*<10*		
4b	$COCH_3$	48	75	113–114 (0.4)	55:45
1c	$N(C_2H_5)_2$	15	<20	109 (1.5)	100:<1
4c[b]	$N(C_2H_5)_2$	30	<3		
1d	CH_3	15	89[c]	66 (0.45)	47:53
4d	CH_3	48	92[d]	88–90 (2.1)	36:64
1e	$OCOCH_3$	15	51	102 (0.45)	57:43
4e	$OCOCH_3$	48	96[d]	129 (2.3)	47:54

[a] Ortho cyclization affords the 5-substituted chromene (**3** or **6**) and para cyclization affords the 7-substituted chromene (**2** or **5**). Ortho:para ratios were determined by glc. [b] Insufficient quantities of the product(s) did not permit accurate determination of boiling point and isomer ratios. [c] The cyclization of 3-(*p*-methylphenyloxy)propyne (**19**) afforded only a 67% yield of 6-methyl-3-chromene [**20**, bp 73–74° (1.6 mm); 15 hr reaction time]. [d] These yields were calculated on the basis of *ca.* 20% recovery of starting material.

Table II
Europium-Induced Shifts in the Nmr Spectra (CCl_4, TMS) of 5- and 7-Aceto-4-methyl-3-chromene (6b and 5b)

Compd	Downfield shift, Hz C-2	C-3	C-4′	CH_3CO
5b	18	10	13	129
6b	35	35	101	163

generalization was noted in the case of **5b** and **6b**; in the case of **6b** the ketone carbonyl shielded the C-4′ methyl protons, causing them to appear at higher field than the corresponding methyl protons in the 7 isomer (**5b**).

The nmr spectra of **5b** and **6b** were recorded with added Euroshift-F and the shifts are reported in Table II. The magnitude of the shift for the methyl ketone signal, compared to that for the C-2 and C-3 protons, clearly indicates that the europium formed a complex with the ketone moiety and not the ring oxygen. The magnitude of the shift for the C-4′ methyl protons in **6a** compared to **5a** clearly establishes the structures of the two isomers. The europium-induced shifts in the aromatic region of the spectra of **5b** and **6b** also permitted unambiguous interpretation of the aromatic substitution pattern which was confirmed by spin–spin decoupling experiments.

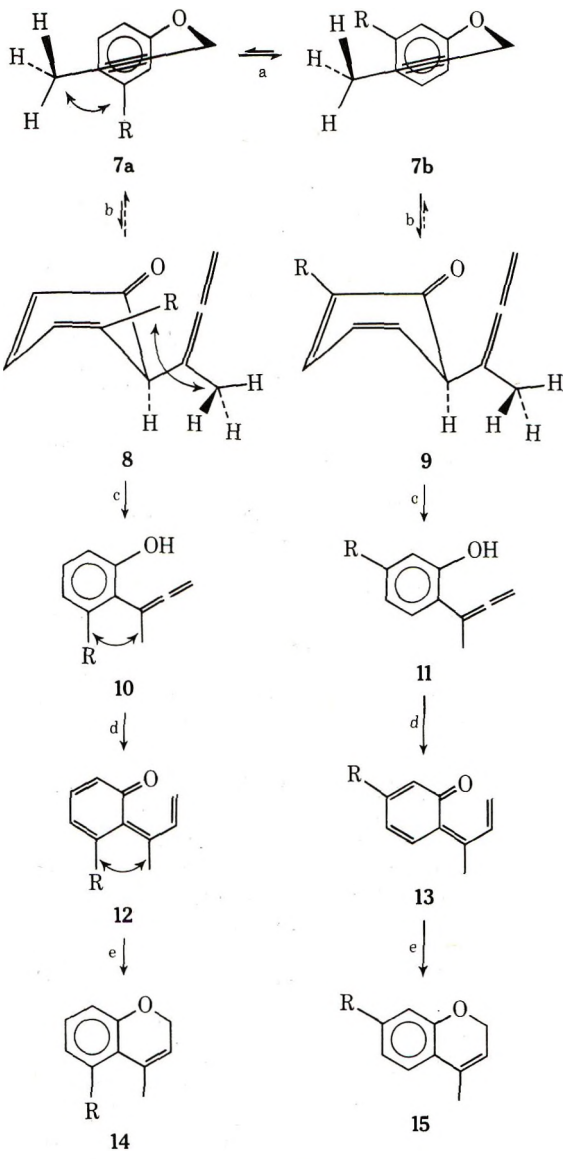
Support for the nmr structural assignments was obtained from a comparison of the ir spectra of the 5- and 7-substituted isomers in the out-of-plane bending region below *ca.* 900 cm^{-1}.

It is evident, from examination of the data presented in Table I, that the incorporation of a 3′-methyl substituent in the aryl propargyl ether usually resulted in an increased tendancy for the cyclization to occur para to the 3 substituent on the aromatic ring (*cf.* para:ortho ratios in the cyclization of **4** relative to **1**).

In the thermal cyclization of aryl propargyl ethers (*e.g.*, **7**) the obvious determinant of regioselectivity is the initial Claisen rearrangement (reaction b, Scheme I). It is difficult, however, to propose a specific rationalization for the regioselectivity, since the product-determining step in the *mechanistic sequence*[5] *is not known.*

The initial [3,3] sigmatropic rearrangement can occur either ortho or para to the 3 substituent on the aromatic ring. In the rearrangement of **7** to **8** (*i.e.*, cyclization ortho to the aryl substituent) the aryl propargyl ether must assume a conformation like **7a**; in this conformation there is a steric interaction between the C-3 substituent and the C-4′ methyl group which could increase the energy requirement in the conversion of **7a** to **8**. In the rearrangement to **9** the conformation necessary for this reaction, **7b**, is not sterically encumbered.

Scheme I



The steric interaction between the C-4′ methyl group and the C-3 substituent may become more severe in the transition state leading to **8**. As C-2 and C-3′ rehybridize the substituents on these two carbon atoms move closer together. While the exact geometry of the transition state is uncertain, this latter interaction is evident from the structure of the allene intermediate (**8**) wherein these two substituents lie in somewhat closer proximity relative to

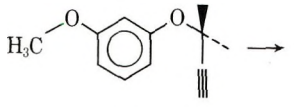
7a. Once again a similar steric interaction does not exist in the rearrangement of 7b to 9.

The observation (Table I) that the highest degree of regioselectivity was attained in the cyclization of 4d would support this hypothesis, since the tetravalent carbon would be expected to offer the greatest degree of steric hindrance in the series examined.

The next step in the mechanistic sequence is the enolization of the dienone (8 or 9). Normally the enolization process is considered to be rapid; however, in the case of the Claisen rearrangement of meta-substituted allyl phenyl ethers steric hindrance has been suggested as a factor which may retard this process.[6] Thus if the rearrangement of 7a to 8 is reversible then the steric hindrance of enolization of 8 would tend to drive the reaction through 9 to yield the 7-substituted 3-chromene (15).

It would appear unlikely that the phenolic allene intermediate (10 or 11) would revert back to the dienone; thus any observed regioselectivity must be a consequence of one or both of the first two steps.

Recently the cyclization of the meta-substituted aryl α,α-dimethylpropargyl ether 16 was reported to proceed in a regioselective fashion to yield 17.[7] Based upon our experience with this reaction the regioselectivity appeared unlikely. In our hands the cyclization of 16 afforded a mixture of 17 and 18 in approximately equal amounts. The nmr spectrum of the mixture of 17 and 18 very clearly showed the presence of the two isomers and the structures were confirmed by nmr and ir following glc separation. The discrepancy between our results and those of Hlubucek, *et al.*,[7] is difficult to rationalize, particularly since the latter workers did report the nmr spectrum of 17. Furthermore, these workers did examine the crude reaction product (glc and nmr) and concluded that if 18 was formed it was present to the extent of less than 3%.[7]



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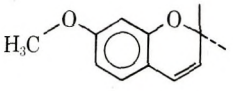

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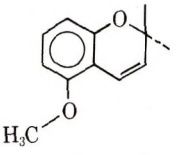

18

More recently it has been reported that 2-hydroxy-4-(1′,1′-dimethylprop-2-ynyloxy)acetophenone undergoes regioselective ortho cyclization. 2-Acetoxy-4-(1′,1′-dimethylprop-2-ynyloxy)acetophenone, on the other hand, cyclized to give a 1:2 ratio of para- and ortho-cyclized products.[8]

Iwai and Ide, on the basis of a few examples, concluded that resonance electron-donating substituents in the meta position (*i.e.*, ortho or para to the aromatic terminus in the Claisen rearrangement) facilitated the cyclization of the aryl propargyl ethers to the corresponding 3-chromenes (*i.e.*, higher product yield).[3] In our study we chose a range of electron-withdrawing ($OCOCH_3$ and $COCH_3$) and electron-donating (CH_3, OCH_3, and NEt_2) substituents to study the electronic effects (on the yield in this reaction).

Based upon the data given in Table I and on previous observations[2,5c] it is obvious that electronic effects do have a significant influence upon the reaction.

In the cyclization of 1 both strongly electron-donating and electron-withdrawing substituents appear to have an adverse effect upon the reaction. In the cyclization of both 1b and 1c the yield of chromenes was low and the reaction was accompanied by extensive polymerization. In the cyclization of 4 the reaction proceeded reasonably well with a strong electron-withdrawing substituent (*cf.* 4b); however, it gave little or no cyclized product in the case of a strong electron-donating substituent (*cf.* 4c).

A comparison of 4a, 4d, and 4e revealed that the yields increased as the electron-donating properties of the meta substituent decreased. Furthermore, based on reaction times and recovery of starting material, the reactions appeared to proceed faster with electron-donating meta substituents.

The data are most readily explained with the assumption that the initial Claisen rearrangement is the rate-limiting step[5a] in the reaction sequence. Electron-withdrawing meta substituents will decrease the electron density at the aromatic terminus of the Claisen rearrangement and retard the reaction. Thus, in the case of a strong electron-withdrawing substituent the rate of the Claisen rearrangement is sufficiently slow so as to permit polymerization of the terminal acetylene to become a major side reaction. This would explain the marked increase in yield that was observed in the cyclization of the nonterminal acetylene, 4b, compared to the terminal acetylene, 1b.

Electron-donating meta substituents would increase the rate of the initial Claisen rearrangement and retard the enolization of the allenic dienone intermediates, 8 and 9. Strong electron-donating substituents could retard the enolization to the extent that side reactions with 8 and 9 become dominant.[9] This effect along with a possible steric hindrance of enolization could explain why the cyclization of 4c proceeded so poorly.

Further research will be directed toward a study of solvent effects on the regioselectivity of this cyclization reaction. It is possible that contaminants (*e.g.*, mono-*N*-ethylaniline or trace metals) may exert an influence which could explain the difference between our data and those previously reported for the cyclization of 16.[7]

Table III
Preparation of the Aryl Propargyl Ether Intermediates

Compd[a]	R	R′	Bp, °C (mm)	Yield, %
1a	H	OCH_3	109.5 (4.5)	84
4a	CH_3	OCH_3	96 (0.6)	85
1b	H	$COCH_3$	99 (0.32)	86
4b	CH_3	$COCH_3$	114 (0.9)	79
1c	H	$N(C_2H_5)_2$	118 (0.4)	31
4c	CH_3	$N(C_2H_5)_2$	159 (3.0)	56
1d	H	CH_3	75 (1.5)	95
4d	CH_3	CH_3	90 (2.1)	80
1e	H	$OCOCH_3$	114 (0.7)	69
4e	CH_3	$OCOCH_3$	113–114 (0.5)	55
19	H	*p*-CH_3	69 (1.4)	79

[a] Satisfactory microanalytical data (±0.3% for C, H, and N) were reported for all compounds listed.

Experimental Section

Nmr spectra were determined in CCl_4 solution (containing *ca.* 1% TMS as an internal standard) on a Varian T-60 spectrometer; peak positions of multiple signals were confirmed by spin-spin decoupling. Infrared spectra were determined neat using a Perkin-Elmer Model 237 spectrophotometer. The uv spectra were determined in 95% ethanol solution on a Beckman DB-G grating spectrophotometer. The purity of analytical and spectral samples was confirmed by glc and ortho:para ratios were determined by photocopying the chromatogram, cutting out the chromatographic peak, and weighing the paper (Varian Aerograph Model 90-P with a thermal conductivity detector); nitrogen was used as the carrier gas and gas flow rates were *ca.* 176 ml/min except for that of 5d and 6d, which was *ca.* 52 ml/min. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

The aryl propargyl ethers were prepared according to the method previously described.[2] The yields and boiling points of the aryl propargyl ethers are given in Table III.

The 3-chromenes were prepared according to the method previously described[2] and reaction times, per cent yields, boiling points, and isomer ratios are given in Table I. Satisfactory microanalytical data (±0.4% for C, H, and N) were reported for all new compounds prepared.

5-Methoxy- and 7-Methoxy-4-methyl-3-chromene (6a and 5a). The isomeric mixture was separated by preparative glc (30% Carbowax, 12 ft × 0.375 in. column at 240° with 50-μl injection) to yield **6a** and **5a** with retention times of 21.4 and 27.5 min, respectively. **6a** had ir 938 (w), 909 (w), 780 (m), 763 (m), and 733 cm^{-1} (w); uv max 228 nm (ε 9330) and 276 (4650); nmr δ 2.14 (q, 3, $J_{4',3} \cong J_{4',2}$ = 1.6 Hz), 3.77 (s, 3), 4.53 (pair of q, 2, $J_{2,3}$ = 4.5 Hz), 5.44–5.64 (m, 1), 6.34–6.75 (m, 2), and 7.05 (t, 1, J_o = 8 Hz). **5a**[10] had ir 998 (w), 839 (w), 807 (m), and 745 cm^{-1} (w); uv max 228 nm (ε 16,400), 272 (3890), and 312 (1600); nmr δ 1.97 (q, 3, $J_{4',3} \cong J_{4',2}$ = 1.6 Hz), 3.72 (s, 3), 4.75 (pair of q, 2, $J_{2,3}$ = 4.0 Hz), 5.32–5.52 (m, 1), 6.32–6.53 (m, 2), and 6.91–7.13 (pair of t, 1).

5-Aceto- and 7-Aceto-4-methyl-3-chromene (6b and 5b). The isomeric mixture was separated by preparative glc (30% Carbowax, 12 ft × 0.375 in. column at 220° with 100-μl injections) to yield **6b** and **5b** with retention times of 78 and 147.6 min, respectively. **6b** had ir 1686 (s), 922 (w), 876 (m), 790 (s), 770 (w), 747(m), and 710 cm^{-1} (w); uv max 223 nm (ε 10,800), 262 (6310), and 328 (2940); nmr δ 1.87 (q, 3, $J_{4',3} \cong J_{4',2}$ = 1.5 Hz), 2.50 (s, 3), 4.58 (pair of q, 2, $J_{2,3}$ = 4.4 Hz), 5.65–5.89 (m, 1), and 6.85–7.40 m, 3). **5b** had ir 1678 (s), 958 (w), 918 (w), 884 (m), 835 (s), and 749 cm^{-1} (w); uv max 237 nm (ε 12,700), 291 (6480), and 340 (3650); nmr δ 2.02 (q, 3, $J_{4',3} \cong J_{4',2}$ = 1.9 Hz), 2.46 (s, 3), 4.38 (pair of q, 2, $J_{2,3}$ = 3.7, $J_{2,4'}$ = 1.9 Hz), 5.57–5.83 (m, 1), and 7.07–7.60 (m, 3).

5-(*N,N*-Diethylamino)-3-chromene (3c) was purified by preparative glc (20% SE-30, 5 ft × 0.375 in. column at 220° with 25-μl injections) with a retention time of 9.4 min: ir 1018 (m), 977 (w), 766 (s), and 750 cm^{-1} (s); uv max 218 nm (ε 15,100), 225 (9490), and 292 (5730); nmr δ 1.0 (t, 6, J = 7 Hz), 3.02 (q, 4), 4.70 (pair of d, $J_{2,3}$ = 4, $J_{2,4}$ = 1.9 Hz), 5.72 (pair of t, 1, $J_{3,4}$ = 9.5 Hz), 6.48–6.68 (m, 4), and 7.09 (t, 1, J_o = 8 Hz).

7-Methyl- and 5-Methyl-3-chromene (2d and 3d). The isomeric mixture was separated by preparative glc (30% Carbowax, 12 ft × 0.375 in. column at 180° with 50-μl injection) to yield **2d** and **3d** with retention times of 40.3 and 45.8 min, respectively. **2d** had ir 1035 (s), 1021 (w), 945 (w), 812 (s), 742 (w), and 679 cm^{-1} (w); uv max 226 nm (ε 14,600), 271 (4230), and 310 (3160); nmr δ 2.27 (s, 3), 4.83 (q, 2, $J_{2,3}$ = 3.5, $J_{2,4}$ = 1.9 Hz), 5.70 (pair of t, 1, $J_{3,4}$ = 9.5 Hz), 6.43 (pair of t, 1), and 6.55–6.95 (m, 3). **3d** had ir 1020 (m), 951 (w), 772 (s), 753 (s), 678 (w), and 653 cm^{-1} (w); uv max 228 nm (ε 10,700), 272 (4470), and 310 (2080); nmr δ 2.25 (s, 3), 4.76 (q, 2, $J_{2,3}$ = 3.8, $J_{2,4}$ = 1.9 Hz), 5.81 (pair of t, 1, $J_{3,4}$ = 9.5 Hz), 6.66 (pair of t, 1), 6.49–6.80 (m, 2), and 7.00 (t, 1, J_o = 7.7 Hz).

7-Methyl- and 5-Methyl-4-methyl-3-chromene (5d and 6d). The isomeric mixture was separated by preparative glc (30% Carbowax, 12 ft × 0.375 in. column at 220° with 10-μl injections) to yield **5d** and **6d** with retention times of 127.2 and 139.8 min, respectively. **5d** had ir 1020 (m), 936 (w), 814 (s), and 784 cm^{-1} (w); uv max 221 nm (ε 13,200), 260 (3820), and 307 (2530); nmr δ 1.96 (q, 3, $J_{4',2} \cong J_{4',3}$ = 1.8 Hz), 2.26 (s, 3), 4.75 (pair of q, $J_{2,3}$ = 4.0, $J_{2,4'}$ = 1.8 Hz), 5.46–5.66 (m, 1), and 6.54–7.13 (m, 3). **6d**[10] had ir 1015 (m), 937 (m), 911 (w), 784 (s), 771 (s), 741 (m), and 708 cm^{-1} (w); uv max 223 nm (ε 17,200), 263 (5910), and 305 (2650); nmr δ 2.17 (q, 3, $J_{4',2} \cong J_{4',3}$ = 1.6 Hz), 2.44 (s, 3), 4.43 (pair of q, $J_{2,3}$ = 4.5 Hz), 5.56–5.91 (m, 1), and 6.56–7.24 (m, 3).

5-Acetoxy- and 7-Acetoxy-3-chromene (3e and 2e). The isomeric mixture was separated by preparative glc (30% NPGA, 12 ft × 0.375 in. column at 180° with 50-μl injections) to yield **3e** and **2e** with retention times of 76.4 and 88.6 min, respectively. **3e** had ir 1770 (s), 982 (m), 921 (m), 793 (w), 772 (m), and 749 cm^{-1} (s); uv max 228 nm (ε 16,400), 272 (3890), and 312 (1596); nmr δ 2.23 (s, 3), 4.82 (q, 2, $J_{2,3}$ = 3.5, $J_{2,4}$ = 1.9 Hz), 5.77 (pair of t, 1, $J_{3,4}$ = 10 Hz), 6.44 (pair of t, 1), 6.50–6.75 (m, 2), and 7.09 (t, 1, J = 8 Hz). **2e** had ir 1767 (s), 1034 (m), 1007 (w), 783 (m), and 753 cm^{-1} (s); uv max 229 nm (ε 10,500), 275 (3370), and 311 nm (3320); nmr δ 2.20 (s, 3), 4.90 (q, 2, $J_{2,3}$ = 3.5, $J_{2,4}$ = 1.6 Hz), 5.76 (pair of t, 1, $J_{3,4}$ = 10 Hz), 6.46 (pair of t, 1), 6.46–6.64 (m, 2), and 6.82–7.05 (m, 1).

5-Acetoxy- and 7-Acetoxy-4-methyl-3-chromene (6e and 5e). The isomeric mixture was separated by preparative glc (30% SE-30, 20 ft × 0.375 in. column at 230° with 50-μl injections) to yield **6e** and **5e** with retention times of 41.6 and 50.0 min, respectively. **6e** had ir 1764 (s), 970 (m), 916 (w), 865 (w), 789 (m), 769 (m), 738 (w), and 698 cm^{-1} (w); uv max 225 nm (ε 10,400), 267 (3240), and 307 (2960); nmr δ 2.07 (q, 3, $J_{4',2} \cong J_{4',3}$ = 1.5 Hz), 2.20 (s, 3), 4.62 (pair of q, 2, $_{2,3}$ = 4 Hz), 5.48–5.68 (m, 1), 6.56 (pair of d, 1, J_o = 10, J_m = 1.4 Hz), 6.72 (pair of d, 1), and 7.13 (t, 1). **5e** had ir 1767 (s), 1015 (m), 950 (w), 907 (m), 897 (m), 819 (m), 787 (w), and 761 cm^{-1} (w); uv max 220 nm (ε 8730), 267 (2540), and 306 (3140); nmr δ 2.00 (q, 3, $J_{4',3} \cong {}_{4',2}$ = 1.6 Hz), 2.22 (s, 3), 4.83 (pair of q, 2, $J_{2,3}$ = 3.5 Hz), 5.46–5.66 (m, 1), 6.50–6.89 (m, 2), and 6.93–7.30 (m, 1).

7-Methoxy- and 5-Methoxy-2,2-dimethyl-3-chromene (17 and 18). 3-(3-Methoxyphenyloxy)-3-methylbutyne (**16**)[7] was cyclized in *N,N*-diethylaniline heated under reflux according to the method of Hlubucek, *et al.*[7] In two additonal experiments **16** was cyclized in a *N,N*-diethylaniline solution heated on an oil bath at 210–215° for 8 hr under a nitrogen atmosphere. In all three experiments the results were substantially the same [*ca.* 85% yield, bp 104–105° (1.4 mm)].

The isomeric mixture was separated by preparative glc (30% Carbowax, 12 ft × 0.375 in. column at 220° with 100–200 μl injections) to yield **17** and **18** with retention times of 28.9 and 23.6 min, respectively, in a ratio of 49:51. **17** had ir 1031 (m), 998 (m), 831 (w), 799 (w), and 702 cm^{-1} (w); uv max 222 nm (ε 19,800), 281 (6970), and 304 (6270); nmr δ 1.40 (s, 6), 3.75 (s, 3), 5.41 (d, 1, $J_{3,4}$ = 10 Hz), 6.23 (d, 1, $J_{3,4}$ = 10 Hz), 6.43 (m, 2), and 6.84 (d, 1, J_o = 9 Hz). **18** had ir 989 (w), 888 (m), 791 (w), and 750 cm^{-1} (s); uv max 226 nm (ε 18,100) and 278 (7260); nmr δ 1.40 (s, 6), 3.80 (s, 3) 5.48 (d, 1, $J_{3,4}$ = 10 Hz), 6.32 (d of d, 2, J_o = 8, J_m = 2.5 Hz), 6.63 (d, 1), and 6.99 (t, 1, J_o = 8 Hz).

6-Methyl-3-chromene (20)[11] had ir 1038 (s), 1031 (m), 936 (w), 920 (w), 874 (w), 816 (s), 760 (m), 753 (m), 705 (w), and 680 cm^{-1} (w); uv max 223 nm (ε 19,600), 265 (4010), and 314 (3000); nmr δ 2.21 (s, 3), 4.77 (q, 2, $J_{2,3}$ = 3.4, $J_{2,4}$ = 1.9 Hz), 5.72 (pair of t, 1, $J_{3,4}$ = 9.5 Hz), 6.39 (pair of t, 1), and 6.52–7.06 (m, 3).

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Registry No.—**1a**, 41580-72-7; **1b**, 34264-13-6; **1c**, 50584-90-2; **1d**, 5651-89-8; **1e**, 50584-91-3; **2a**, 18385-89-2; **2d**, 18385-88-1; **2e**, 50584-92-4; **3a**, 41580-69-2; **3c**, 50584-93-5; **3d**, 50584-94-6; **3e**, 13849-33-7; **4a**, 50584-95-7; **4b**, 50584-96-8; **4c**, 50584-97-9; **4d**, 50584-98-0; **4e**, 50584-99-1; **5a**, 50585-00-7; **5b**, 50585-01-8; **5d**, 50585-02-9; **5e**, 50585-03-0; **6a**, 50585-04-1; **6b**, 50585-05-2; **6d**, 50585-06-3; **6e**, 50585-07-4; **16**, 34191-90-7; **17**, 17598-02-6; **18**, 13162-78-2; **19**, 5651-90-1; **20**, 18385-83-6.

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Gas-Phase and Liquid-Phase Oxidations of Isobutylene and Cyclopentene

Frank R. Mayo,*[1] Peter S. Fredricks, Theodore Mill, Jane K. Castleman, and Timothy Delaney

Department of Chemistry, Stanford University, and Stanford Research Institute, Menlo Park, California 94025

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Radical-initiated oxidations of isobutylene in benzene solution at 80 and 147° and several atmospheres of total pressure are compared with gas-phase oxidations at 147 and 197° and 0.1–0.5-atm total pressure. The isobutylene reacts mostly by the addition mechanism and all oxidations give mostly acetone, isobutylene oxide, and a high-boiling residue as primary products. Radical-initiated oxidations of cyclopentene have been investigated at 100°, from 9 *M* in the neat hydrocarbon to 0.025 *M* in chlorobenzene and from 0.027 *M* to 0.056 *M* in the gas phase. The rates and products of oxidation appear to be similar in the two phases. Gas-phase oxidations have also been carried out at 155° and good material balances obtained. The main primary product from oxidation of cyclopentene appears to be cyclopentenyl hydroperoxide, but this peroxide is less stable than the products from isobutylene or alkanes, and it causes autocatalysis and gives secondary products. The gas-phase decomposition of cyclopentenyl hydroperoxide was studied at 100° and the effects of some additives were determined. The principal product is cyclopentenol, but, in the presence of cyclopentene and oxygen and in many oxidations of cyclopentene, a high-boiling residue is obtained, apparently a secondary product.

Other work from this laboratory has shown that, except for concentration effects, gas-phase and liquid-phase oxidations of isobutane[2] and *n*-butane[3] are remarkably similar in rates and products. The present paper compares liquid-phase oxidations of isobutylene at 80 and 147° with its gas-phase oxidations at 147 and 197° and compares liquid-phase oxidations of cyclopentene at 100° with its gas-phase oxidations at 100 and 155°. Our findings are discussed in our Summary and Conclusions. The following paper describes liquid-phase oxidations of α-methystyrene above 110° and the nature of the residues obtained in that oxidation.[4]

Gas-Phase Oxidations of Isobutylene at 147°[5a]

Experimental. Most oxidations were initiated by di-*tert*-butyl peroxide and were carried out in a 526-ml Pyrex flask for 2 hr at 147°, using conventional vacuum techniques. An unheated trap of volume 26 ml was connected to the reaction vessel, just above the level of the oil bath, to facilitate collection and determination of the highest boiling oxidation products. Experiments 42 and 43 were carried out in a new flask without the trap. This change in comparison with expt 38 and 39 seems to have decreased oxygen consumption without affecting the yield of acetone.

The following analytical procedure was ultimately adopted. At the end of an oxidation, the residue trap was cooled and filled with liquid nitrogen and the stopcocks from the reaction vessel were opened slowly. The noncondensable gases, O_2, CO, and N_2 (from *t*-Bu_2N_2), were then pumped off by a Toepler pump. Their volume and pressure were measured and they were then determined by mass spectrometric analysis. The residue trap was then allowed to warm to room temperature, and the most volatile material distilled into the first cold trap in the vacuum train. The residue not volatile at room temperature was weighed by cutting the residue trap off from the reaction flask at about 0.01 mm. The second trap in this train was cooled in liquid nitrogen and the first one was warmed to −125° in a methylcyclohexane slush bath. The pressure increase as the volatile material distilled was followed on a McLeod gauge. When the pressure had decreased to the original value, the condensate in the second trap was warmed to room temperature, measured with the Toepler pump, and subjected to mass spectrometric analysis. Formaldehyde has been found in this fraction, as shown in Table I. The liquids that remain in the first trap were then analyzed by gc after the addition of an exact quantity of benzene as internal standard. Although no formaldehyde has been found in this fraction, some may have polymerized here or elsewhere in the apparatus.

Experiment 37 in Table I is the best of our first oxidations, where the blanks appeared to consume more oxygen, for reasons that are still obscure. This experiment checked well with expt 35 and 36 (not shown), where the analyses are less complete, and is consistent with the blanks 38 and 39 (without isobutylene), which illustrate the reproducibility of our experiments. In expt 35–37, the total pressures decreased by about 2 mm during reaction, very close to the change calculated from the analyses.

Hydroperoxide was estimated in expt 35 by iodometric titration of the condensable liquids,[6] which were washed from the trap with isopropyl alcohol, the solvent used for the titration. No attempt was made to identify the hydroperoxide, which was obtained in 8.4% yield on the oxygen consumed.

From the work of Batt and Benson,[7] the first-order rate constant for decomposition of *t*-Bu_2O_2 at 147° is 1.35×10^{-4}/sec, and 62.2% of it should decompose in 2.0 hr. The data in Table I show that the experimental fractions decomposed fall in the satisfactory range of 62–66% in five out of seven listed experiments.

Results. The most useful of our many experiments (many with less complete analyses) are summarized in Table I. The numbers indicate the order in which experiments were carried out. These results show that, although successive experiments would check fairly well, there were some abrupt and significant shifts in results that we are unable to account for. Thus, the blank experiments, 38, 39, 42, and 43, show similar rates of decomposition of *t*-Bu_2O_2 and similar yields of acetone but different absorptions of oxygen and productions of carbon oxides. Experiment 13 (not shown because of incomplete analyses) should have been entirely comparable to these blanks, but it gave a quantitative yield of acetone, as expected from the work of Raley, *et al.*,[8] for the same rate of disappearance of peroxide.

If any *tert*-butyl alcohol was formed it was not resolved from the methanol by gc. Very little is expected because so many of the *tert*-butoxy radicals cleave in the gas phase at 150°.[2] Further, the 73–88% yields of acetone in the blanks limit the yields of *tert*-butyl alcohol to 27 to 12% and there is never enough methanol and other one-carbon compounds to match the acetone.

Table II summarizes the products of oxidation of isobutylene, calculated in the following way. The products of oxidations 37, 45, and 40 at 147° are approximated by subtracting from the total reaction products those that are formed in the blanks with peroxide but without isobutylene, adjusting the blanks slightly and proportionately so that the same amount of *t*-Bu_2O_2 is decomposed in the blank as in the corresponding oxidation.[9] All the results are then expressed in terms of 1 mol of isobutylene reacting. The isobutylene accounted for is the sum of the acetone, isobutylene oxide, methacrolein, and residue. On this basis, essentially all the isobutylene is accounted for in expt 37 and 40 but only 78% in 45, which is not very consistent with the blank. However, it appears that about one-half to three-fourths of a molecule of isobutylene is oxidized per initiating *tert*-butoxy radical regardless of the initial concentration of isobutylene. Of the isobutylene

Table I
Gas-Phase Oxidations of Isobutylene for 2 Hr at 147°[a]

Expt no.	38	39	37	45	42	43	40	46[a]	47[a]
Reactants									
i-C_4H_8	0	0	65.2	65.2	0	0	16.8	0	15.2
O_2	16.8	16.8	16.28	16.8	15.6	15.6	16.8	14.3	15.2
t-Bu_2O_2	2.68	2.68	2.68	2.68	2.47	2.47	2.68	2.29[a]	2.43[a]
Initial pressure, Torr	89	89	397	391	90	89	165.5	90	165.5
Change			−2	−2	+11	+13	+5.5	+8	+3.5
Reactants consumed									
i-C_4H_8	0	0	2.51	1.5	0	0	1.2	0	1.63
O_2	1.84	2.14	5.55	4.53	1.21	1.6	3.42	1.45	3.62
t-Bu_2O_2	1.77	1.68	1.69	1.56	1.57	1.74	1.76	1.35[a]	1.32[a]
Products									
Acetone	2.58	2.60	3.37	2.56	2.79	2.62	3.32	0.75	1.28
MeOH (+ t-BuOH)	1.04	1.26	1.48	0.98	1.24	1.29	1.48	0.99	0.99
CH_2O				Trace		0.35		0.02	0.01
CO	0.48	0.58	0.64	0.28	0.32	0.31	0.46	0.15	0.32
CO_2	0.14		0.71	0.23		0.05	0.26[d]	0.06	0.17
$Me_2C(O)CH_2$	0	0	0.68	0.49	0	0	0.33	0	0.30
$H_2C{=}C(Me){-}CHO$	0	0	0.2	0.2	0	0	0.1	0	0
RO_2H			0.46[c]						
Residue[b]	0	0	0.80	0.46	0	0	0.35[d]	0	0.23

[a] Quantities are in moles × 10^4. Experiments 46 and 47 used t-Bu_2N_2 instead of t-Bu_2O_2 and were run for 30 min at 197°. Isobutylene and N_2 were also formed (see text). [b] Estimated (C in residue)/4; see text. [c] Result is not available; figure comes from the very similar expt 35. [d] Result is not available; figure is from duplicate run, corrected to same amount of i-C_4H_8 reacting.

Table II
Net Reactions in Gas-Phase Oxidations of Isobutylene at 147 and 197°[a]

	Quantities in moles/mole of i-C_4H_8									
Expt. no.	i-C_4H_8	+ O_2	→ AcMe	+ CH_2O	+ MeOH	+ $Me_2C(O)CH_2$	+ $H_2C{=}C(Me){-}CHO$	+ residue[b]	+ CO	+ CO_2
37 − 39[c]	1	1.36	0.31		0.09	0.27	0.08	0.32	0.02_4	0.21
45 − (42 43)[d]	1	2.10	0.01		−0.14	0.33	0.13	0.31	0.01	0.14
40 − (42 43)[e]	1	1.56	0.37		0.11	0.27	0.08	0.29	0.11	0.20
47 − 46[f]	1	1.35	0.34	0.19	0.01	0.18	0	0.14	0.10	0.07

[a] Results of oxidation of i-C_4H_8 are corrected by subtracting results of indicated blank without i-C_4H_8, correcting proportionately the products from the blank so that the same amount of initiator was decomposed in the oxidation and the blank. In two instances, the blank is taken as the average of expt 42 and 43. [b] (Gram-atom C)/4. [c] Early experiment with high [i-C_4H_8] at 147°. [d] Late experiment with high [i-C_4H_8] at 147°. [e] Intermediate experiment with low [i-C_4H_8] at 147°. [f] 197° experiment with low [i-C_4H_8].

brought into reaction, about one-third appears as acetone (and presumably formaldehyde and its oxidation product, CO), a little less as isobutylene oxide and residue. Methacrolein is a minor product.

Residues of Gas-Phase Oxidations of Isobutylene at 147°. Several large-scale runs were made to obtain material for investigation. These products had essentially the same infrared spectrum as the residues from experiments in Table I. One residue contained 52.31% C, 9.05% H, and 38.64% O by difference, and had an average molecular weight of 145, corresponding to the average empirical formula $(C_4H_{8.25}O_{2.22})_{1.58}$. Another residue was distilled at about 100° (1 Torr) to yield a distillate containing 50.6% C, 8.7% H, and 40.7% O by difference and having an average molecular weight of 229, corresponding to the average empirical formula $(C_4H_{8.21}O_{2.41})_{2.41}$. The higher molecular weight corresponds to better removal of volatile materials. Note that the indicated H:C ratios are slightly higher than in isobutylene starting material, suggesting the presence of *tert*-butoxy or methyl groups from the initiator.

Gas-phase chromatography indicated the presence of many components but only two major high-boiling components. There was no certainty either that all the sample had eluted or that the residue had not decomposed in the injection block (~160°). Thin layer chromatography on alumina with benzene containing 10% methanol showed considerable streaking but again showed two major components.

The nmr spectrum in CCl_4 solution was complicated. Methyl protons in four different environments were present and there was no splitting of the peaks, indicating the absence of protons on adjacent carbons. The position of the methylene protons in the spectrum showed that they were probably close to oxygen functions. Hydroxyl and aldehyde protons were found and there was also the possibility of vinyl protons. A rough estimate of the numbers of different types of protons is shown in Table III. The combined residues distilled at ~0.1 Torr, and attempts were made to split them into fractions of different volatility. All samples have similar ir spectra, but molecular weight determinations have given values ranging from 150 to 725.

The possibility that this residue was a polymer of methacrolein was investigated. Mixtures of methacrolein vapor, isobutylene, and oxygen were kept in the reaction vessel at 147° for 2 hr and a somewhat similar residue was isolated (identified by infrared). In this case it seems that the methacrolein initiates the oxidation, as no residue was found with methacrolein alone or admixed with either isobutylene or oxygen separately. Methacrolein was polymerized in the vapor phase with di-*tert*-butyl peroxide as initiator at 147°, and the infrared spectrum of the product

Table III
Nmr Investigation of High-Boiling Residue

Type of proton	Relative numbers: H atoms	Relative numbers: Groups
Methyl (four types)	18	6
Methylene	~6	3
Hydroxyl	4	4
Aldehyde	1	1
(Vinyl)	4	2

Table IV
Liquid-Phase Oxidations of Isobutylene in Benzene Solution at 147 ± 3°

Expt no.	L4	L5	L6
Time, min	95 ± 5	95 ± 5	50 ± 5
Reactants, mmol			
Isobutylene	30.9	31.2	36.0
t-Bu_2O_2	0.075	0	0
Benzene	81.0	84.2	82.9
Oxygen, psi[a]	22.5–36.5 (225.5)	28–47 (222)	179–210 (240)
Products, mmol			
O_2 consumed[b]	~7.2	8.6	8.9
O_2 accounted for[c]	5.5 + 3.1	5.5 + 7	6.6 + 3.7
i-C_4H_8 accounted for[c]	8.9	9.6	10.1
Acetone	4.2–0.08[d]	4.2	5.9
Isobutylene oxide	2.6	2.5	1.3
Hydroperoxides[e]	0.05	0.07	0.07
Residue	8.7[f]	12.7[g]	11.7[h]

[a] Estimated partial pressures of oxygen in excess of the calculated vapor pressures of isobutylene and benzene (in parentheses). For these calculations the vapor pressures of pure isobutylene and benzene are taken as 82.5 and 600 psi, respectively, and their partial pressures in mixtures are taken as proportional to their mole fractions. The gauge pressures were 15 psi less than the indicated total pressures. [b] By pressure decrease in reservoir. [c] First figure for O_2 includes O in acetone, the assumed formaldehyde, and epoxide; second is oxygen in whole residue based on O content of less volatile fraction. Figure for i-C_4H_8 is sum of acetone, epoxide and (gram-atoms of C in residue)/4. [d] 0.08 mmol of acetone is calculated to have arisen from decomposition of 0.042 mmol of t-Bu_2O_2. [e] By iodometric titration. [f] Distillation at 10 Torr pressure gave 48 mg, bp 85–90°, and 182 mg of less volatile material, 45.3% C, 10.4% H, 44.3% O by difference, mol wt 233, corresponding to $C_{8.78}H_{24.0}O_{6.46}$. [g] Residue from distillation to 120° (1 atm) absorbed 0.24 mmol of H_2 on a rhodium on alumina catalyst. For calculations, it is assumed to have the same analysis as the residue in expt L6. [h] Distillation at 15 mm pressure gave 112 mg, bp 95–115°, and 174 mg of less volatile material, 48.9% C, 9.37% H, 41.73% O by difference, mol wt 229, corresponding to $C_{9.32}H_{21.3}O_{5.97}$.

was similar to that of the residue formed in the oxidation. However, the H:C ratios in our residues, 2:1, preclude much contribution from polymer or oxidation products of methacrolein, C_4H_6O.

Gas-Phase Oxidations of Isobutylene at 197° [5a]

Because of the slight reaction of isobutylene with oxygen at 147°, expt 46 and 47 were carried out at 197°. The results, summarized in Tables I and II, indicate that the products and yields per initiating radical are about the same at 197° as at 147°.

In these experiments, 2,2′-azoisobutane was used as initiator. It was prepared from *tert*-butylamine by the procedure of Boozer and Moncrief.[10] Its rate of gas-phase decomposition agreed well with that reported by Levy and Copeland.[11] The thermal decomposition of azoisobutane in oxygen (expt 46, Table I) gave acetone, CO, and CO_2, and also 1.10×10^{-4} mol of nitrogen and 0.70×10^{-4} mol of isobutylene, for which corrections were made in expt 47, Table II.

Oxidations of Isobutylene in Benzene Solution at 147° [5a]

Experimental. Oxidations were carried out in a glass liner of 23-ml capacity in a heated stainless steel rocker bomb, with interior temperatures measured by an iron–constantan thermocouple. Oxygen consumption was measured from the pressure drop in a calibrated reservoir. Reaction mixtures contained the indicated amounts of isobutylene (measured as the cold liquid) and di-*tert*-butyl peroxide in a total volume of 10 ml of benzene solution. Each mixture was placed in the glass liner and the bomb was quickly assembled. Oxygen pressure about 100 psi above the expected vapor pressure was applied and the bomb was rocked at 147 ± 3° for 95 ± 3 min. The bomb was then cooled to room temperature and a sample of the remaining gas was taken for mass spectrometric analysis. The liquid products were analyzed by gc and distillation. The small volume of solution, the high oxygen pressure, and the 95-min reaction time assure an adequate supply of oxygen in solution.

A blank experiment with t-Bu_2O_2 and oxygen but without isobutylene showed no perceptible absorption of oxygen and only the expected traces of acetone from decomposition of the peroxide. Thus benzene appears to be a suitably inert solvent.

Results. Table IV shows that oxidations of isobutylene in benzene solution are about as fast in the absence as in the presence of t-Bu_2O_2. Thus the reaction is self-initiating and we know nothing about kinetic chain lengths. At the higher oxygen pressure, without t-Bu_2O_2, the consumptions of isobutylene and oxygen are higher in 50 min than in 95 min at lower pressure. In expt L4 and L5 at about 2 atm of oxygen, the products are about 45% acetone, 28% isobutylene oxide, and 26% residue on the isobutylene consumed. These are all products of the addition mechanism of oxidation.[12a] Products of the abstraction mechanism, methacrolein and methallyl hydroperoxide, were missing or almost negligible. The acetone/epoxide ratio is higher at higher oxygen pressure, as expected.[13] The H:C ratio in the residue L4 is implausibly high, 2.73 being considerably higher than in isobutylene. The H:C ratio in residue L6 is 2.3, also high but comparable to those in gas-phase residues. We conclude that the stated analysis for L6, at least, is probably too low in carbon and too high in oxygen.

Oxidations of Cyclopentene[5b]

The major primary product of oxidation of cyclopentene is cyclopentenyl hydroperoxide, but the instability of this compound under oxidation conditions has resulted in severe analytical difficulties and in experimental data that are below our usual standard. Our results on cyclopentene are therefore presented as supplementary material (see paragraph at end of paper). However, the qualitative results are clear and our conclusions and a comparison with isobutylene appear below.

Summary and Conclusions

This work preceded most of our work on liquid-phase and gas-phase oxidations of isobutane[2] and n-butane[3] and presented more difficult problems before we had acquired later experience. Difficulties with cyclopentene were more serious; the major primary product is the allylic hydroperoxide. The instability of this peroxide is demonstrated by the autocatalysis in the oxidation of cyclopentene at 50°, established since this work was completed.[12b] Our rates of initiated oxidations at higher temperatures are therefore suspect. In our gas-phase decompositions of cyclopentenyl hydroperoxide at 100°, 30–40% was found to decompose in 8 hr. The major product of the decomposition is cyclopentenol, but with added cyclopentene and oxygen, considerable high-boiling residue was found.

Table V
Summary of Oxidations of Isobutylene at 80–197°

Medium	Benzene solution		Gas phase	
Expt no.	Ref 14	L4	37 – 39	47 – 46
Temp., °C	80	147	147	197
$[i\text{-}C_4H_8]_0$, M	~3.3	<3[a]	0.012	0.0027
Conversion, mol %	4	29	4	11
Products, %				
RO_2H	7.7[b]	0.6	(16[c])	
Methacrolein	10.3	~0	8	0
Acetone	18.6	46	31	34
Isobutylene oxide	24.2[d]	29	27	18
Residue	40.7	25	32	14
Residue composition[e]	$C_4H_7O_{1.6}$	$C_4H_{11}O_3$[e]	$C_4H_{9.2}O_{2.2}$	
Addition mechanism, %	81	~99	76	70–100

[a] Concentration of $i\text{-}C_4H_8$ in cold solution was ~3 M. [b] 2.7%, mostly methallyl hydroperoxide, in volatile fraction, 5.0% in residue. [c] In residue, included in yield of residue. [d] Includes 1.6% isobutylene glycol and 0.3% of its monoformate. [e] Average composition as four-carbon units; analysis of L4 is probably low in C, high in O.

Isobutylene reacts mostly by the addition mechansim to give saturated and more stable products; these data are more easily interpreted even if some of the products have a fairly high molecular weight. However, the expected minor products of the abstraction mechanism were often undetected at 147 and 197°.

Because of autocatalysis with the alkenes, we still do not have a quantitative comparison of rates of liquid-phase and gas-phase oxidations at the same concentration and temperature. With cyclopentene at 100°, the apparent $k_p/(2k_t)^{1/2}$ in chlorobenzene solution was found to be about four times that in the gas phase; we think that autocatalysis was small but significant. With isobutylene at 80°, autocatalysis was insignificant;[14] at 147°, autocatalysis was overwhelming. We have some good-looking rate and product data on gas-phase oxidations of cyclopentene at 155°, but the probability of autocatalysis makes them quantitatively suspect.

Isobutylene gives substantial proportions of high-boiling residue under all conditions that we have investigated.[14] This result appears to be associated with formation of polyperoxides and the addition mechanism.[4] The nature of this residue[14] is indicated below. However, cyclopentene reacts mostly by the abstraction mechanism and gives only a little dimeric peroxide residue under conditions where the products are stable.[12a] The higher proportions of residues in some experiments in this paper appear to be associated with secondary reactions of the hydroperoxide.

In our gas-phase oxidations of both alkenes below 1 atm pressure, there is little chain reaction and much of the involvement of alkene is due to the initiating radicals or their reaction products. The products from isobutylene, like those from α-methylstyrene in the liquid phase,[4] are unexpectedly high in hydrogen content, apparently owing to incorporation of methyl radicals from the initiator in the former instance and of formaldehyde from oxidation in the latter.

We now use the new data above on oxidations of isobutylene at 147 and 197° and previously published data[14] in benzene solution at 80°, all summarized in Table V, to consider the effects of phase change and temperature on the oxidation of isobutylene. We start with previously published results[14] in benzene solution at 80°. Here at least 18% of the isobutylene consumed is supposed to react by the hydrogen abstraction mechanism to give methallyl hydroperoxide, its decomposition product, methacrolein, and hydroperoxide groups in the residue. At least 81% reacts by the addition mechanism, to give mostly residue, and less isobutylene oxide and acetone. The residue consists mostly of C_4 units, joined together by peroxide or ether groups or by polymerization and condensation reactions of saturated and unsaturated aldehydes, but contains some alcohol and hydroperoxide groups associated with the hydrogen-abstraction mechanism.[14]

In a similar experiment at 147°, the oxidation becomes self-initiating and much faster. The yield of acetone increases, mostly at the expense of residue, but 25% of the latter is still found. This shift could be due to greater pyrolysis of polyperoxide groups, either during chain propagation or in secondary reactions. The obvious products of the abstraction mechanism (methallyl hydroperoxide and methacrolein) were not found, probably because they do not survive at the higher temperature and conversions used. Kinetic chain lengths must be fairly long at both temperatures, with considerable propagation by addition of peroxy radicals to double bonds, as shown in the yields of both acetone and epoxide.

In the gas phase at 147° the concentrations of both alkene and oxygen are much lower and the oxidations are much slower. Experiments 37 and 40 (Table I) show that less than one molecule of isobutylene is consumed per potential initiating radical. By hydroperoxide titration, which may measure both primary and secondary products, about half the residue comes from each of the addition and abstraction mechanisms. On this basis, the total contribution of the abstraction mechanism is 24%, somewhat more than the 18% in benzene solution at 80°. Since acetone, but little or no *tert*-butyl alcohol, is formed in the blanks in Table I, t-BuO· radicals from the t-Bu_2O_2 initiator must cleave, and most of the gas-phase attack of isobutylene must come from attack by methylperoxy and methoxy radicals. From product analyses, most of these radicals added to isobutylene, although alkoxy radicals are supposed to have more preference for abstraction than alkylperoxy radicals.[15,16] The high H:C ratios in the residues also point to incorporation of methyl radicals. Our experiments tell us little about any simple repeating chain process in the gas-phase oxidation of isobutylene; such processes require considerably higher concentrations (pressures) of reactants, as shown in gas- and liquid-phase oxidations of isobutane[2] and *n*-butane.[3]

The gas-phase oxidation at 197° is faster than at 147°, but the material balance is not adequate to tell us much about the competition between addition and abstraction mechanisms. Here the initiator produces *tert*-butyl radicals, which are oxidized to more isobutylene, which is probably brought into reaction by t-BuO_2·, MeO_2·, and MeO· radicals. Comparison of expt 40 and 47 (at the same concentrations, Table I) shows that each initiating radical brings only 0.62 molecule of isobutylene into the reaction at 197°, and only 0.34 at 147°. This small increase in reactivity for a 50° temperature change and the higher

yield of abstraction products in the 147° gas-phase run than in the 147° liquid-phase run are consistent with the increasing tendency of radical–alkene addition products to dissociate at high temperatures and low concentrations and to be superseded by abstraction reactions.[17]

The initial products of the gas-phase oxidation of isobutylene at 293° in clean Pyrex are 80% acetone (and formaldehyde + CO), 17% isobutylene oxide, and methacrolein.[18] In an unpacked quartz reactor at 400–550°, a 60% yield of methacrolein has been reported.[19] Together, these results illustrate again the tendency of higher temperatures to cause more reaction by the abstraction mechanism. However, wall reactions[18] have a still undetermined effect on these high temperature oxidations. That the addition/abstraction ratios are not consistent with our own below 200° may also be due to replacement of alkylperoxy radicals by some other, undetermined, chain carrier at high temperatures.

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Registry No.—Isobutylene, 115-11-7; cyclopentene, 142-29-0.

Supplementary Material Available. Full discussion and experimental data for our oxidations of cyclopentene and the decomposition of cyclopentenyl hydroperoxide will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N. W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-885.

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Oxidations of α-Methylstyrene at 110–160°

Frank R. Mayo,* Jane K. Castleman, Theodore Mill, R. M. Silverstein, and O. Rodin

Stanford Research Institute, Menlo Park, California 94025

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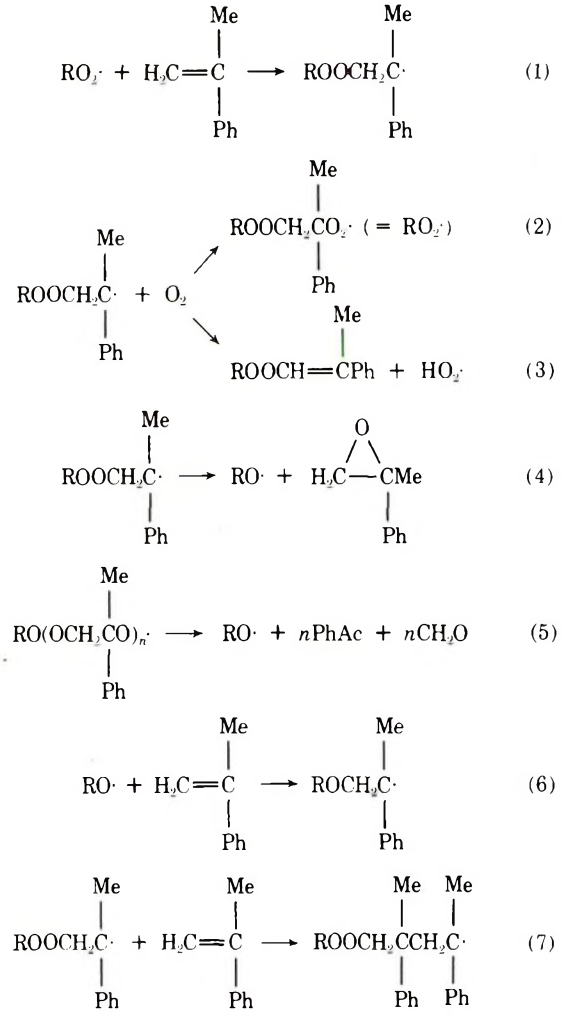
This paper considers the transition between the previously reported oxidations of α-methylstyrene[1] at 50 and 170°, with special attention to the nature of the nonvolatile residue, which changes from an alternating copolymer of α-methylstyrene and oxygen to a very complex mixture. Increasing reaction temperature and rate of oxidation result in lower effective oxygen concentrations, formation of increasing ratios of α-methylstyrene oxide to acetophenone, rapidly decreasing formation of polyperoxide above 100°, increasing involvement of primary products in secondary reactions, and gradual replacements of peroxide groups by ether groups, including $-OCH_2O-$ groups, in the residue. The residues average about two α-methylstyrene units, one ether link, and one hydroxy group per molecule, but contain some vinylidene groups. However, vigorous reduction with HI and red P and then with $LiAlH_4$ gives alkylbenzenes with one to four aliphatic carbon atoms and various dimers of α-methylstyrene.

Previous work[1] on the oxidation of α-methylstyrene showed that the principal products at 50° are a polyperoxide, acetophenone, formaldehyde, and α-methylstyrene oxide. The principal chain propagation steps are shown in eq 1–7.

The competition among these reactions largely determines the products of reaction. Alternation of reactions 1 and 2 produces a polymeric peroxide radical that is stabilized as a polyperoxide molecule by some chain transfer step (not yet established but reaction 3 is suggested). Competition between reactions 2 and 4 depends on oxygen pressure and determines how much acetophenone and epoxide are formed. Whenever reaction 4 occurs, the resulting alkoxy radical (which may contain several alternating C_9H_{10} and O_2 units) "unzips" through all the adjacent polyperoxide groups to give acetophenone, formaldehyde, and a small terminal radical (reaction 5). The ratio of carbonyl compounds to epoxide depends on how many times reaction 2 occurs before reaction 4 occurs. The ratio of polyperoxide to smaller molecules depends on the competition between reactions 3 and 4, the former apparently being independent of oxygen and methylstyrene concen-



trations. At low oxygen pressure, the polymer contains $-OCH_2O-$ and other ether groups. Reactions 6 and 7 illustrate how ether links and new carbon–carbon bonds might be formed.

Near 170°, probably with an inadequate supply of oxygen, the products are about one-third each of acetophenone (and formaldehyde), epoxide, and a residue with the average C, H, O analysis of poly(α-methylstyrene oxide). This residue may be formed by repeating sequences of reactions like 6, 2, 1, and 4. This explanation requires that $RO_2CH_2C(MePh)O\cdot$ radicals react at once by 5 but that $ROCH_2C(MePh)O\cdot$ radicals add "as in 1 or 7." The objectives of the present work are to find out how the mechanism of oxidation changes in the intermediate temperature range, to determine what conditions favor formation of residue, and then to investigate the nature of some of these residues. Our conclusions are near the end of the paper.

Oxidations of α-Methylstyrene[2a]

Experimental. Most oxidations were carried out with approximately 0.5 mol of α-methylstyrene in a wide-necked flask with a 170-ml bulb, fitted with a Vibro-Mixer, thermometer, oxygen inlet, and an oxygen outlet through a trap cooled to −78° and through wet glass wool to absorb formaldehyde. Larger runs without solvent in Table I are pairs of similar smaller runs. The oxygen entering and the gas leaving the vessel at 1 atm were usually passed through flow meters, and an effort was made to supply oxygen fast enough so that some excess left the vessel. However, the exit gases contained considerable formaldehyde, which was not readily removed and which partly polymerized on the exit system and flow meter. The reaction mixture was quickly brought to reaction temperature, usually by heating with a gas flame. Thereafter only occasional gentle heating or cooling with water was required to keep the liquid temperatures within about 5° of the stated temperatures, which are weighted averages. The Vibro-Mixer provided a constant fine dispersion of gas bubbles in the liquid.

The products were distilled at reduced pressure, as indicated in Table I. The distillate was analyzed for acetophenone and α-methylstyrene oxide by infrared or gc, using suitable standards. The residues were analyzed for carbon and hydrogen, and sometimes their molecular weights were determined.

The oxidations with o-dichlorobenzene as solvent employed similar stirring and arrangements. Experiments 53 and 57 used a little over 0.5 l. of solution in a 1-l. flask. The flask contents were maintained at the stated temperatures by keeping them in oil baths at somewhat higher temperatures.

Results and Discussion. What does happen to the mechanism of oxidation of α-methylstyrene between 50 and 170°? In some unrecorded experiments at 100° considerable polyperoxide was still formed (although its half-life is only a few hours), but very little survived our oxidations at 120°. Somewhere between 100 and 120°, reaction 4 outruns reaction 2, partly because 4 has a higher activation energy, but partly because the oxygen required for 2 is unavoidably depleted by increasingly faster reaction.

Our results at 120° and above are summarized in Table I. Runs without diluent at 120° are considered first. According to our mechanism, the ratio of acephenone to α-methylstyrene oxide formed depends on oxygen pressure and the competition between reactions 2 and 4. If enough oxygen is present, more reactions like 1 and 2, and more acetophenone, can eventually be formed when reaction 4 occurs, but the amount of excess acetophenone is variable and dependent on poorly controlled oxygen concentration.

The next point is that two distillation procedures were used for analyses, as indicated in notes *c* and *d* to Table I. Neither is entirely satisfactory, but we can deduce the correct results fairly closely. With procedure *c*, the distillation residue should not decompose but not all the acetophenone and epoxide are recovered and accordingly the yields of residue are 5–15% higher than with procedure *d*. Results of distillation of residue 18 by procedure c at 0.05 Torr are shown in Table I. By mass spectrometry, the first fraction was mostly acetophenone not recovered in the first distillation. The second fraction was partly acetophenone, probably partly resulting from pyrolysis of peroxide in the original residue. These figures suggest that, if this experiment had instead been analyzed according to *d*, the yield of acetophenone might have been about 0.013 mol (7%) higher, two-thirds from incomplete separation and one-third from pyrolysis. Losses of epoxide by poor recovery should be similar since it boils only about 4° lower than acetophenone at 15 Torr. The 5.8% weight loss in the redistillation also sets a low limit on the polyperoxide content of the residue; 20% loss is expected for pyrolysis of polyperoxide into acetophenone and uncondensed formaldehyde.

However, the analyses of the fractions show that they contain about 5% (of the total C_9H_{10}) of unidentified volatile material that contains more hydrogen and more oxygen than acetophenone, α-methylstyrene oxide, or the residues isolated by procedure *d*; this material is neglected in most analyses. The next section suggests that this material is, or contains, α-methylstyrene glycol. Thus procedure *d* may overstate the yield of acetophenone by up to 5% at the expense of residue and neglect up to 5% of unidentified volatile products. Procedure c includes 5–8% each of epoxide, acetophenone, and unidentified high boilers as residue.

The epoxide/acetophenone ratios and the yields of residues in expt 45, 48, and 39 are close to those obtained in the oxidation at 50° (6 Torr) of oxygen,[1] although the compositions of the residues may be different. In view of the higher activation energy for epoxide formation,[3] the

Table I
Oxidation of α-Methylstyrene at 120–170°

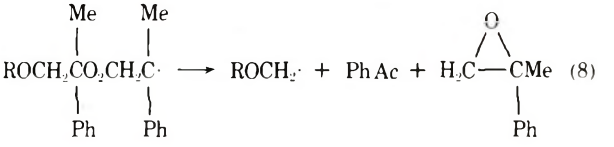
Expt no.	C_9H_{10},[a] mol (g)	Reaction: Av temp, °C	Reaction: Time, min	Conversion, %	Products, mol (% of C_9H_{10} reacting): PhC(O)CH$_2$ Me[b]	PhAc[b]	Residue	Residue: Av composition	Residue: Mol wt[a]
45	1.098 (128.8)	120	12	13.6	0.062 (41)	0.066 (44)	0.021[d] (14)	$(C_9H_{10.3}O_{1.67})_{1.69}$	246
4	0.501 (59.2)	120	37	25.7	0.054 (41)	0.049 (38)	0.027[c] (21)	$(C_9H_{12.0}O_{2.00})_x$	
18	0.525 (62.0)	120	36	37.2	0.070 (36)	0.092 (47)	0.034[c] (17)	$(C_9H_{11.14}O_{2.16})_x$	
					Distillation of 5.16 g of residue at 0.05 Torr gave				
						1.52 g to 95°		$(C_9H_{10.2}O_{1.53})_{1.02}$	146
						1.70 g to 155°		$(C_9H_{11.3}O_{2.0})_{1.43}$	217
						1.33 g to 250°		$(C_9H_{11.3}O_{1.56})_x$	
						0.31 g residue		$(C_9H_{10.9}O_{0.98})_{2.95}$	389
						0.30 g loss			
48	0.534 (63.1)	125	36	46.8	0.117 (47)	0.121 (48)	0.012[d] (5)	$(C_9H_{10.4}O_{1.57})_x$	
39	1.018 (120.2)	120	36	51.1	0.214 (41)	0.266 (51)	0.041[d] (8)	$(C_9H_{10.5}O_{1.46})_{2.60}$	369
57	1.01 (119.2 + 512 g o-$C_6H_4Cl_2$)	120	5	3.30	0.0127 (38)	0.020 (60)	0.0006[d,e] (2)	$(C_9H_{10.5}O_{1.66})_{1.54}$	220
53	0.986 (116.5 + 507 g o-$C_6H_4Cl_2$)	118	58				0.0780[d]	$(C_9H_{10.1}O_{1.44})_{1.66}$	236
61	0.489 (57.8 + 263.5 g o-$C_6H_4Cl_2$)	110	58	30.9	0.0284 (19)	0.113 (75)	0.0093[d] (6)	$(C_9H_{9.8}O_{1.22})_{3.49}$)	480
8	0.507 (59.9)	140	15	3.3	0.030 (41)	0.028 (37)	0.017[c] (22)	$(C_5H_{11.30}O_{1.26})_x$	
22	0.562 (66.5)	140	18	12.1	0.029 (43)	0.020 (31)	0.018[c] (26)	$(C_9H_{10.8}O_{1.61})_x$	
26	0.516 (60.9)	160	8	5.1	0.0097 (37)	0.0084 (32)	0.0081[c] (31)	$(C_9H_{10.7}O_{1.92})_x$	
Ref 1	0.764 (90.4)	167–168	30	26.5	0.077 (38)	0.066 (33)	0.059 (29)	$\sim(C_9H_{10}O)_x$	

[a] Molecular weight of α-methylstyrene is 118.18. [b] Values obtained by ir analysis, except 39, 45, 48, and 57 by gc. [c] Material not distilled at 70–100° (0.10 Torr). Residue contained some PhAc and epoxide. Moles based on C content, assuming C_9 units. [d] Material not distilled from 180° bath at 0.10 Torr. Moles based on C content assuming C_9 units. [e] After molecular distillation at 180° had removed 33% of material from an ordinary residue.

effective oxygen pressure at 120° must be higher than 6 Torr, but we do not know how much higher.

The average compositions of the residues (and fractions from expt 18) show that nearly all of them have both higher H:C and higher O:C ratios than α-methylstyrene units, the polymer of its epoxide, or acetophenone. The only obvious oxidation product with both higher H and O ratios is formaldehyde.[1] In the absence of a better explanation, we propose that the residues, and even the distillates, in expt 18 contain more $-CH_2O-$ residues than acetophenone residues, or some $-CH_2O-$ units in the α-methylstyrene or 1:1 peroxide residues, the $-CH_2O-$ units being left by "unzipping" of polyperoxide units (see below) or incorporated by condensation, copolymerization, or as paraformaldehyde.

The H:C in the first residue (expt 18) corresponds to almost two formaldehyde units per methylstyrene unit (more if some hydrogen has been lost from the latter) and would account for 60% of the formaldehyde expected from the yield of acetophenone found. Although this high proportion suggests some paraformaldehyde in this residue, not much was found. Samples of this residue were heated with concentrated aqueous hydrochloric acid for 3 hr at 90° or with 2 *M* acid for 2 hr at 70°; 0.83 and 0.68 wt % formaldehyde (about 4 mol %) was found by the dimedon and chromatrophic acid methods, respectively, but this low result could be due to incomplete hydrolysis. Table I shows that the last residue (expt 18) contains lower proportions of both hydrogen and oxygen than the first residue. These observations suggest that the residues contain some peroxide or formal groups that pyrolyze to formaldehyde or one of its condensation products and are lost during distillation (although excess hydrogen persists in the final residue). Such groups could arise by incomplete unzipping of structures containing ether groups, which may also protect peroxide groups in R. The resulting alkoxy-



(8)

methyl radical might react with oxygen (eventually releasing formaldehyde) or with methylstyrene to give C_{11} units (see next section), or possibly with some form of formaldehyde. The alternating polyperoxide of α-methylstyrene has the same H:C ratio as the hydrocarbon and does not account for the high H:C ratios in residues.

The experiments in *o*-dichlorobenzene in Table I were carried out to slow the oxidation and thus to increase the concentration of oxygen in solution. Experiment 57 shows that this effort was successful, as measured either by the higher acetophenone/epoxide ratio or by the small proportion of residue, all after pyrolysis as in expt 48 and 37. The less epoxide that is formed, the fewer should be the ether links to stabilize the decomposing peroxy radicals.

Experiment 53 was carried to 58% conversion to supply the residue for the investigation in a later section. Experiment 61 was carried out to obtain full data on a duplicate of expt 53, but, because of difficulties in temperature control, expt 61 shows mostly the effects of a higher oxygen supply and a low temperature (110°): the highest yield of

acetophenone after strong heating and the lowest proportions of hydrogen and oxygen in the residues listed in Table I, indicating low incorporation of formaldehyde. We do not know how much polyperoxide was formed and pyrolyzed during analysis.

Comparison of the incomplete data for expt 53 and 57 at 120° suggests that a tenfold increase in reaction time increased the yield of residue about 100-fold and therefore that part of the residue is a secondary product. This latter suggestion has been supported by oxidizing α-methylstyrene in the presence of added *p*-chloroacetophenone. A mixture of 0.426 mol of α-methylstyrene and 0.124 mol of distilled Eastman *p*-chloroacetophenone was stirred in a stream of oxygen for 73 min at 120°. A weight gain of 4.13 g corresponded to 0.30 mol of oxygen/mol of α-methylstyrene initially present. Distillation at reduced pressure gave 3.16 g of residue not distillable at 180° (0.4 Torr). This residue contained no free chloroacetophenone (23.0% Cl) by gc but it contained 6.83% chlorine (29% *p*-chloroacetophenone units), 4.9% of all the chlorine added initially. By ultraviolet absorption, at least 65% of the incorporated *p*-chloroacetophenone appeared as *p*-chlorobenzoyl groups. The nmr spectrum of this residue differed from typical residues in that it contained about 1.0 (instead of 0.75) aromatic per aliphatic proton and in that -OCHO- and PhCHO- protons were missing.

Treatment of the distillate from expt 39 with small amounts of formic acid in the absence of oxygen, with and without paraformaldehyde to duplicate some of the conditions during an oxidation, failed to produce significant amounts of residue. These results seem to exclude the possibility of an acid-catalyzed condensation of primary products to residue.

In comparison with expt 4 and 18 in Table I, which employed the same analytical procedure, experiments at 140–168° show very similar results, although there may be some tendency for acetophenone to decrease, for residue to increase, and the hydrogen and oxygen content to decrease with increasing oxidation temperature. Since the rates of oxidation (conversion/time) are lower at the higher temperatures, oxygen supply must have been more limited than at 120°. Since the residues of these high-temperature runs cannot contain peroxides, similarity in products supports our conclusion that the 120° residues did not contain much peroxide.

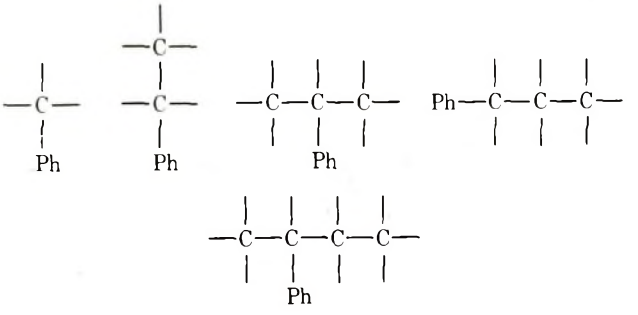
Investigations of Oxidation Residues

Results of investigating two kinds of residues in Table I are summarized. (See paragraph at end of paper regarding supplementary material.) The first kind of residue resulted from high-conversion oxidations of neat α-methylstyrene at 120° where rapid oxidation reduced the availability of oxygen. Most of these data come from the residue of expt 39; some come from expt 18. These residues averaged about one benzoyl and one ester group per molecule, and four aliphatic for three aromatic protons (1:1 in methylstyrene). They also contained methyl, benzyl, and benzyloxy groups. These results, along with the elementary analysis, suggest the incorporation of formaldehyde units in the residues in some form. A similar oxidation to lower conversion (expt 45) gave a similar product except that the molecular weight was lower and the proportion of methyl (end) groups and of ether groups was higher.

In the second kind of oxidation, the methylstyrene was diluted with 3.0 volumes of *o*-dichlorobenzene, to slow the oxidation and to permit maintaining higher concentrations of oxygen. Residue 57, which was examined most carefully, had an average molecular weight of 220 and an average composition of $C_9H_{10.5}O_{1.66}$. This residue was saponified to give 78% of a neutral, viscous oil, which was a mixture of more than 50 components. The "average" composition of these components was $C_{18}H_{18.4}O_{2.28}$. The "average" molecule contained 1.34 ether oxygen atoms and 0.94 hydroxyl oxygen atom. A small number of hydroxylated eight- to ten-carbon compounds accounts for the low carbon content of the "average" empirical formula. α-Methylstyrene glycol (6%), an expected pyrolysis product of the polyperoxide, was isolated and identified. One out of every four or five molecules contained a terminal $PhC{=}CH_2$ group.

The only other component identified tentatively was ~0.2% of 2,5-diphenyl-1-hexene, a dimer of α-methylstyrene. Fragmentary information was obtained on several other fractions, both single compounds and mixtures. All these materials contained $H_2C{=}C<$, hydroxyl, and phenyl groups; most of them contained ether groups, and the grouping PhC(O-)Me was identified in one case.

Treatment of the neutral mixture with hydriodic acid and phosphorus and subsequently with $LiAlH_4$ gave a mixture of hydrocarbons that was separated into a mixture of five alkylbenzenes and a mixture of α-methylstyrene dimers. The alkylated benzenes resulted from cleavage of the ether molecules. The principal alkylbenzene (75% of the mixture) was cumene; present in much smaller amounts were toluene, ethylbenzene, *n*-propylbenzene, and *sec*-butylbenzene. These results mean that the following groups could be present in the neutral fraction,



where most of the free valences are attached to hydrogen but at least one in each unit is attached to oxygen. The first two formulas show loss of carbon from α-methylstyrene units; the last shows gain of carbon, and the fourth shows either gain and loss together, or rearrangement. Any $-OCH_2O-$ groups would have been lost in the procedure used.

The α-methylstyrene dimer mixture gave ir and nmr spectra that resembled those obtained from a sample of polymerized α-methylstyrene. Eight peaks were obtained on gas chromatography of the α-methylstyrene dimer mixture. One peak, which accounted for about 50% of the mixture, was isolated and was subsequently shown by capillary gas chromatography to consist of two components. No further effort was made to separate these.

The acid fraction recovered from the saponification consisted of a mixture of at least three acids. The major component, and the only one identified, was benzoic acid.

Conclusions

In oxidations of α-methylstyrene with ample oxygen up to 100° the principal product is the alternating polyperoxide, which is reasonably stable at reaction temperature but pyrolyzes cleanly to acetophenone and formaldehyde on heating at reduced pressures. Between 100 and 120°, at 1 atm total pressure, the principal product of oxidation of α-methylstyrene changes from polyperoxide to α-methylstyrene oxide and acetophenone, with minor amounts of residue and still less peroxide. In this range, a combina-

tion of a higher activation energy for epoxide formation (reaction 4) in competition with absorption of oxygen (reaction 2) and the difficulty in maintaining saturation of the solution with oxygen leads to the formation of increasing proportions of both α-methylstyrene oxide and distillation residue and less acetophenone. Slowing the oxidation (and presumably increasing the oxygen concentration) by dilution with *o*-dichlorobenzene increases the yield of acetophenone at the expense of epoxide and residue. Residues are associated with epoxide formation and the formation of ether links, reactions 4 and 6. Residues made at low oxygen concentrations have H:C ratios that seem also to require incorporation of $-OCH_2O-$ groups,[1] particularly in residues that have not been strongly heated. At higher conversions, residues also contain condensation products of acetophenone, formaldehyde, and α-methylstyrene oxide, the major primary products of oxidation.

Detailed investigations of some residues confirm the presence of ether groups and $-OCH_2O-$ units but they bring out the great complexity of the residue and, with the exception of 6% of α-methylstyrene glycol, the absence of important proportions of any single component. This work shows that the hydrocarbon units between the ether links contain seven, eight, and ten carbon atoms as well as two kinds of C_9 units. Some of the cuts in this investigation contained many more than 50 individual components.

This work is consistent with, and extends, our findings that oxidations of isobutylene[4,5] and cyclopentene[5,6] also give high-boiling residues. Those residues also consist of monomer units, or fragments of them, joined together with ether links (and some peroxide links in oxidations below 100°), some with additional oxygen-containing groups on the chains.

Acknowledgment. This research was part of a basic study of reactions of organic compounds with oxygen, supported by a group of oil and chemical companies in the United States, Europe, and Japan.

Registry No.—α-Methylstyrene, 98-83-9.

Supplementary Material Available. Details of investigations of residues 18, 39, 45, and 53 will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N. W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-889.

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α-Methylenelactam Rearrangement

David L. Lee, Cary J. Morrow, and Henry Rapoport*

Department of Chemistry, University of California, Berkeley, California 94720

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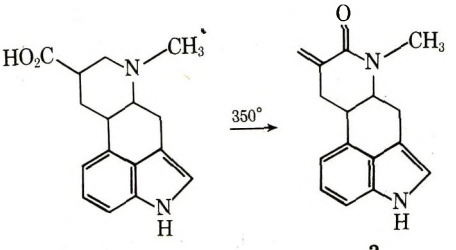
The acetic anhydride promoted rearrangement of cyclic β-amino acids to α-methylenelactams has been investigated. In particular, the effect of ring size, N substitution, and α substitution on the yield of the rearranged product was determined. When applicable, the stereochemistry of the rearrangement was also examined. These observations have led to elucidation of the mechanism of the α-methylenelactam rearrangement which is initiated by a cyclic β-amino acid reacting in its zwitterionic form with acetic anhydride to yield the protonated amino mixed anhydride. β elimination then readily occurs, and recyclization takes place by nucleophilic attack of the amino group on the mixed anhydride function.

The rearrangement of a cyclic β-amino acid to an α-methylenelactam was first observed[1] in an attempt to purify dihydrolysergic acid (**1**). Sublimation of acid **1** led to a substantial portion of rearranged product, dihydrolysergic lactam (**2**). Subsequently, this rearrangement was utilized in the transformation of lysergic acid (**3**) to 6,8-dimethylergoline (**4**).[2]



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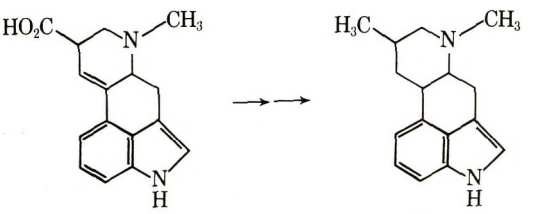
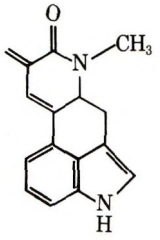


3 **4**

In addition to the above pyrolytic route, the rearrangement of cyclic β-amino acids to α-methylenelactams has been effected through the use of acetic anhydride. In seeking to racemize the C-8 asymmetric center of lysergic acid (**3**), it was treated[3] with acetic anhydride in the expectation of preparing lysergic acetic anhydride. The product obtained was lactam **5**. Similarly, the rearrangement of

N-methylnipecotic acid (**6**) to 1-methyl-3-methylene-2-piperidone (**7**) has been reported.[4]



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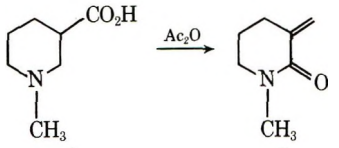
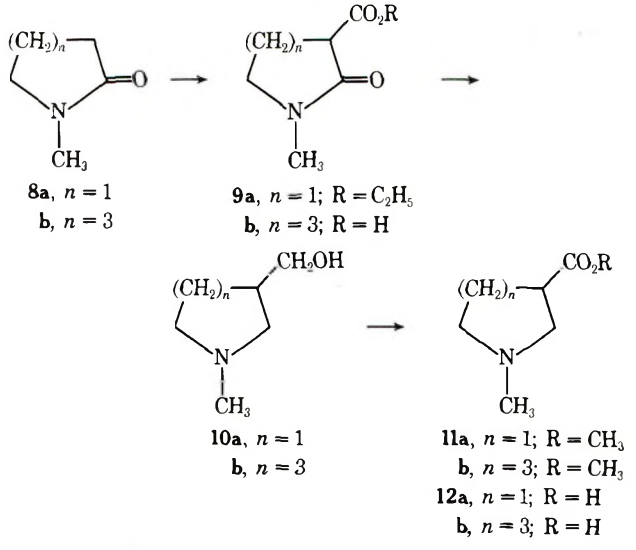


6 **7**

Since then, this reaction appears to have gone unnoticed until the recent[5] utilization of this rearrangement for nicotinic acid degradation. Recognition of the reaction's synthetic potential was achieved when the rearrangement was employed as a key step in the synthesis of camptothecin and camptothecin analogs.[6,7] The multitude of possible subsequent transformations of the product lactams, for which the synthesis of camptothecin is a good example, makes these lactams very versatile synthons. With this in mind, we have explored the mechanism and some aspects of the scope of this rearrangement. In particular, the yield of rearranged product as a function of ring size, N substitution, and α substitution was of prime interest. The stereochemistry of the rearrangement of α-substituted derivatives was also examined.

Syntheses. The five- and seven-membered ring β-amino acids **12a** and **12b** were prepared as outlined in Scheme I.

Scheme I



8a, $n = 1$
b, $n = 3$

9a, $n = 1$; R = C_2H_5
b, $n = 3$; R = H

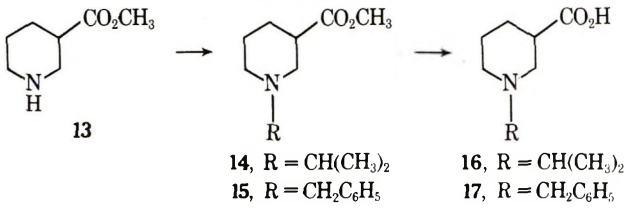
10a, $n = 1$
b, $n = 3$

11a, $n = 1$; R = CH_3
b, $n = 3$; R = CH_3
12a, $n = 1$; R = H
b, $n = 3$; R = H

Treatment of the corresponding amides **8a** and **8b** with lithium diisopropylamide followed by the addition of diethyl carbonate or carbon dioxide yielded the carboxyl derivatives **9a** and **9b**, respectively. Lithium aluminum hydride reduction of the carboxyl and amide functions afforded the aminols **10a** and **10b**, and chromium trioxide–sulfuric acid oxidation of the alcohols gave acids **12a** and **12b**, purified *via* their respective methyl esters, **11a** and **11b**.

Preparation of the N-substituted acid derivatives **16** and **17** was accomplished as outlined in Scheme II. Methyl nipecotate (**13**) was treated with either isopropyl iodide or benzyl bromide to yield the N-alkyl derivatives **14** or **15**. Acid hydrolysis of the esters then afforded the desired acids **16** and **17** as the hydrochloride salts.

Scheme II

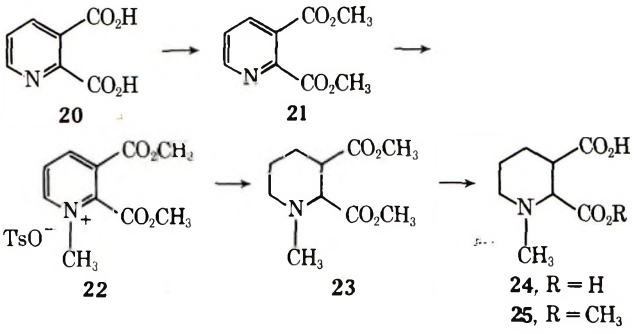


13

14, R = $CH(CH_3)_2$
15, R = $CH_2C_6H_5$

16, R = $CH(CH_3)_2$
17, R = $CH_2C_6H_5$

Scheme III

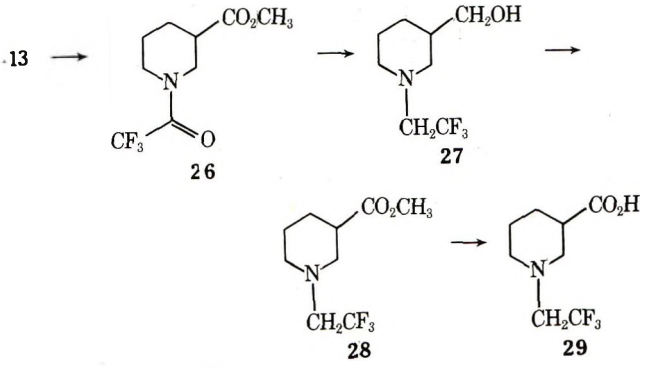


20 **21**

22 **23**

24, R = H
25, R = CH_3

Scheme IV



26 **27**

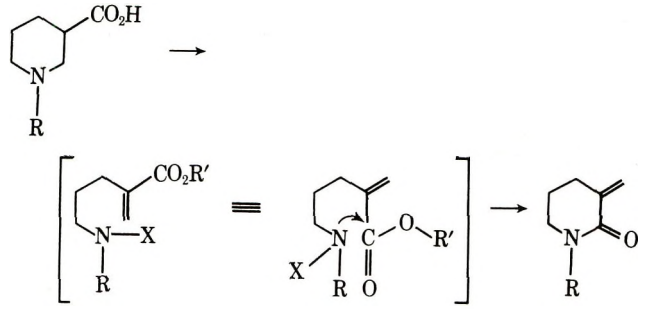
28 **29**

Three 1-methyl 2-substituted nipecotic acids were examined. The 2-methyl- and 2-phenyl-1-methylnipecotic acids (**18** and **19**, respectively) were made from the known ethyl esters.[8] Scheme III delineates the preparation of the 2-carboxynipecotic acid derivatives **24** and **25**. 2,3-Pyridinedicarboxylic acid (**20**) was esterified with methanol–HCl to yield pyridine diester **21**. Subsequent treatment of **21** with methyl *p*-toluenesulfonate afforded the *N*-methylpyridinium carboxylic ester salt **22**, which was hydrogenated employing platinum as the catalyst to yield the piperidine **23**. Hydrolysis of diester **23** was effected in 6 *N* HCl, selectively to monoester **25** at room temperature overnight and totally to diacid **24** on refluxing for 20 hr.

1-(2,2,2-Trifluoroethyl)nipecotic acid (**29**) was prepared as shown in Scheme IV. Methyl nipecotate **13** was treated with excess trifluoroacetic anhydride to yield the amido ester **26**. Selective reduction of the amide function in **26** could not be accomplished with diborane,[9] which converted **26** to the aminol **27**. Oxidation of **27** with chromium trioxide–sulfuric acid followed by esterification with methanol–HCl yielded the amino ester **28**, which was hydrolyzed in 6 *N* HCl to produce acid **29**.

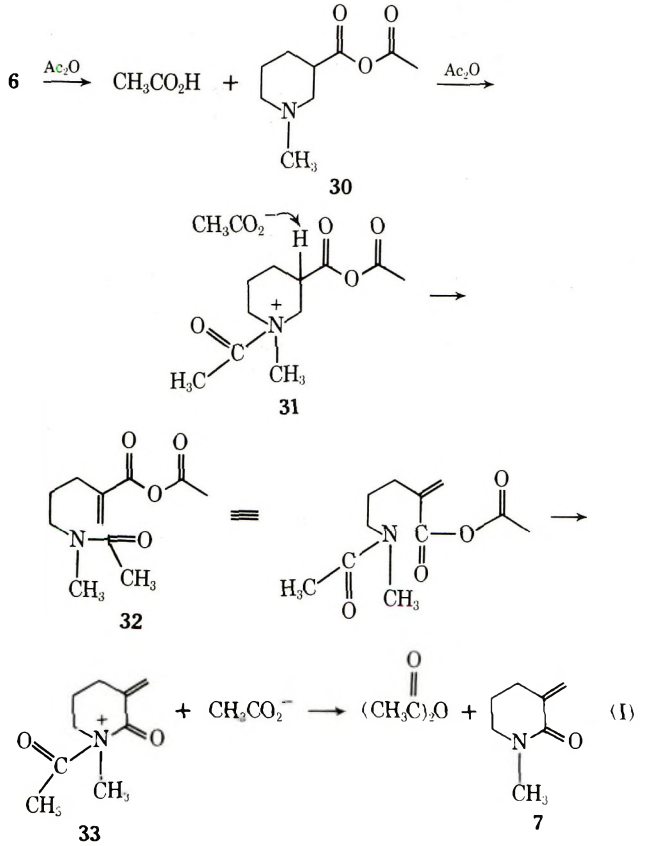
Mechanism. Experiments using a carbon-14 label established[5] that the carboxyl carbon of *N*-methylnipecotic acid (**6**) becomes C-2 of lactam **7** after rearrangement in refluxing acetic anhydride. This fact, coupled with the fact that β-amino acids are known to undergo elimination to α,β-unsaturated acids, allows the following mechanism

to be postulated initially. In the simplest view, a cyclic β-amino acid undergoes β elimination to yield an open-



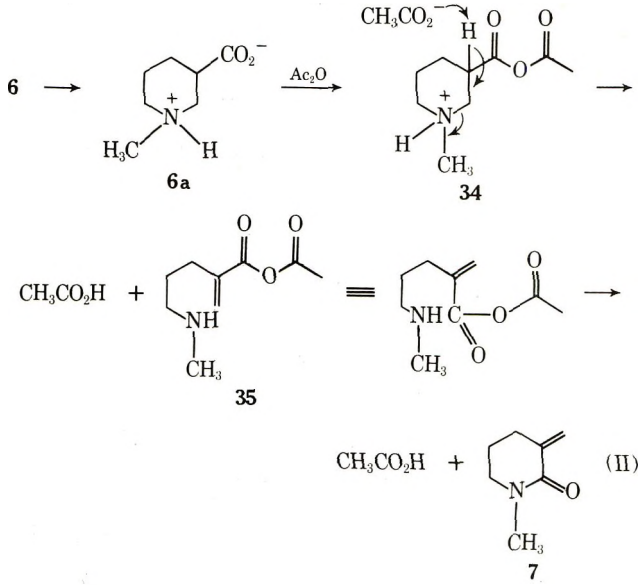
chain intermediate. Subsequent ring closure of the intermediate then occurs through attack of the nitrogen atom on the carboxyl carbonyl group. Conceivably, the amine in the open-chain intermediate can exist either as its *N*-acetyl derivative or as the free amine. Also, the carboxyl function in the open-chain intermediate may exist either as the acid or as the mixed anhydride. The fact that cyclic β-amino acids do not rearrange at 140° in the absence of acetic anhydride, *i.e.*, in refluxing xylene or in refluxing xylene containing acetic acid, indicates that mixed anhydride formation is a prerequisite for rearrangement. Thus, mixed anhydride formation increases the acidity of the α hydrogen, facilitating β elimination. Additional evidence in support of this postulate is the fact that the ester derivatives also do not rearrange or undergo β elimination under these conditions. Therefore, the mechanism is limited to one of the two possibilities, I or II.

According to mechanism I, mixed anhydride formation followed by acetylation of the tertiary amine would yield the intermediate **31**. The quaternary nitrogen, now being

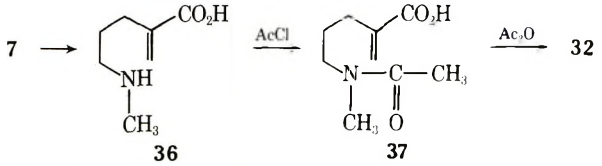


a better leaving group, promotes β elimination, possibly by an E1 mechanism; however, owing to the increased acidity of the hydrogen α to the mixed anhydride moiety, elimination can also be of the E2 or E1cB nature. Ring opening would yield the *N*-acetyl derivative **32**, followed by ring closure to the ionic imidium intermediate **33**. Attack of the imidium ion intermediate by acetate ion would then yield lactam **7**, regenerating acetic anhydride.

The alternative mechanism II again starts with mixed anhydride formation but from the zwitterionic ion form of **6**, **6a**. Acetate ion, formed concurrently, is the base which promotes elimination readily in the protonated amine **34** to give the open-chain intermediate **35**. Intramolecular nucleophilic attack by the free secondary amine then leads to ring closure, forming lactam **7**.



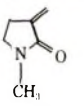
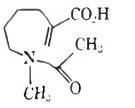
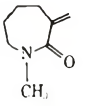
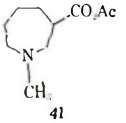
To differentiate between these mechanisms, the open-chain derivative **32** was prepared by acid hydrolysis of lactam **7** to the open-chain amino acid **36** hydrochloride, followed by treatment with acetyl chloride in the presence of K_2CO_3 to form the *N*-acetyl derivative **37**. Heating the acid **37** in acetic anhydride at reflux for 3 hr gave only mixed anhydride **32**; no ring closure occurred.



This observation eliminated mechanism I and focused attention on mechanism II. Evidence for this latter hypothesis was obtained when the acid **36** was refluxed in acetic anhydride and yielded, after an aqueous isolation, the lactam **7** and the open-chain *N*-acetyl derivative **37**. Since it had been established that *N*-acetyl derivatives **37** and **32** did not ring close to **7** in refluxing acetic anhydride and that the acid **37** did not close to **7** simply by heating at 140°, it could be inferred that production of **7** must be derived from the amine mixed anhydride intermediate **35**.

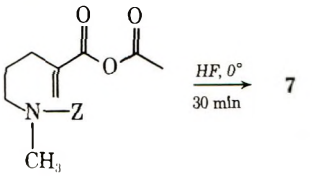
The formation of both lactam **7** and *N*-acetyl mixed anhydride **32** (isolated after hydrolysis as **37**) on heating the amino acid **36** in acetic anhydride can be rationalized as the result of competition between two reactions. One is N-acetylation, which then prevents ring closure and results in formation of **32**. The other is O-acetylation (mixed anhydride formation) followed by internal N-acylation forming lactam **7**. When one begins with the cyclic amino acid **6**, none of the *N*-acetyl derivatives **37** and **32** are formed. Since the mixed anhydride **34** is the primary product, the initial ring-opened product is amine mixed anhydride **35**. None of the open-chain amino acid **36** is formed, and ring closure by internal N-acylation completely excludes bimolecular N-acetylation.

Table I
α-Methylenelactam Rearrangement of 3-Carboxy-1-methylpyrrolidine, -piperidine, and -hexahydroazepine

Compd	Reaction conditions[a]	Products: Lactam	Yield, %	Other	Yield, %
12a	Ac_2O, K_2CO_3	 40	95		
12b	Ac_2O, K_2CO_3			 43	93
12b	150 mol % Ac_2O in xylene, K_2CO_3	 42	40	**43**	40
 41	100 mol % AcOH in xylene	**42**	40	**43**	10
6	Ac_2O	**7**	93		

[a] All reactions were conducted for 3 hr at reflux.

Further evidence for the plausibility of amine mixed anhydride intermediate **35** ring closing to lactam **7** was sought by treating the benzyloxycarbonyl derivative **38** with anhydrous hydrogen fluoride at 0° in an attempt to isolate **35** hydrofluoride under these mild reaction conditions. However, only lactam **7** was produced. Since mixed anhydrides can form acyl fluorides in the presence of hydrogen fluoride,[10] the integrity of the mixed anhydride function is in doubt in this experiment, and it cannot be claimed as definitive evidence for the intermediacy of **35**.



38

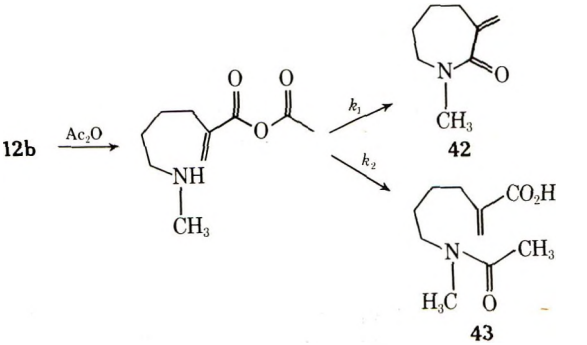
Similarly, lactam **7** was obtained when anhydride **38** was treated with *p*-toluenesulfonic acid in ether at room temperature for 15 min. Mixed sulfonic-carboxylic anhydride formation was not anticipated as a possible complication, since formation of such mixed anhydrides normally requires heating the anhydride with *p*-toluenesulfonic acid at temperatures ≥120° for at least 30 min.[11] However, a control experiment at room temperature for 15 min using acetic anhydride and *p*-toluenesulfonic acid gave mixed sulfonic carboxylic anhydride almost quantitatively.

To circumvent the possible problem of mixed anhydride exchange in the mechanism proof, sulfuric acid was employed as the acid for benzyloxycarbonyl removal. Thus, when the anhydride **38** was treated with sulfuric acid in ether at room temperature, the lactam **7** was obtained. Since mixed sulfate-carboxylic anhydride formation does not occur under these conditions, amine anhydride **35** as a viable intermediate is strongly indicated.

Scope. Rearrangement of β-Amino Acid Salts. Both the hydrochloride and the sodium salts of the β-amino acids can be employed in the rearrangement. Though solution of the sodium salt in acetic anhydride is slow, the reaction time is comparable to that required for the free amino acid. The rate of reaction of the hydrochloride is considerably slower than that of the free amino acid; however, the reaction of the hydrochloride can be considerably accelerated if 1 equiv of base (50 mol % potassium carbonate) is added. Since considerable difficulties in the purification of the zwitterionic intermediates frequently are encountered, the acids are normally used as the hydrochlorides, which are obtained directly from acid hydrolysis of the purified methyl esters.

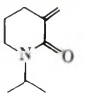
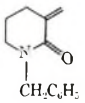
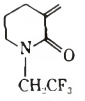
Variations in Reaction Conditions. Normally the reaction is conducted at the temperature of refluxing acetic anhydride; however, it has been found that the lower temperature limit to effect rearrangement is around 100°, with increased reaction time to obtain comparable yields. Although potassium carbonate was the base most commonly employed in the rearrangement of the hydrochloride salts of the acids, triethylamine can be substituted and might be advantageous when a homogeneous solution is desired.

Effect of Ring Size. As can be seen from Table I, the α-methylenelactam rearrangement is quite facile in the five- and six-membered ring systems. However, when the seven-membered ring acid **12b** was treated under the usual reaction conditions with excess acetic anhydride, no lactam **42** was obtained, and the sole product was the *N*-acetyl derivative, isolated as acid **43** after an aqueous treatment. Apparently, intermolecular acylation (k_2) with acetic anhydride was occurring faster than intramolecular acylation (k_1) in the open-chain intermediate.



Examination of the stoichiometry of the proposed reaction mechanism shows that only 1 mol of acetic anhydride

Table II
Effect of the N Substituent on the α-Methylenelactam Rearrangement of Nipecotic Acids

Compd	Reaction time,[a] hr	Product: Lactam	Yield, %
16	3	 44	90
17	3	 45	92
29	3	 46	17
29	24	**46**	93

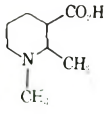
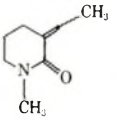
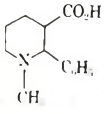
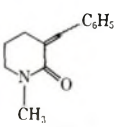
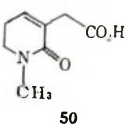
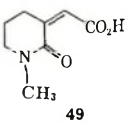
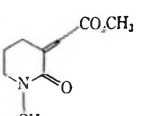
[a] All reactions were conducted at reflux in acetic anhydride containing potassium carbonate.

is required to effect the rearrangement. Therefore the acid **12b** was refluxed in xylene in the presence of 1.5 mol of acetic anhydride. Under these conditions a substantial amount of the lactam **42** was formed as well as *N*-acetyl derivative **43**. In an attempt to minimize the amount of free acetic anhydride present in the reaction mixture so as to diminish the formation of *N*-acetyl compound **43**, two further modifications of the normal experimental procedure were tried. In the first, the acetic anhydride was added to a mixture of the acid **12b** in xylene at reflux over a period of 4 hr. No improvement in the yield of the lactam **42** or attenuation of the amount of *N*-acetyl derivative **43** was noticed *via* this dilution technique. The second modification consisted of preforming the mixed anhydride of the acid **12b** prior to heating it to effect rearrangement. One equivalent of acetic acid was added as a source of base (acetate ion). No improvement in lactam formation was noted, though the amount of the *N*-acetyl derivative **43** was diminished. Evidently mixed anhydride disproportionation[12] was occurring.

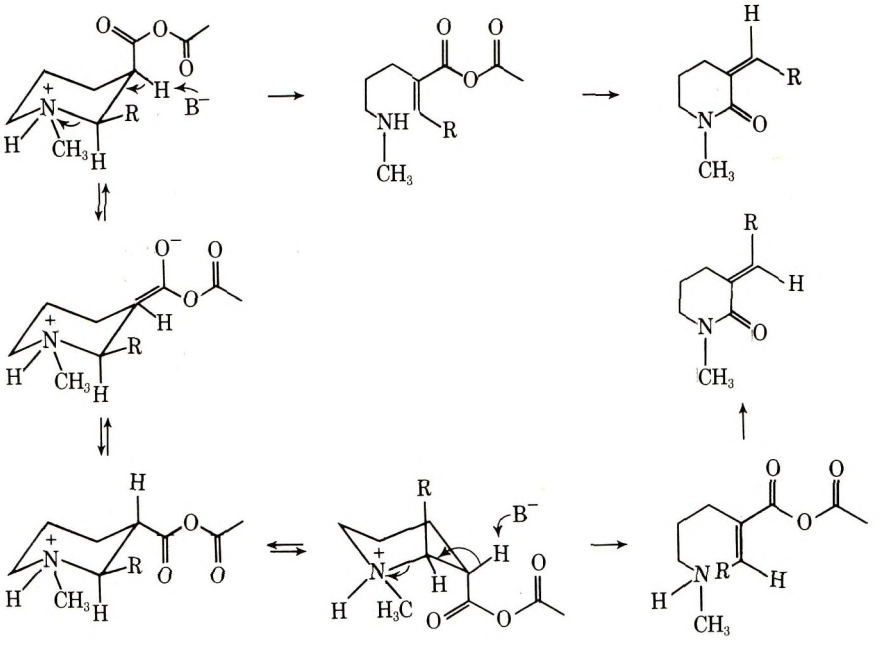
Effect of N Substitution. Examination of the effect of N substitution on the yield and rate of the rearrangement was confined to the six-membered ring systems. The N substituents employed were methyl, isopropyl, benzyl, and 2,2,2-trifluoroethyl. The *N*-isopropyl group illustrates the fact that steric hindrance about nitrogen does not affect the rearrangement, and the *N*-benzyl group indicates the further utility of the lactams as synthons since the benzyl group is potentially easily removable. The *N*-trifluoroethyl derivative was chosen to determine the effects of a strong electron-withdrawing substituent situated on nitrogen. As seen from Table II, the *N*-2,2,2-trifluoroethyl derivative **29** required a substantially longer reaction time to give an acceptable yield. This observation is in agreement with the proposal that β elimination must occur through the protonated amine. Owing to the decreased basicity of amine **29** ($pK_a \cong 5$),[13] a smaller fraction of the amine would be protonated in the reaction mixture, and therefore, a slower rate of reaction would be expected.

Effect of α Substitution. In the rearrangement of the 2-substituted nipecotic acid derivatives, shown in Table III, a mixture of lactam isomers was obtained with the trans isomer (trans to the carbonyl group) generally predominating. Assignments of cis and trans are based on the chemical shift of the olefinic proton, which is farther

Table III
α-Methylenelactam Rearrangement of 2-Substituted 1-Methylnipecotic Acids

Compd	Reaction conditions[a]: Reagents	Time, hr	Products: Lactam	Trans:cis ratio	Yield, %	Other	Yield, %
 18	Ac_2O, K_2CO_3	3	 47	50:50	93		
 19	Ac_2O, K_2CO_3	3	 48	70:30	90		
24	Ac_2O, K_2CO_3	3				 50	93
24	Xylene[b]	24	 49	0	75	**50**	15
25	Ac_2O, K_2CO_3	3	 51	77:23	94		

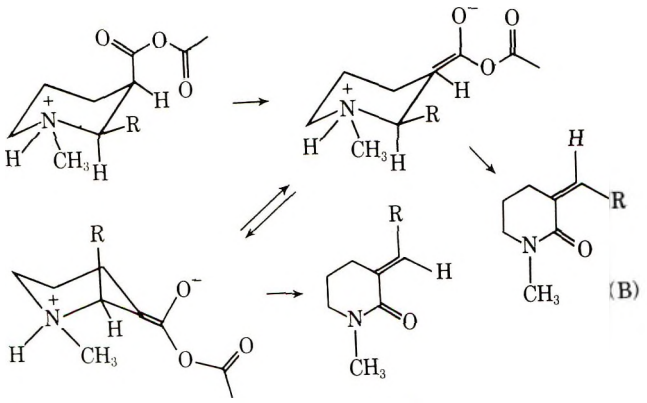
[a] All reactions were conducted at reflux. [b] Condensate was returned through Soxhlet thimble containing anhydrous $MgSO_4$.



(A)

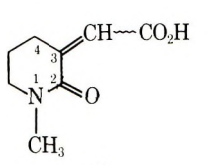
downfield (δ 6.6–7.6) in the trans isomer (proton cis to amide carbonyl) as compared to the cis (olefinic proton, δ 5.6–6.3, trans to amide carbonyl). Since (1) the starting acids were of one specific stereochemical configuration, presumably cis based on the nmr coupling constants of the C-2 protons ($J_{2,3}$ = 4 Hz), and (2) the product lactams did not isomerize under the reaction conditions, the fact that both lactam isomers were obtained indicated a loss of the stereospecificity of the starting acid prior to β elimination. Several possible explanations for this observation can be envisaged. One possibility, path A, which is schematically illustrated, assumes that β elimination is primarily E2 in nature with elimination occurring antiperiplanar. Moreover, equilibration at the C-3 center prior to β elimination is assumed.

Another possibility, path B shown below, assumes that β elimination is of the E1cB nature with cis elimination occurring. Of course, it is possible that elimination is also antiperiplanar, but, in either case, demonstration of the loss of stereospecificity from the starting acids is clear. In either case, there appears to be no obvious explanation for the predominant formation of the trans lactams. Clearly more studies with various α-substituted derivatives are required for a definitive elucidation of the stereochemical course of the rearrangement.

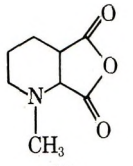


(B)

In the rearrangement of the 2-carboxynipecotic acid derivative **24**, neither of the exocyclic olefinic lactams **49** was obtained; instead, the endocyclic olefinic lactam **50** was the exclusive product. The assignment of the double bond as endo is based on the appearance of a two-proton doublet downfield at δ 3.1 as compared to the higher field multiplets for the allylic methylene group when the double bond is exo. The olefinic proton appears at δ 6.10 in the endocyclic isomer whereas in the two exo isomers it is at δ 5.66 in the cis and δ 6.66 in the trans.



49



52

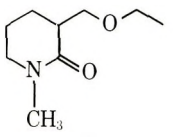
Unlike most of the other lactam products, where the C-4 hydrogens were only allylic, the C-4 hydrogens of the anticipated exocyclic olefinic lactam **49** would also be γ to an α,β-unsaturated carboxyl system, and in the reaction mixture they would be γ to an α,β-unsaturated mixed anhydride. Thus, one would expect a greater acidity for the C-4 hydrogens, and, when the C-4 hydrogens are sufficiently acidic, isomerization of the exocyclic olefin to the endocyclic olefin occurs and is favored. The C-4 hydrogens of the lactam **51** are also γ to an α,β-unsaturated carbonyl system, but no isomerization of the olefin to the endocyclic position was observed with this ester. As was previously discussed in relation to the mechanism, the mixed anhydride function increases the acidity of its α hydrogens sufficiently for anion formation and isomerization with the base present under the reaction conditions; when the conjugating group is an ester, anion formation and isomerization do not occur.

As was pointed out, mixed anhydride formation is a prerequisite for arrangement, and this activation has been accomplished conveniently with acetic anhydride. The 2-carboxynipecotic acid derivative also lends itself to internal anhydride formation, and rearrangement of internal anhydride **52** to lactam should proceed merely through the addition of base (acetate or triethylamine) and heat. Moreover, owing to the internal constraints of the system, the only exocyclic olefinic lactam produced should be the cis. In an attempt to obtain the internal anhydride **52**, diacid **24** was refluxed in xylene in the presence of magnesium sulfate. The product obtained was not **52** but the lactams **49** and **50**. Again some exo to endo double bond isomerization had occurred; however the lactam **49** produced in this reaction was all cis, as predicted.

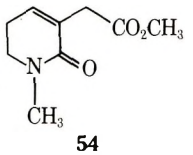
Exo–Endo Double Bond Stability. Since rearrangement of the diacid **24** in acetic anhydride–K_2CO_3 yielded

only the endocyclic olefinic lactam **50**, the question arose whether the other exocyclic olefinic lactams could be isomerized to the endocyclic form through the use of stronger base. Treatment of the lactam **7** with sodium ethoxide yielded the Michael-like product **53**. Lithium diisopropylamide, potassium *tert*-butoxide, or lithium cyclohexylisopropylamide also apparently resulted in 1,4-addition products, as indicated by the loss of olefinic absorption in the nmr, while use of lithium 2,2,6,6-tetramethylpiperidide[14] as a means of minimizing 1,4 addition to the lactam **7** yielded only unidentified products lacking any olefinic absorptions.

Treatment of the cis methoxycarbonyl substituted lactam **51a** with sodium methoxide in refluxing methanol for 4 days resulted in a 90% conversion to the endocyclic lactam **54**. Aliquots of the reaction mixture were monitored periodically, and at no time was any of the trans exocyclic olefin **51b** detected. This indicates, at least in the methoxycarbonylmethylene-substituted lactams, that the endocyclic olefin is more stable.



53



54

Treatment of the benzylidene lactam **48** with lithium 2,2,6,6-tetramethylpiperidide resulted only in the recovery of starting material. To determine if anion formation was occurring, the reaction was quenched with deuterated acetic acid and the resulting lactam showed incorporation of deuterium at C-4. Thus, the double bond is more stable exocyclic in this case.

Summary

The rearrangement of cyclic β-amino acids to α-methylenelactams by heating with acetic anhydride appears to be quite general with yields mostly exceeding 90%. The rearrangement occurs with facility to a single product in the five- and six-membered ring systems, while with the seven-membered ring a competing side reaction gives the open-chain *N*-acetyl compound as well as the α-methylenelactam. Substituents on nitrogen may vary with no adverse effect on the yield of rearranged product, and the rearrangement is compatible with a variety of substituents α and α′ to the nitrogen.[6,7]

The rearrangement has been shown to proceed *via* the zwitterion of the amino acid through the protonated amine–mixed anhydride which then undergoes β elimination followed by recyclization. We are now directing our efforts to further applications of this reaction to other heterocyclic systems and to the synthesis of more complex molecules.

Experimental Section

Solvent evaporations were carried out *in vacuo* using a Berkeley rotary evaporator. All melting points are uncorrected. Infrared (ir) spectra were measured in Nujol (unless otherwise noted) for solids and as thin films for liquids on a Perkin-Elmer 137 spectrophotometer. Nuclear magnetic resonance (nmr) spectra were obtained in CCl_4 (unless otherwise noted) with a Varian T-60 spectrometer; peak positions are given as δ values downfield from tetramethylsilane as internal standard, except that sodium trimethylsilylpropanesulfonate was used as internal standard in aqueous solutions. Gas chromatography (gc) was performed on a 5% QF-1 on Chromosorb W column, 10 ft × 0.25 in., at 125–200°. All elemental analyses were performed by the Analytical Laboratory, Department of Chemistry, University of California, Berkeley.

Rearrangement of Acids to Lactams. General Procedure. A. To 10 mmol of the cyclic β-amino acid was added 100 ml of acetic anhydride. The solution was then heated at reflux for 3 hr under nitrogen, cooled, poured into an aqueous solution of potassium carbonate (100 g in 200 ml of H_2O), and stirred for 4 hr at 0°. At the end of this time additional potassium carbonate was added, if necessary, to adjust to pH 8. The aqueous solution was then extracted with chloroform (3 × 100 ml), and the chloroform extracts were combined, dried over magnesium sulfate, filtered, and evaporated to yield the lactam. Analytical samples were obtained through preparative gc. Isomer ratios were also determined by gc.

B. To 10 mmol of the cyclic β-amino acid hydrochloride was added 100 ml of acetic anhydride and 0.69 g (5 mmol) of potassium carbonate. The mixture was then treated as above.

3-Carboxyl-1-methyl-2-oxohexahydroazepine (9b). To an acetone–Dry Ice bath cooled solution of 11.3 g (0.11 mol) of diisopropylamine and 150 ml of ether was added 64 ml of a 1.5 *M* solution of butyllithium in hexane. Stirring for 15 min was followed by addition of 10.1 g (80 mmol) of *N*-methylcaprolactam (**8b**)[15] in 50 ml of ether over a period of 5 min. After an additional 10 min, the cooling bath was removed, carbon dioxide was bubbled in for 10 min, the reaction mixture was poured into 300 ml of ice–water, and the layers were separated. The aqueous phase was adjusted to pH 2 with 2 *N* HCl and extracted with chcloroform (4 × 200 ml) and the combined chloroform extracts were evaporated to yield 12.0 g (87%) of the crude acid. Recrystallization from methylene chloride–ethyl ether afforded analytically pure acid **9b**: mp 118–119°; ir (KBr) 1640, 1750, 3000–3400 cm^{-1}; nmr ($CDCl_3$) δ 1.41–2.57 (m, 6 H), 3.06 (s, 3 H), 3.29, 3.99 (m, 3 H), 14.3 (s, 1 H).

Anal. Calcd for $C_8H_{13}NO_3$: C, 56.1; H, 7.7; N, 8.2. Found: C, 56.2; H, 7.7; N, 8.1.

3-Hydroxymethyl-1-methylhexahydroazepine (10b). To a mixture of 2.28 g (60 mmol) of lithium aluminum hydride and 100 ml of tetrahydrofuran (THF) was added 3.42 g (20 mmol) of the acid **9b** in 100 ml of THF over a period of 30 min. After being stirred overnight at room temperature, the mixture was refluxed for 5 hr and cooled, and the excess $LiAlH_4$ was destroyed with water and 15% NaOH. The mixture was filtered, and the dried filtrate was evaporated to yield 2.8 g (98%) of the aminol **10b**: ir 3400 cm^{-1}; nmr δ 1.10–1.98 (m, 6 H), 2.35 (s, 3 H), 2.39–3.00 (m, 3 H), 3.34–3.71 (m, 2 H), 4.78 (s, 1 H).

Anal. Calcd for $C_8H_{17}NO$: C, 67.1; H, 12.0; N, 9.8. Found: C, 67.2; H, 11.8; N, 9.6.

3-Methoxycarbonyl-1-methylhexahydroazepine (11b). A solution of 2.1 g (15 mmol) of the aminol **10b**, 0.35 ml of concentrated sulfuric acid, and 17 ml of water was treated at 0° with a solution of 1.25 g (12 mmol) of chromium trioxide, 0.85 ml of concentrated sulfuric acid, and 20 ml of water. The reaction mixture was stirred for an additional 5 min at 0°, heated at 100° for 2 min, and cooled to 0°, after which another solution of 1.25 g of chromium trioxide, 0.85 ml of concentrated acid, and 20 ml of water was added. Heating at 100° for 30 min was followed by cooling and adding sodium bisulfite to destroy excess oxidant. The pH was adjusted to 10 with 6 *N* NaOH, the mixture was filtered, and the filtrate was acidified (pH 2) with 6 *N* HCl and evaporated to dryness. Methanol (100 ml, previously saturated with HCl gas) was added to the dry residue and the mixture was stirred overnight at room temperature. The methanol was evaporated, 100 ml of water was added, and the pH was adjusted to 8 with potassium carbonate. After extraction of the aqueous solution with chloroform, the combined chloroform extracts were dried and evaporated to yield 1.1 g (41%) of the ester **11b**: ir 1750 cm^{-1}; nmr δ 1.50–1.97 (m, 6 H), 2.31 (s, 3 H), 2.39–3.0 (m, 5 H), 3.53 (s, 3 H).

Anal. Calcd for $C_9H_{17}NO_2$: C, 63.1; H, 10.0; N, 8.2. Found: C, 63.0; H, 10.0; N, 8.1.

3-Hydroxymethyl-1-methylpyrrolidine (10a). 3-Ethoxycarbonyl-1-methyl-2-pyrrolidinone (**9a**)[16] was reduced as described for the reduction of **9b** to **10b**, to yield the aminol **10a**:[17] nmr δ 1.1–2.2 (m, 3 H), 2.23 (s, 3 H), 2.45 (m, 4 H), 3.37 (d, 2 H), 4.75 (s, 1 H).

3-Methoxycarbonyl-1-methylpyrrolidine (11a). The aminol **10a** was oxidized as described for the oxidation of **10b** to **11b** to yield the acid followed by esterification to **11a**: bp 45–46° (3 mm); ir 1750 cm^{-1}; nmr δ 1.74–2.11 (m, 2 H), 2.15 (s, 3 H), 2.35–3.16 (m, 5 H), 3.59 (s, 3 H),

Anal. Calcd for $C_7H_{13}NO_2$: C, 58.7; H, 9.2; N, 9.8. Found: C, 58.5; H, 9.0; N, 9.6.

3-Carboxyl-1-methylpyrrolidine Hydrochloride (12a). The ester **11a** was stirred overnight at room temperature in 6 *N* HCl and the solution was evaporated to yield quantitatively the acid **12a**: nmr (D_2O) δ 2.40 (m, 2 H), 2.9–4.0 (m, 5 H), 2.95 (s, 3 H); high-resolution mass spectrum, calcd for $C_6H_{11}NO_2$ ($M^+ - HCl$), 129.0790; found, 129.0805.

Methyl *N*-Isopropylnipecotate (14). To a mixture of 7.5 g (53 mmol) of methyl nipecotate (**13**),[18] 7 g (50 mmol) of potassium carbonate, and 100 ml of benzene was added 10.5 g (63 mmol) of isopropyl idiode over a period of 45 min. The mixture was heated at reflux for 20 hr, cooled, and poured into 50 ml of water. The layers were separated, and the benzene was evaporated to a residue which on distillation yielded 5.27 g (58.5%) of the ***N*-isopropyl derivative 14:** bp 80–82° (5 mm); ir 1750 cm^{-1}; nmr ($CDCl_3$) δ 1.02 (d, J = 3 Hz, 6 H), 1.35–3.10 (m, 10 H), 4.65 (s, 3 H).

Anal. Calcd for $C_{10}H_{19}NO_2$: C, 64.8; H, 10.3; N, 7.6. Found: C, 64.7; H, 10.4; N, 7.4.

Methyl *N*-Benzylnipecotate (15). The ester **15** was prepared from methyl nipecotate (**13**)[18] and benzyl bromide in a manner analogous to the alkylation of **13** to **14**. Distillation afforded an analytically pure sample of the ester **15:** bp 108–109° (1 mm); ir 1750 cm^{-1}; nmr δ 1.3–3.1 (m, 9 H), 3.49 (s, 2 H), 3.61 (s, 3 H), 7.22 (s, 5 H).

Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.1; H, 8.2; N, 6.0. Found: C, 71.9; H, 8.0; N, 6.1.

***N*-Isopropylnipecotic Acid Hydrochloride (16).** The methyl ester **14** was stirred overnight in 6 *N* HCl at room temperature. Evaporation quantitatively yielded the acid **16:** nmr (D_2O) δ 1.27 (d, J = 3 Hz, 6 H), 1.6–2.0 (m, 4 H), 2.4–2.8 (m, 1 H), 2.9–3.65 (m, 5 H).

1,2-Dimethylnipecotic Acid Hydrochloride (18). A solution of 1.0 g (5.4 mmol) of the ethyl 1,2-dimethylnipecotate[8] and 50 ml of 6 *N* HCl was stirred overnight at room temperature. Evaporation to dryness and recrystallization of the residue from isopropyl alcohol yielded the hydrochloride **18:** mp 184–186°; nmr (D_2O) δ 1.23 (d, J = 6 Hz, 1.5 H), 1.44 (d, J = 6 Hz, 1.5 H), 1.6–2.2 (m, 4 H), 2.82, (s, 1.5 H), 2.86 (s, 1.5 H), 2.88–4.27 (m, 4 H). Based on the nmr, this material appears to be a mixture of two compounds, and a nmr–temperature study indicates that they are isomers; however, repeated recrystallization does not affect the isomer ratio or melting point.

1-Methyl-2-phenylnipecotic Acid Hydrochloride (19). A mixture of 2.0 g (8.1 mmol) of ethyl 1-methyl-2-phenylnipecotate[8] and 50 ml of 6 *N* HCl was heated at reflux overnight, followed by evaporation to yield the acid **19:** nmr (D_2O) δ 2.05–2.35 (m, 4 H), 2.74 (s, 3 H). 2.95–3.90 (m, 3 H), 4.50 (d, 1 H, $J_{2,3}$ = 4 Hz), 7.46 (s, 5 H).

Dimethyl 1-Methylpiperidine-2,3-dicarboxylate (23). A mixture of 5.48 g (28 mmol) of the diester **21**[19] and 5.25 g (28 mmol) of methyl *p*-toluenesulfonate was heated under nitrogen at 100° for 1 hr. The resultant **22** as a viscous oil was dissolved in 50 ml of methanol, the solution was hydrogenated utilizing a platinum catalyst for 20 hr at 38 psi, the solution was poured into 100 ml of aqueous potassium carbonate, and the aqueous solution was extracted with chloroform (3 × 75 ml). The chloroform extracts were dried, filtered, and evaporated to an oily residue, which was distilled to yield 1.2 g (20%) of the piperidine **23:** bp 72–75° (1 mm); nmr δ 1.5–1.85 (m, 4 H), 2.1–2.95 (m, 4 H), 2.29 (s, 3 H), 3.55 (s, 6 H).

Anal. Calcd for $C_{10}H_{17}NO_4$: C, 55.8; H, 8.0; N, 6.5. Found: C, 55.6; H, 7.8; N, 6.6.

1-Methyl-2,3-piperidinedicarboxylic Acid Hydrochloride (24). A mixture of 0.50 g (2.3 mmol) of the diester **23** and 25 ml of 6 *N* HCl was heated at reflux overnight. Evaporation to dryness quantitatively yielded the diacid hydrochloride **24:** nmr (D_2O) δ 1.44–2.12 (m, 4 H), 2.83 (s, 3 H), 2.78–3.49 (m, 3 H), 3.90–4.14 (m, 1 H).

2-Methoxycarbonyl-3-carboxy-1-methylpiperidine Hydrochloride (25). A mixture of 0.50 g (2.34 mmol) of the diester **23** and 25 ml of 6 *N* HCl was stirred overnight at room temperature. When the dimethyl ester **23** was added to 6 *N* HCl, the OCH_3 absorption at δ 3.55 (6 H) was split into two, one at δ 3.71 (3 H) and the other at δ 3.77. The course of this selective hydrolysis was followed by the disappearance of the δ 3.71 absorption, and the reaction mixture was then poured into 100 ml of aqueous potassium carbonate and extracted with chloroform. The aqueous solution was acidified with HCl and applied to a cation exchange column (250 ml, AG-50W-X-1, H^+ form, 20–50 mesh). The column was washed with water until neutral, and then with 300 ml of *N* ammonium hydroxide, collecting and evaporating the first 250 ml of alkaline eluent to yield the free amino acid ester: nmr (D_2O) δ 1.5–2.0 (m, 4 H), 2.83 (s, 3 H), 2.7–3.37 (m, 3 H), 3.60 (s, 3 H), 3.91 (d, 1 H, $J_{2,3}$ = 4 Hz). To the dry residue was added 10 ml of 1 *N* HCl, and the resultant solution was again evaporated to dryness to yield 0.45 g (82%) of the acid **25:** nmr (D_2O) δ 1.60–2.17 (m, 4 H), 2.80–3.6 (m, 3 H), 3.08 [s, 3 H), 3.77 (s, 3 H), 4.22–4.45 (m, 1 H).

Methyl *N*-Trifluoroacetylnipecotate (26). To a solution of 3.9 g (27 mmol) of methyl nipecotate (**13**) and 50 ml of ether at 0° was added 20 g (0.1 mol) of trifluoroacetic anhydride. The reaction mixture was stirred for 1 hr at room temperature and poured into 100 ml of ice–water, the aqueous layer was separated and extracted with chloroform (3 × 75 ml), and the combined organic extracts were dried, filtered, and evaporated, yielding 5.9 g (91%) of the ester **26:** ir 1680, 1730 cm^{-1}; nmr δ 1.35–2.18 (m, 4 H), 2.20–2.78 (m, 1 H), 2.88–3.47 (m, 2 H), 3.64 (s, 3 H), 3.77–4.49 (m, 2 H).

Anal. Calcd for $C_9H_{12}NO_3F_3$: C, 45.2; H, 5.1. Found: C, 45.2; H, 5.0.

1-(2,2,2-Trifluoroethyl)-3-hydroxymethylpiperidine (27). To a solution of 3.0 g (12 mmol) of the ester **26** and 25 ml of tetrahydrofuran (THF) at 0° was added 35 ml of a 1 *M* THF solution of borane over a period of 15 min. The reaction mixture was heated at reflux for 2 hr and cooled to 0°, methanol (25 ml) was added, and the mixture was again heated at reflux for 1 hr. After cooling, the mixture was poured into 100 ml of saturated sodium bicarbonate solution which was then extracted with chloroform (3 × 75 ml). The organic extracts were combined, dried, and evaporated to yield 2.28 g (93%) of the aminol **27:** ir 3500 cm^{-1}; nmr δ 0.72–2.53 (m, 8 H), 2.54–3.15 (m, 4 H), 3.38 (d, 2 H, J = 5 Hz).

Anal. Calcd for $C_8H_{14}NOF_3$: C, 48.7; H, 7.2; N, 7.1. Found: C, 48.8; H, 7.1; N, 7.0.

Methyl *N*-(2,2,2-Trifluoroethyl)nipecotate (28). The alcohol **27** was oxidized to the acid followed by esterification to **28** in 41% yield as previously described for the conversion of **10b** to **11b**. Gc yielded an analytically pure sample of the ester **28:** ir 1730 cm^{-1}; nmr δ 1.37–2.03 (m, 4 H), 2.17–3.27 (m, 7 H), 3.57 (s, 3 H).

Anal. Calcd for $C_9H_{14}NO_2F_3$: C, 48.0; H, 6.3; N, 6.2. Found: C, 47.9; H, 6.2; N, 6.3.

2-Methylene-5-(*N*-methylamino)pentanoic Acid Hydrochloride (35). A solution of 1.25 g (10 mmol) of the lactam **7** and 50 ml of 6 *N* HCl was heated at reflux for 20 hr. The cooled solution was extracted with chloroform to remove starting lactam, and the aqueous phase was then evaporated to dryness to yield 1.5 g (82%) of the acid hydrochloride **36:** mp 94–98°; nmr (D_2O) δ 1.69–2.16 (m, 2 H), 2.24–2.60 (m, 2 H), 2.67 (s, 3 H), 2.90–3.24 (m, 3 H), 5.64 (br s, 1 H), 6.14 (s, 1 H).

Anal. Calcd for $C_7H_{14}NO_2Cl$: C, 46.8; H, 7.9; N, 7.8. Found: C, 46.7; H, 7.9; N, 7.8.

5-(*N*-Acetyl-*N*-methylamino)-2-methylenepentanoic Acid (37). To a mixture of 0.950 g (5.3 mmol) of the acid hydrochloride **36**, 1.46 g (10.6 mmol) of potassium carbonate, and 40 ml of glyme at 0° was added 2.1 g (27 mmol) of acetyl chloride. The reaction mixture was stirred overnight at room temperature and then poured into 100 ml of ice–water. Extraction with chloroform and evaporation of the combined, dried chloroform extracts yielded 0.5 g (52%) of the acid **37:** mp 79–80°; nmr ($CDCl_3$) δ 1.50–2.10 (m, 3 H), 2.11 (s, 3 H), 2.12–2.53 (m, 2 H), 2.95 (d, 3 H, J = 2 Hz), 3.10–3.55 (m, 2 H), 5.57 (s, 1 H), 6.19 (s, 1 H).

Anal. Calcd for $C_9H_{15}NO_3$: C, 58.4; H, 8.2; N, 7.6. Found: C, 58.2; H, 8.0; N, 7.6.

Reaction of 36 with Acetic Anhydride. A mixture of 1.8 g (10 mmol) of the acid **36** and 25 ml of acetic anhydride was stirred overnight at room temperature. The reaction mixture was then poured into 100 ml of saturated aqueous sodium carbonate and stirred for 3 hr. Additional sodium carbonate was added to pH 8, and the aqueous solution was extracted with chloroform. The chloroform extracts were dried, filtered, and evaporated to yield 0.69 g (55%) of the lactam **7.** Acidification of the aqueous layer and extraction with chloroform yielded after evaporation of the chloroform 0.83 g (45%) of the acid **37.**

5-(*N*-Benzyloxycarbonyl-*N*-methylamino)-2-methylenepentanoic Acid (39). To a solution of 0.81 g (5.7 mmol) of the amino acid **36** and 3 ml of 2 *N* sodium hydroxide at 0° were simultaneously added 0.96 g (5.7 mmol) of benzyl chloroformate and 3 ml of 2 *N* sodium hydroxide over a period of 10 min. After stirring for 20 min more, the aqueous solution was washed once with ether, and the aqueous phase was acidified to pH 2 with 10% HCl. The aqueous solution was extracted with chloroform, and the dried chloroform extracts were evaporated to yield 1.01 g (64%) of the acid **39:** nmr ($CDCl_3$) δ 1.36–1.89 (m, 2 H), 2.01–2.35 (m, 2 H), 2.76 (s, 3 H), 3.13 (t, 2 H, J = 6 Hz), 4.95 (s, 2 H), 5.41 (s, 1 H), 6.08 (s, 1 H), 7.07 (s, 5 H), 11.2 (s, 1 H).

Anal. Calcd for $C_{15}H_{19}NO_4$: C, 65.0; H, 6.9; N, 5.1. Found: C, 64.8; H, 6.8; N, 5.2.

5-(*N*-Benzyloxycarbonyl-*N*-methylamino)-2-methylenepentanoic Acetic Anhydride (38). A mixture of 1.0 g (3.6 mmol) of the acid **39** and 40 ml of acetic anhydride was stirred overnight at

room temperature. Evaporation of the acetic acid and excess acetic anhydride afforded a quantitative yield of the mixed anhydride **38**: ir 1725, 1750, 1848 cm^{-1}; nmr δ 1.62–2.14 (m, 2 H), 2.34 (s, 3 H), 2.35–2.60 (m, 2 H), 2.99 (s, 3 H), 3.30–3.50 (t, 2 H), 5.09 (s, 2 H), 5.82 (s, 1 H), 6.19 (s, 1 H), 7.10 (s, 5 H).

Reaction of 38 with *p*-Toluenesulfonic and Sulfuric Acid. A solution of 1.1 g (3.5 mmol) of the anhydride **38** in 20 ml of ether at room temperature was treated with 3.5 mmol of *p*-toluenesulfonic acid or 2 mmol of concentrated sulfuric acid. Conversion to lactam **7** was immediate and dramatic (by gc) in both instances.

1-Methyl-3-methylene-2-pyrrolidinone (40). The acid **12a** was rearranged as described in the general procedure to yield the lactam **40**: ir 1680 cm^{-1}; nmr δ 2.78 (m, 2 H), 2.83 (s, 3 H), 3.35 (t, 2 H), 5.10 (m, 1 H), 5.66 (m, 1 H).

Anal. Calcd for C_6H_9NO: C, 64.8; H, 8.2; N, 12.6. Found: C, 64.8; H, 8.3; N, 12.5.

1-Methyl-3-methylene-2-oxohexahydroazepine (42) and 6-(*N*-Methyl-*N*-acetylamino)-2-methylenehexanoic Acid (43). The methyl ester **11b** was stirred overnight in 6 *N* HCl at room temperature. Evaporation of the solution gave a quantitative yield of the acid hydrochloride **12b** which was used for the following experiments without further purification: nmr (D_2O) δ 1.42–1.98 (m, 6 H), 2.74 (s, 3 H), 2.76–3.64 (m, 5 H).

A. When the acid **12b** was submitted to the general procedure for rearrangement, none of the lactam **42** was obtained. Reacidification of the aqueous solution, followed by extraction with chloroform and subsequent evaporation of the chloroform and acetic acid, afforded the open-chain derivative **43** in 93% yield. Recrystallization from ethyl acetate gave analytically pure acid **43**: mp 94–95°; ir ($CHCl_3$) 1650, 1725, 3000–3500 cm^{-1}; nmr ($CDCl_3$) δ 1.38–1.80 (m, 4 H), 2.15 (s, 3 H), 2.20–2.57 (m, 2 H), 2.98 (d, *J* = 2 Hz, 3 H), 3.16–3.58 (m, 2 H), 5.60 (m, 1 H), 5.25 (m, 1 H), 11.3 (s, 1 H).

Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.3; H, 8.6; N, 7.0. Found: C, 60.5; H, 8.5 N, 7.1.

B. A mixture of 0.43 g (2.7 mmol) of the acid **12b**, 0.42 g (4.1 mmol) of acetic anhydride, 0.2 g (1.4 mmol) of potassium carbonate, and 30 ml of xylene was heated at reflux for 5 hr. The product was isolated as described in the general procedure to yield 0.22 g (40%) of the *N*-acetyl derivative **43** and 0.15 g (40%) of the lactam **42**: ir 1650 cm^{-1}; nmr δ 1.54–1.81 (m, 4 H), 2.14–2.42 (m, 2 H), 2.88 (s, 3 H), 3.12–3.36 (m, 2 H), 5.05 (m, 1 H), 5.30 (m, 1 H).

Anal. Calcd for $C_8H_{13}NO$: C, 69.0; H, 9.4; N, 10.1. Found: C, 68.8; H, 9.4; N, 10.3.

C. A mixture of 2.5 g (11 mmol) of the mixed anhydride **41** (prepared by stirring the acid **12b** overnight at room temperature in acetic anhydride), 0.7 g (5 mmol) of potassium carbonate, 0.60 g (10 mmol) of acetic acid, and 70 ml of xylene was heated at reflux for 4 hr. Isolation as before yielded 0.63 g (42%) of the lactam **42** and 0.5 g of the *N*-acetyl derivative **43**.

1-Isopropyl-3-methylene-2-piperidone (44). The acid **16** was rearranged as described in the general procedure to yield lactam **44**: **ir 1680 cm^{-1}**; nmr ($CDCl_3$) δ 1.10 (d, *J* = 3 Hz, 6 H), 1.6–2.5 (m, 2 H), 2.37–2.72 (m, 2 H), 3.15 (t, 2 H), 4.90 (heptet, 1 H), 5.19 (s, 1 H), 6.12 (s, 1 H).

Anal. Calcd for $C_9H_{15}NO$: C, 70.6; H, 9.9; N, 9.1. Found: C, 70.5; H, 10.0; N, 9.3.

1-Benzyl-3-methylene-2-piperidone (45). The methyl ester **15** was stirred overnight in 6 *N* HCl at room temperature. Evaporation of the solution afforded a quantitative yield of the acid hydrochloride **17** [nmr δ 1.5–2.4 (m, 4 H), 2.8–3.3 (m, 3 H), 3.35–3.85 (m, 2 H), 4.38 (s, 2 H), 7.50 (s, 5 H)] which was rearranged as described in the general procedure to yield the lactam **45**: ir 1680 cm^{-1}; nmr δ 1.23–1.74 (m, 2 H), 2.12–2.40 (m, 2 H), 2.98 (t, *J* = 6 Hz, 2 H), 4.38 (s, 2 H), 5.00 (m, 1 H), 6.00 (m, 1 H), 7.04 (s, 5 H).

Anal. Calcd for $C_{13}H_{15}NO$: C, 77.6; H, 7.5; N, 7.0. Found: C, 77.4; H, 7.4; N, 6.9.

3-Methylene-2-oxo-1-(2,2,2-trifluoroethyl)piperidine (46). A solution of the ester **28** and 6 *N* HCl was stirred overnight at room temperature. Evaporation of the solution afforded a quantitative yield of the acid hydrochloride **29** [nmr (D_2O) δ 1.68–2.15 (m, 4 H), 2.7–3.9 (m, 5 H), 4.20 (q, 2 H, *J* = 9 Hz)] which was rearranged as described in the general procedure with the exception that the reaction time was increased from 3 hr to 24 hr. A 93% yield of the lactam **46** was obtained: ir 1630, 1680 cm^{-1}; nmr δ 1.67–2.22 (m, 2 H), 2.41–2.80 (m, 2 H), 3.40–3.66 (t, 2 H, *J* = 6 Hz), 3.83–4.38 (q, 2 H, *J* = 10 Hz), 5.22–5.35 (m, 1 H), 6.05–6.18 (m, 1 H).

Anal. Calcd for $C_8H_{10}NOF_3$: C, 49.7; H, 5.2; N, 7.3. Found: C, 49.9; H, 5.1; N, 7.3.

3-Ethylidene-1-methyl-2-piperidone (47). The acid **18** was rearranged as described in the general procedure to yield a 50:50 mixture of cis and trans lactams **47a** and **47b**, respectively. Chromatography using ethyl ether as the eluent separated the isomers and gc yielded a pure sample of the cis lactam **47a**: nmr δ 1.68–2.14 (m, 5 H), 2.19–2.55 (m, 2 H), 2.93 (s, 3 H), 3.15 (t, 2 H), 5.65 (q of t, 1 H, *J* = 7, 1 Hz).

Anal. Calcd for $C_8H_{13}NO$: C, 69.0; H, 9.4; N, 10.1. Found: C, 68.8; H, 9.2; N, 10.0.

Similarly, gc afforded an analytically pure sample of the trans lactam **47b**: nmr δ 1.57–2.08 (m, 5 H), 2.22–2.60 (m, 2 H), 2.90 (s, 3 H), 3.30 (t, 2 H), 6.67 (q of t, 1 H, *J* = 7, 1 Hz).

Anal. Calcd for $C_8H_{13}NO$: C, 69.0; H, 9.4; N, 10.1. Found: C, 68.9; H, 9.2; N, 9.9.

3-Benzylidene-1-methyl-2-piperidone (48). The acid **19** was rearranged as described in the general procedure to yield a 30:70 mixture of the cis and trans lactams **48a** and **48b**, respectively, separated by chromatography employing ethyl ether as the eluent. Gc yielded a pure sample of the oily cis lactam **48a**: nmr δ 1.70–2.18 (m, 2 H), 2.37–2.64 (m, 2 H), 2.84 (s, 3 H), 3.24 (t, 2 H, *J* = 6 Hz), 6.32 (br s, 1 H), 6.95–7.45 (m, 5 H).

Anal. Calcd for $C_{13}H_{15}NO$: C. 77.6; H, 7.5; N, 7.0. Found: C, 77.4; H, 7.3; N, 7.0.

Recrystallization from petroleum ether (bp 30–60°)–ether afforded a pure sample of the trans lactam **48b**: mp 70–72°; nmr δ 1.57–2.04 (quintet, 2 H), 2.57–2.85 (m, 2 H), 2.94 (s, 3 H), 3.33 (t, 2 H), *J* = 5 Hz), 7.18 (s, 5 H), 7.55 (br s, 1 H).

Anal. Calcd for $C_{13}H_{15}NO$: C, 77.6; H, 7.5; N, 7.0. Found: C, 77.6; H, 7.3; N, 6.9.

Rearrangement of 1-Methyl-2,3-piperidinedicarboxylic Acid Hydrochloride (24). A. A mixture of 0.33 g (1.5 mmol) of the diacid **24**, 20 ml of acetic anhydride, and 0.21 g (1.5 mmol) of potassium carbonate was heated at reflux under nitrogen for 3 hr. The reaction mixture was cooled, poured into 100 ml of ice-water, stirred for 4 hr, and extracted with chloroform (3 × 75 ml). The chloroform extracts were dried, filtered, and evaporated to yield 0.22 g (88%) of the endocyclic α,β-unsaturated lactam acid **50**: nmr ($CDCl_3$) δ 2.32–2.63 (m, 2 H), 3.00 (s, 3 H), 3.24–3.75 (m, 4 H), 6.50 (t, 1 H, *J* = 4 Hz).

The lactam acid **50** was then treated with diazomethane to yield the ester **54**, and gc afforded a pure sample of **54**: ir 1626, 1681, 1739 cm^{-1}; nmr δ 2.20–2.55 (m, 2 H), 2.93 (s, 3 H), 3.10 (d, 2 H, *J* = 1 Hz), 3.33 (t, 2 H, *J* = 5 Hz), 3.60 (s, 3 H), 6.10 (t, 1 H, *J* = 3 Hz).

Anal. Calcd for $C_9H_{13}NO_3$: C, 59,0; H, 7.2; N, 7.7. Found: C, 58.8; H, 7.3; N, 7.7.

B. A mixture of 0.40 g (1.8 mmol) of the diacid **24**, 1.0 g of magnesium sulfate, and 50 ml of xylene was heated at reflux under nitrogen for 20 hr. The reaction mixture was cooled, filtered, and evaporated to yield 0.28 g (91%) of a 17:83 mixture of the lactams **50** and **49**, respectively. The lactams were also further characterized as their respective methyl ester derivatives **54** and **51a**.

Lactam 51. The acid **25** was rearranged as described in the general procedure to yield a 23:77 mixture of the cis and trans lactams **51a** and **51b**, respectively. Gc afforded analytically pure samples. Cis lactam **51a** had nmr δ 1.78–2.2 (m, 2 H), 2.42–2.76 (m, 2 H), 2.95 (s, 3 H), 3.37 (t, 2 H, *J* = 5 Hz), 3.6 (s, 3 H), 5.66 (t, 1 H, *J* = 1 Hz).

Anal. Calcd for $C_9H_{13}NO_3$: C, 59.0; H, 7.2; N, 7.7. Found: C, 58.8; H, 7.2; N, 7.8.

Trans lactam **51b** had ir 1610, 1650, 1710 cm^{-1}; nmr δ 1.6–2.1 (m, 2 H), 2.8–3.18 (m, 2 H), 2.98 (s, 3 H), 3.2–3.55 (m, 2 H), 3.65 (s, 3 H), 6.66 (t, 1 H, *J* = 1 Hz).

Anal. Calcd for $C_9H_{13}NO_3$: C, 59.0; H, 7.2; N, 7.7. Found: C, 58.9; H, 7.2; N, 7.6.

Isomerization of Lactam 51a to Lactam 54. A solution of 0.030 g (0.16 mmol) of the lactam **51a**, 0.010 g (0.16 mmol) of sodium methoxide, and 10 ml of anhydrous methanol was heated at reflux under nitrogen for 96 hr. The cooled reaction mixture was poured into 50 ml of water, the aqueous phase was acidified (pH 2) and extracted with chloroform (3 × 50 ml), and the chloroform extracts were dried, filtered, and evaporated to yield an oil whose nmr spectrum was commensurate with a 90:10 ratio of the lactams **54** and **51a**, respectively, as confirmed by gc analysis.

1-Methyl-3-ethoxymethyl-2-piperidone (53). To 25 ml of absolute ethanol was added 0.46 g (20 mmol) of sodium. After the sodium had dissolved, 2.5 g (20 mmol) of 1-methyl-3-methylene-2-piperidone (**7**) was added and the reaction mixture was boiled for 7 days, cooled, poured into 100 ml of water, and extracted with chloroform. The dried extracts were evaporated and the residue

was analyzed by gc, indicating a 40% conversion of **7** to **53**. A pure sample of **53** was obtained as an oil by gc: ir 1650 cm^{-1}; nmr (CCl_4) δ 1.19 (t, 3 H, J = 6 Hz), 1.5–2.5 (m, 5 H), 2.95 (s, 3 H), 2.73–3.14 (m, 6 H).

Anal. Calcd. for $C_9H_{17}NO_2$: C, 63.1; H, 10.0; N, 8.2. Found: C, 63.0; H, 9.9; N, 8.3.

Reaction of 1-Methyl-3-benzylidene-2-piperidone (48b) with Lithium 2,2,6,6-Tetramethylpiperide. To 0.28 g (2 mmol) of 2,2,6,6-tetramethylpiperidine in 10 ml of ether was added 1.3 ml of a 1.5 M solution of butyllithium in hexane. After stirring for 10 min, 0.4 g (2 mmol) of lactam **48b** was added, and the reaction mixture was refluxed for 20 hr, cooled, and quenched with 5 ml of CH_3COOD. The ethereal solution was washed with 2 N hydrochloric acid and saturated bicarbonate solution, dried, and evaporated to yield lactam **48b** partially deuterated at C-4: nmr δ 1.57–2.04 (q, 2 H), 2.57–2.85 (m, 1.2 H), 2.94 (s, 3 H), 3.33 (t, 2 H, J = 5 Hz), 7.18 (s, 5 H), 7.55 (br s, 1 H).

Registry No.—7, 1690-73-9; **8b**, 2556-73-2; **9a**, 30932-85-5; **9b**, 50585-84-7; **10a**, 5021-33-0; **10b**, 50585-85-8; **11a**, 34616-29-0; **11b**, 50585-86-9; **12a**, 50585-87-0; **12b**, 50585-88-1; **13**, 50585-89-2; **14**, 50585-90-5; **15**, 50585-91-6; **16**, 50678-87-0; **17**, 50585-92-7; *cis*-**18**, 50585-51-8; *trans*-**18**, 50585-52-9; **19**, 50585-93-8; **21**, 605-38-9; **23**, 50585-94-9; **24**, 50585-95-0; **25**, 50585-96-1; **26**, 50585-97-2; **27**, 50585-98-3; **28**, 50585-99-4; **29**, 50586-00-0; **36**, 50586-01-1; **37**, 50586-02-2; **38**, 50586-03-3; **39**, 50586-04-4; **40**, 50586-05-5; **41**, 50586-06-6; **42**, 50586-07-7; **43**, 50586-08-8; **44**, 50586-09-9; **45**, 50586-10-2; **46**, 50586-11-3; **47a**, 50585-53-0; **47b**, 50586-54-1; **48a**, 50586-55-2; **48b**, 50586-56-3; **50**, 50586-12-4; **51a**, 50585-57-4; **51b**, 50585-58-5; **53**, 50586-13-5; **54**, 50586-14-6; diisopropylamine, 108-18-9; isopropyl iodide, 75-30-9; benzyl bromide, 100-39-0; ethyl 1,2-dimethylnipecotate, 14997-01-4; ethvl 1-methyl-2-phenylnipecotate, 50586-15-7; methyl *p*-toluenesulfonate, 80-48-8; benzyl chloroformate, 501-53-1.

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Interconversions of Aziridine Carboxylates and β-Lactams[1]

James A. Deyrup* and Stuart C. Clough[2]

Department of Chemistry, University of Florida, Gainesville, Florida 32601

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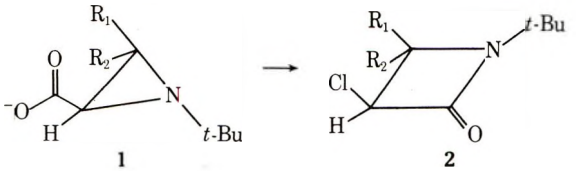
A variety of carboxylate activitating groups convert aziridine carboxylates to 3-halo-2-azetidinones. Yields are in the 20–80% range. The reaction is stereospecific and believed to proceed *via* a 1-azabicyclo[1.1.0]butan-2-one cation. Confirmation for this postulate is found by nmr spectral studies in liquid sulfur dioxide of aziridinecarboxylic anhydrides. In this solvent, equilibrium appears to exist between the anhydride on one hand and the cation and aziridine carboxylate on the other. This equilibrium is displaced toward the cation with arylsulfonyl halides. Attempts to generate the same intermediate from the halolactams were not successful. Ring contraction of the 3-halo-2-azetidinones has also been observed.

In a previous communication, we reported the stereospecific conversion of certain aziridine carboxylates (**1**) to γ-halo-β-lactams (**2**).[1a] In this original communication we



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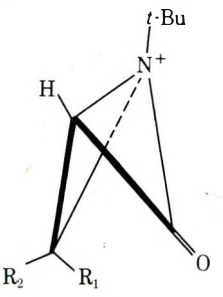
sketched some evidence for product structures and suggested that the ring expansion might proceed *via* the novel and strained bicyclic intermediate **3**. In this paper, we present an elaboration on the previous publication



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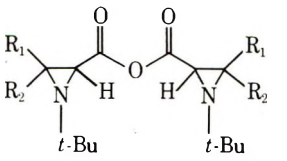
with experimental details and give additional evidence for intermediate **3**.

Preparation of Starting Materials and Structure Proof of Products. The aziridine carboxylates were prepared *via* hydrolysis of the appropriate aziridine ester. The nmr spectrum of each salt in D_2O was in agreement with the assigned structure. The aziridine anhydrides (**4**)



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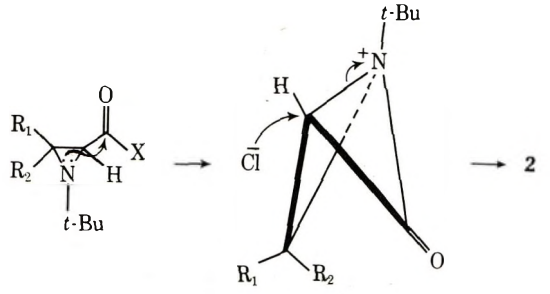
were prepared by reaction of the aziridine carboxylates with 1 equiv of arenesulfonyl chloride. Although the resultant anhydrides were not crystalline and were too reactive for further purification, their spectral and chemical properties were in full agreement with the assigned structure. The infrared spectra of these substances showed characteristic anhydride carbonyl peaks at 1820 and 1760 cm^{-1}. Their nmr spectra revealed typical monosubstituted aziridine splitting patterns with chemical shifts which were almost identical with those of the ring protons of corresponding aziridine esters.[2] In addition, **4a** reacted with

Table I
Aziridine Ring Expansions

Starting material[b]	Product[b]	Conditions	Yield, %
1a	**2a**	$C_2O_2Cl_2$–C_6H_6	26
1a	**2a**	$C_2O_2Cl_2$–Et_3N–C_6H_6	29
1a	**2a**	$SOCl_2$–THF–NaH	33
4a	**2a**	Et_4NCl–CH_3CN[a]	14
1b	**2b**	$C_2O_2Cl_2$–C_6H_6	79
4b	**2b**	Et_4NCl–CH_3CN[a]	75
1c	**2c**	$C_2O_2Cl_2$–C_6H_6	63

[a] In the absence of Et_4NCl, β-lactam products apparently formed from the reaction of **2** with TsO^- and CH_3CN. These products were unstable and difficult to purify, and were not characterized further. [b] **a**, $R_1 = R_2 = H$; **b**, $R_1 = CH_3$; $R_2 = H$ (cis); **c**, $R_1 = H$; $R_2 = CH_3$ (trans).

Scheme I



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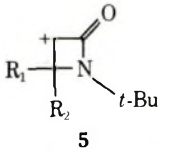
sodium methoxide in methanol to give **1a** and methyl 1-*tert*-butyl-2-aziridinecarboxylate.

Empirical formulae were assigned to the halolactams on the basis of analytical and mass spectral data. The infrared spectra of these compounds showed carbonyl absorption at 1760 cm^{-1} as would be expected for the 2-azetidinone structure. Hydrogenolysis of **2a** yielded 1-*tert*-butyl-2-azetidinone, which was identical with an authentic sample prepared by an alternative procedure. The nmr spectra of the products was also in agreement with the proposed structure. Extraction of the coupling constants from these spectra allowed assignment of the cis–trans stereochemistry based on the expectation that J_{cis} is greater than J_{trans}.[3]

Ring Expansion and Mechanism. The conditions for ring expansion of **1** and **4** are described in Table I. All reactions were carried out at ambient temperature. Although sensitive to structural change, it is significant that changes in the carboxylate activating reagent and proton scavenger had relatively little effect on the yield. We thus conclude that the mechanism for ring expansion does not involve acid-catalyzed nucleophilic ring opening of the aziridine ring and that the activating reagent plays no role other than to foster acyl-oxygen cleavage. Within limits of nmr spectral detection (approximately 1% in this case) formations of **2b** and **2c** were totally stereospecific. It is unlikely, therefore, that "free" carbonium ions (*e.g.*, **5**)



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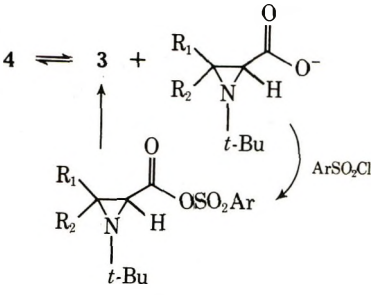
intervene in the expansion process. In view of these considerations; there appears to be only one mechanism which fits the experimental data. This mechanism is shown in Scheme I. Among other things, this mechanism is in agreement with the observed stereochemistry of products **2a** and **2b** by virtue of expected back-side attack on the C_3–N_1 bond.

Table II
Sulfur Dioxide Nmr Spectra of Cis Aziridine Derivatives[a]

	Compd			
Group	Methyl *cis*-1-*tert*-butyl-3-methyl-2-aziridinecarboxylate	**4b**	**3b**	Δδ, ppm[b]
t-Bu	0.40	0.39	0.76,[c] 0.78[d]	0.38
CHCH	1.72	1.78	2.76,[c] 2.80[d]	1.00
CH_3	0.58	0.62	0.93,[c] 0.95[d]	0.32

[a] Chemical shifts (δ) relative to external tetramethylsilane in carbon tetrachloride. [b] Difference in chemical shifts of **4b** and average of ions **3b**.[c,d] [c] Counterion was tosylate. [d] Counterion was nosylate.

Scheme II



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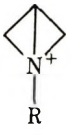
Participation by nitrogen has considerable precedent and recent work in several laboratories has provided convincing evidence for the intermediacy of **6** and its derivatives.[4] The added strain imposed by the C=O group in a three-membered ring and the relationship of **3** to β-lactam chemistry caused us to seek more information concerning the properties of **3** and additional support for its intermediacy.



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Spectral Studies. Strong evidence for the bicyclic cation **3** was obtained from the nmr spectra of the aziridine anhydrides **4a** and **4b** in sulfur dioxide. A dilute sulfur dioxide solution of **4b**, after standing at room temperature for a short time in an nmr tube, gave two sets of nmr spectral signals with similar splitting patterns. One set had chemical shifts comparable to those of the corresponding aziridine ester and was attributed to the anhydride itself. The second set was displaced downfield by 0.3–1.0 ppm (Table II). We assign this latter set to the bicyclic ion **3b**. Addition of nosyl chloride or tosyl chloride to these solutions resulted in the disappearance of the upfield sets of signals and enhancement of the downfield set of signals. This result is readily explainable in terms of the equilibria depicted in Scheme II. Similar results were obtained with the trans anhydride **4c**. A sulfur dioxide solution of this anhydride in the presence of excess nosyl chloride showed both upfield and downfield sets of signals (Table III). If this solution was maintained at −20° for a short period of time, a clean spectrum of bicyclic ion **3c** was obtained. On warming to room temperature, peaks assigned to **3c** disappeared and were replaced by peaks identical with those of authentic β-lactam **2c** in sulfur dioxide.

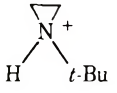
The downfield protons described in Tables II and III are reminiscent of previously observed aziridinium species. Olah has obtained the nmr spectra of 1-*tert*-butylaziridinium ion (**8**) in both antimony pentafluoride–

Table III
Sulfur Dioxide Nmr Spectra of Trans Aziridine Derivatives[a]

Group	Compd: Methyl *trans-tert*-butyl-3-methyl-2-aziridinecarboxylate	3c[b]	Δδ, ppm[c]
t-Bu	0.62	0.88	0.26
CHCH	2.04	2.80	0.76
CH_3	0.83	1.15	0.32

[a] Chemical shifts (δ) relative to external tetramethylsilane in carbon tetrachloride. [b] Counterion was nosylate. [c] Difference in chemical shifts between the trans methyl ester and **4c**.

sulfur dioxide and acidic sulfur dioxide.[5] The values of Δδ (1.20) for the ring hydrogens and for the *tert*-butyl group (1.26) are in reasonable agreement with corresponding Δδ values found in this work. Discrepancies between the monocyclic aziridinium ion and our bicyclic aziridinium ion are readily attributable to such factors as differences in counterion, the anisotropic effect of the carbonyl group, etc.



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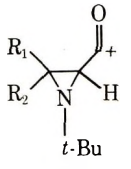
In view of the lack of precedent for structure **3**, it is necessary to consider other species which could give the downfield nmr spectral signals which we attribute to **3**. One such structure is the acylium ion **9**. Acylium ions



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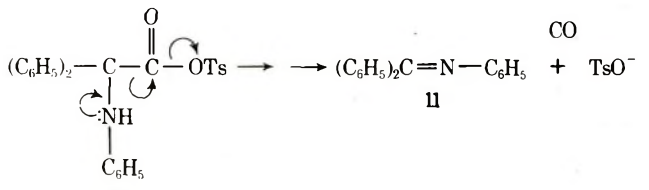
have been observed by Olah, who obtained them from the reaction of acyl halides with Lewis acids.[6] Once formed, these acylium ions were effective acylating agents when quenched by a variety of nucleophiles. In the absence of Lewis acids, these acyl halides were apparently inert toward ionization in SO_2. In contrast to these normal acyl halides, precursors of **3** apparently produced ionized species rapidly in SO_2 without Lewis acid catalysis. It is difficult, therefore, to account for the reactivity of these precursors without invoking participation by nitrogen. When solutions of **3b** were quenched with tetraethylammonium chloride in acetonitrile, **2b** was the only isolated product.

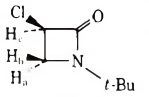
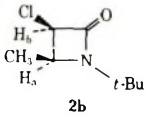
In this connection, it is interesting to contrast the behavior of the mixed anhydride **7** with that of **10**.[7] The latter compound undergoes rapid fragmentation to produce iminium ion **11**. The difference between the two systems is readily explainable in terms of expected and previously observed strain inhibition to ionization in small-ring heterocycles.[3,6]

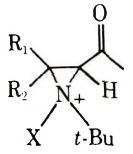


10 **11**

Other obvious sources of the observed spectra may be readily discounted. Nmr spectra in liquid SO_2 of both **2** and its coordinated derivatives have been obtained (*vide infra*) and are distinctly different from the spectra of **3**. Our careful attempts to exclude proton sources and the nature of the product of quenching would appear to convincingly rule out any monocyclic aziridinium species **12**.

Table IV
Sulfur Dioxide Spectra of β-Lactams

Compd	R	SO_2	SO_2–SbF_5	Δδ, ppm
 **2a**	*t*-Bu	0.75	1.15	0.40
	H_c	4.08	4.89	0.81
	H_b	3.18	4.02	0.84
	H_a	2.70	3.59	0.89
 **2b**	*t*-Bu	0.76	1.08	0.32
	H_b	4.22	4.95	0.73
	H_a	3.56	4.37	0.81
	CH_3	0.80	1.25	0.45



12 (X = H, RCO, etc.)

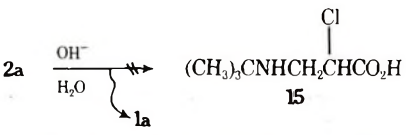
Chemistry of the β-Lactams. The chlorolactams could also potentially serve as precursors to bicyclic ion **3**. Based on the extensive precedents of Olah, antimony pentafluoride was chosen to assist in removing the chloride group. Thus the 3-chloro-2-azetidinones **2a** and **2b** were dissolved in a saturated solution of antimony pentafluoride in sulfur dioxide. The nmr spectrum of the resulting solution was compared to that of the azetidinones in sulfur dioxide (relative to external TMS in CCl_4). Considerable downfield shifts were observed (Δδ, Table IV) for the antimony pentafluoride solutions, but little change in the splitting pattern was noted.

The spectra of the antimony pentafluoride solutions are quite different from the sulfur dioxide spectra of the same supposed ions generated from the anhydride precursors.

However, when attempts were made to quench these supposed ions with methanol, only the original chloroazetidinones could be recovered. These results are interpreted as indicating donor–acceptor complex formation, probably either with oxygen and/or nitrogen and antimony pentafluoride, but not ionization.[8]

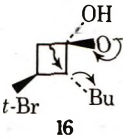
The reluctance of the 3-substituted 2-azetidinones to ionize to the bicyclic cations can be rationalized on stereochemical grounds. An examination of models shows that the unshared pair of electrons on nitrogen is not oriented favorably for overlap at the incipient cation center. Considerable bond deformation, and hence strain, is required for participation and thus ionization to occur. Furthermore, the planar amide linkage would presumably inhibit such a deformation.

One other aspect of the chemistry of these halo-β-lactams proved to be of particular interest. Attempts to selectively convert β-lactam **2a** to amino acid **15** instead reformed the original aziridine carboxylate **1a** in nearly quantitative yield. Reaction with methoxide in methanol



produced the corresponding methyl ester. This ring contraction apparently is stereospecific, since both **2b** and **2c** formed **1b** and **1c**, respectively, stereospecifically. This stereospecific ring contraction has precedent in the carbocyclic case, where the reaction is thought to involve con-

certed (Favorskii type) rearrangement of tetrahedral intermediate **16**.[9] Although a similar Favorskii-type path is



16

possible in the contraction of **2**, an alternate route is possible. This route involves a nucleophilic attack on the C=O, formation of **1b**, and subsequent ring closure to **15**. Since both routes would be stereospecific, we have no basis at the present time for selecting between these two mechanisms. In either case, this and similar ring contraction may have general utility in interconversion of small-ring heterocycles.

Experimental Section

The melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Boiling points are recorded as the temperature at which the material distils, are at atmospheric pressure unless otherwise noted, and are uncorrected. Evaporative distillations were performed on small samples of material following the (Kugelrohr) procedure of Graeve and Wahl.[10] The infrared spectra were recorded on a Perkin-Elmer Model 137 instrument. The routine nmr spectra were recorded on a Varian Associates A-60A 60-MHz recording spectrometer. The nmr data are presented as follows: chemical shift (splitting pattern, number of hydrogens, coupling constant, assignment). Chemical shifts are expressed in parts per million and, in carbon tetrachloride and chloroform, are relative to internal tetramethylsilane. In deuterium oxide chemical shifts are relative to a position 4.99 ppm upfield from the DOH signal. In sulfur dioxide chemical shifts are relative to external tetramethylsilane in carbon tetrachloride. Molecular weights were determined by mass spectrometry. The mass spectra were recorded on a RMU 6E mass spectrometer at 70 eV. The fragments are reported as *m/e* (rel intensity). Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn., and by PCR, Inc., Gainesville, Fla.

Methyl *cis*-1-*tert*-Butyl-3-methyl-2-aziridinecarboxylate. Methyl 2,3-dibromobutyrate[11] (100 g, 0.38 mol), triethylamine (100 g, 0.96 mol), and methanol (400 ml) were stirred at room temperature for 3 hr. *tert*-Butylamine (70 g, 0.96 mol) was added, and the mixture was allowed to stand at room temperature for 2 days. Water was added, and the solution was extracted two times with benzene, dried ($MgSO_4$), and evaporated to an oil which on distillation gave 51 g (78%) of a mixture of methyl *cis*-1-*tert*-butyl-3-methyl-2-aziridinecarboxylate (85%) and methyl *trans*-1-*tert*-butyl-3-methyl-2-aziridinecarboxylate (15%). The pure cis isomer was obtained by spinning band distillation: bp 65° (3.0 mm); ir (liquid film) 2900 (CH) and 1750 cm^{-1} (C=O); nmr (CCl_4) δ 0.95 (s, 9, *tert*-butyl), 1.17 (d, 3, J = 5.3 Hz, CH_3), 2.05 (m, 2, J = 6.3 Hz, CHCH), and 3.65 (s, 3, OCH_3); mol wt 171.

Anal. Calcd for $C_9H_{17}NO_2$: C, 63.13; H, 10.01; N, 8.18. Found: C, 63.03; H, 9.99; N, 7.95.

Methyl *trans*-1-*tert*-Butyl-3-methyl-2-aziridinecarboxylate. Methyl 2,3-dibromobutyrate (26 g, 0.10 mol) and triethylamine (39 g, 0.015 mol) were dissolved in benzene (50 ml) and left at room temperature overnight. The amine hydrobromides were removed by filtration, and the filtrate was evaporated to an oil. The oil was dissolved in *tert*-butylamine (18.2 g, 0.25 mol) and left at room temperature for 4 days. The amine hydrobromides were removed by filtration, and the filtrate was evaporated to an oil which on distillation gave 12.4 g (72%) of a mixture of *cis*- (33%) and *trans*- (67%) methyl 1-*tert*-butyl-3-methyl-2-aziridinecarboxylate. The trans isomer, after washing with aqueous sodium carbonate, was completely separated from the cis isomer by spinning band distillation: bp 65° (0.2 mm); ir (liquid film) 2950 (CH) and 1730 cm^{-1} (C=O); nmr (CCl_4) δ 1.10 (s, 9, *tert*-butyl), 1.26 (d, 3, J = 5.5 Hz, CH_3), 2.13 (d, 1, J = 2.4 Hz, C_2H), 2.46 (m, 1, C_3H), 3.63 (s, 3, OCH_3); mol wt 171.

Anal. Calcd for $C_9H_{17}NO_2$: C, 63.13; H, 10.01; N, 8.18. Found: C, 63.44; H, 10.14; N, 8.31.

Sodium *cis*-1-*tert*-Butyl-3-methyl-2-aziridinecarboxylate (1b). Methyl *cis*-1-*tert*-butyl-3-methyl-2-aziridinecarboxylate (7.35 g, 0.043 mol) was stirred overnight at room temperature with sodium hydroxide (1.68 g, 0.042 mol) in water (50 ml). The resulting solution was washed with chloroform and evaporated to 7.44 g (99%) of the sodium salt: ir (Nujol) 1600 cm^{-1} (CO_2^-); nmr (D_2O) δ 1.30 (s, 9, *tert*-butyl), 1.44 (d, 3, CH_3), 2.48 (m, 1, C_3H), and 2.74 (d, 1, J = 6.3 Hz, C_2H).

Sodium *trans*-1-*tert*-Butyl-3-methyl-2-aziridinecarboxylate (1c). Methyl *trans*-1-*tert*-butyl-3-methyl-2-aziridinecarboxylate (1.20 g, 7.0 mmol) and sodium hydroxide (0.28 g, 7.0 mmol) were stirred together in water (15 ml) at room temperature overnight. The resulting solution was evaporated to 1.19 g (96%) of the sodium salt: ir (Nujol) 1615 and 1590 cm^{-1} (CO_2^-); nmr (D_2O) δ 1.45 (s, 9, *tert*-butyl), 1.58 (d, 3, J = 6 Hz, CH_3), and 2.61 (m, 2, ring protons).

Reaction of Lithium 1-*tert*-Butyl-2-aziridinecarboxylate with Thionyl Chloride. A sodium hydride suspension (0.96 g, 20.0 mmol), washed three times with cyclohexane, was added to tetrahydrofuran (25 ml) under nitrogen to form a slurry. Lithium 1-*tert*-butyl-2-aziridinecarboxylate[2] (1.0 g, 6.7 mmol) was added to the slurry followed by dropwise addition of thionyl chloride (1.19 g, 0.01 mol). The resulting mixture was stirred at room temperature for 1.25 hr. Solvent was removed by evaporation and cyclohexane (35 ml) was added followed by careful addition of water to destroy the sodium hydride present. The organic layer was separated and washed with water, dried ($MgSO_4$), and, after evaporation of the solvent, distilled to give 0.25 g (23%) of 1-*tert*-butyl-3-chloro-2-azetidinone (**2a**): bp 70° (0.2 mm); ir (liquid film) 1760 (C=O), 814, 745, and 695 cm^{-1} (CCl); nmr (CCl_4) δ 1.31 (s, 9, *tert*-butyl), 3.18 (dd, 1, CH), 3.78 (dd, 1, CH), and 4.57 (dd, 1, CH); mol wt 161.

Anal. Calcd for $C_{17}H_{12}NOCl$: C, 52.01; H, 7.43; N, 8.67. Found: C, 52.27; H, 7.65; N, 8.46.

Slightly improved yields could be obtained by removing excess sodium hydride and salts by filtration followed by distillation of the residual oil (33%).

Reaction of Sodium 1-*tert*-Butyl-2-aziridinecarboxylate with Oxalyl Chloride. Solid sodium 1-*tert*-butyl-2-aziridinecarboxylate (1.05 g, 6.3 mmol) was added to a solution of oxalyl chloride (0.95 g, 7.5 mmol) in benzene (10 ml) at room temperature. Both heat and gas were evolved. The resulting slurry was refluxed for 15 min. Benzene (20 ml) was added, and the slurry was washed with aqueous sodium carbonate and water and dried ($MgSO_4$). Distillation of the residual oil left after evaporation of the solvent gave 0.266 g (26%) of 1-*tert*-butyl-3-chloro-2-azetidinone (**2a**). This was identified by spectral comparison to an authentic sample, bp 90° (0.7 mm).

Reaction of Sodium 1-*tert*-Butyl-2-aziridinecarboxylate with Oxalyl Chloride in the Presence of Triethylamine. The sodium salt (1.05 g, 6.3 mmol) was slowly added to a mixture of oxalyl chloride (0.95 g, 7.5 mmol) and triethylamine (0.76 g, 0.0075 mol) in benzene (50 ml). The dark brown slurry was stirred at room temperature for 45 min, washed with 5% HCl, sodium carbonate, and water, dried ($MgSO_4$), and evaporated to 0.30 g (29%) of 1-*tert*-butyl-3-chloro-2-azetidinone. This was identified by comparison to an authentic sample.

Reaction of Sodium *cis*-1-*tert*-Butyl-3-methyl-2-aziridinecarboxylate (1b) with Oxalyl Chloride. The sodium salt (**1b**, 3.4 g, 0.019 mol) was added slowly to a solution of oxalyl chloride (3.0 g, 0.0238 mol) in benzene (20 ml). The resulting slurry was stirred at ambient temperature for 1 hour, and then a few chips of ice were added. Benzene (20 ml) was added, and the reaction mixture was washed with sodium carbonate and water, dried ($MgSO_4$), and evaporated to 3.2 g (98%) of a clean oil which was distilled to give 2.6 g (79%) of *cis*-1-*tert*-butyl-3-chloro-4-methyl-2-azetidinone (**2b**): bp 65° (0.1 mm); ir (liquid film) 2930 (CH), 1750 cm^{-1} (C=O); nmr CCl_4) δ 1.35 (s, 9, *tert*-butyl), 1.40 (d, 3, J = 6.4 Hz, CH_3), 4.01 (m, 1, CHN), and 4.70 (d, 1, J = 5.1 Hz, CHCO); mol wt 175.

The oil was redistilled for an analytical sample, but even when stored under vacuum it was unstable at room temperature. Thus it is not surprising that the analytical sample did not check.

Anal. Calcd for $C_8H_{14}NOCl$: C, 54.66; H, 8.03; N, 7.98. Found: C, 53.83; H, 7.93; N, 8.02.

Reaction of Sodium *trans*-1-*tert*-Butyl-3-methyl-2-aziridinecarboxylate (1c) with Oxalyl Chloride. A mixture composed of sodium *trans*-1-*tert*-butyl-3-methyl-2-aziridinecarboxylate (**1c**, 1.3 g, 3.0 mmol) and an inert salt was added slowly to a solution of oxalyl chloride (1.09 g, 8.7 mmol) in benzene (25 ml). The resulting slurry was stirred at room temperature for 1 hr, washed with 5% HCl, aqueous sodium carbonate, and water, and dried ($MgSO_4$). The solution was evaporated to 0.33 g (63%) of *trans*-1-*tert*-butyl-3-chloro-4-methyl-2-azetidinone (**2c**). The oil was distilled for an analytical sample: bp 65° (0.1 mm); ir (liquid film)

2900 (CH) and 1751 cm^{-1} (C=O); nmr (CCl_4) δ 1.34 (s, 9, *tert*-butyl), 1.45 (d, 3, J = 6.1 Hz, CH_3), 3.68 (m, 1, CHN), and 4.09 (d, 1, J = 1.7 Hz, CHCO); mol wt 177.

Anal. Calcd for $C_8H_{14}NOCl$: C, 54.66; H, 8.03; N, 7.98. Found: C, 54.79; H, 7.91; N, 7.87.

Ring Expansion of Sodium 1-*tert*-Butyl-2-aziridinecarboxylate (1a) with Nosyl Chloride in Acetonitrile. The sodium salt (**1a**, 1.29 g, 6.0 mmol) and nosyl chloride (1.34 g, 6.0 mmol) were stirred together in benzene (50 ml) for 4 hr at room temperature. The slurry was washed with water, dried ($MgSO_4$), and evaporated to an oil which consisted of a mixture of nosyl chloride and 1-*tert*-butyl-2-aziridinecarboxylic acid anhydride (**4a**). The oil was taken up in a solution of tetraethylammonium chloride (2.68 g, 16.0 mmol) in acetonitrile and left at room temperature overnight. The resulting orange solution was evaporated to an oil, taken up in petroleum ether (bp 37–46°), washed with water, dried ($MgSO_4$), and evaporated to a pale yellow oil (0.202 g) which was shown by nmr spectroscopy to consist of 0.13 g (14%) of 1-*tert*-butyl-3-chloro-2-azetidinone (**2a**) together wtih some impurities.

Ring Expansion of Sodium *cis*-1-*tert*-Butyl-3-methyl-2-aziridinecarboxylate (1b) with Nosyl Chloride in Acetonitrile. The sodium salt (**1b**, 0.37 g, 2.0 mmol) and nosyl chloride (0.44 g, 2.0 mmol) were stirred together in benzene (50 ml) for 4 hr at room temperature. The slurry was washed with water, dried ($MgSO_4$), and evaporated to an oil. The oil was dissolved in a solution of tetraethylammonium chloride (0.33 g, 2.0 mmol) and left at room temperature overnight. Acetonitrile was removed by evaporatioh and the residual oil was taken up in petroleum ether, washed with water, dried ($MgSO_4$), and evaporated to 0.274 g (75%) of an oil identified as *cis*-1-*tert*-butyl-3-chloro-4-methyl-2-azetidinone (**2b**). Distillation (65°, 0.1 mm) gave 0.17 g.

***cis*-1-*tert*-Butyl-3-methyl-2-aziridinecarboxylic Anhydride (4b).** Sodium *cis*-1-ert-butyl-3-methyl-2-aziridinecarboxylate (1.0 g, 5.8 mmol) and nosyl chloride (0.62 g, 2.8 mmol) were stirred together in benzene at room temperature for 4.5 hr. The resulting slurry was washed with water, aqueous sodium carbonate, and again with water, dried ($MgSO_4$), and evaporated to 0.633 g (76%) of an oil identified as *cis*-1-*tert*-butyl-3-methyl-2-aziridinecarboxylic anhydride (**4b**). The oil was taken up in petroleum ether and filtered to remove a fine, insoluble suspension. Evaporation of the filtrate gave 0.574 g (69%) of the anhydride **4b** as an oily solid: ir (liquid film) 2920 (CH), 1820, 1800, and 1760 cm^{-1} (C=O); nmr (CCl_4) δ 1.0 (s, 9, *tert*-butyl), 1.26 (broad d, 3, CH_3), and 2.15 (m, 2, ring protons).

Reaction of *cis*-1-*tert*-Butyl-3-methyl-2-aziridinecarboxylic Anhydride with Sodium Methoxide in Methanol. Sodium *cis*-1-*tert*-butyl-3-methyl-2-aziridinecarboxylate (**1b**, 0.34 g, 2.0 mmol) and nosyl chloride (0.44 g, 2.0 mmol) were stirred at room temperature in benzene, washed with water, dried ($MgSO_4$), and evaporated in an oil composed of the anhydride **4c** and nosyl chloride. The oil was dissolved in a solution of sodium methoxide (0.10 g, 1.8 mmol) in methanol and left at room temperature overnight. The resulting solution was poured into benzene and washed with water. The benzene layer was dried ($MgSO_4$) and evaporated to an oily solid. The residue was taken up in chloroform and the solids were removed by filtration. The chloroform solution was evaporated to 0.118 g (35%) of an oil identified as methyl *cis*-1-*tert*-butyl-3-methyl-2-aziridinecarboxylate by nmr spectroscopy.

The water layer was evaporated to a solid which was identified as a mixture of sodium nosylate and sodium *cis*-1-*tert*-butyl-3-methyl-2-aziridinecarboxylate (**1b**) by nmr spectroscopy.

Reaction of Sodium *trans*-1-*tert*-Butyl-3-methyl-2-aziridinecarboxylate (1c) with Nosyl Chloride. Sodium *trans*-1-*tert*-butyl-3-methyl-2-aziridinecarboxylate (0.3 g, 1.7 mmol) and nosyl chloride (0.388 g, 1.7 mmol) were stirred in benzene at room temperature for 4 hr. The resulting slurry was washed with aqueous sodium carbonate and water, dried ($MgSO_4$), and evaporated to an oil (0.38 g) consisting of a mixture of *trans*-1-*tert*-butyl-3-methyl-2-aziridinecarboxylic anhydride (**4c**) and unreacted nosyl chloride: nmr (CCl_4) δ 1.17 (s, 9, *tert*-butyl), 1.42 (m, 3, CH_3), 2.30 (d, 1, C_2H), and 2.60 (m, 1, C_3H).

Nmr Spectra of the Anhydrides in Sulfur Dioxide. The anhydrides were dissolved in liquid sulfur dioxide at −10° and transferred in a laboratory atmosphere to nmr sample tubes, which were sealed. Samples of the anhydrides with nosyl or tosyl chloride present were compared by treating the appropriate sodium salts with equimolar amounts of the arylsulfonyl chlorides and dissolving the residual oil left after the usual work-up in sulfur dioxide as above. The same spectra could be obtained by adding the arylsulfonyl chlorides to solutions of the anhydride in sulfur dioxide, but this was found to be less convenient.

The chemical shifts for the ionized and un-ionized anhydrides are reported with reference to external tetramethylsilane in carbon tetrachloride and are tabulated in Tables II and III.

The solution of the cis anhydride in the presence of nosyl chloride or tosyl chloride (after ionization had occurred) was quenched by pouring the sulfur dioxide solution into a solution of tetraethylammonium chloride in acetonitrile. After the usual work-up *cis*-1-*tert*-butyl-3-chloro-4-methyl-2-azetidinone was recovered in yields of 13 and 14%, respectively.

Nmr Spectra of 3-Chloro-2-azetidinones in Antimony Pentafluoride–Sulfur Dioxide. Sulfur dioxide (2 ml) at −10° was saturated with antimony pentafluoride and cooled to −70°. Approximately 300 mg of 1-*tert*-butyl-3-chloro-2-azetidinone (**2a**) was dissolved in the resultant solution, and an aliquot was sealed in an nmr sample tube. The spectrum of the solution was compared to a spectrum of the same azetidinone in sulfur dioxide and both are reported in Table IV. The antimony pentafluoride–sulfur dioxide solution was poured into a solution of sodium methoxide in methanol (−70°). This solution was then warmed to room temperature, poured into water, and extracted with benzene. The benzene layer was dried ($MgSO_4$) and evaporated to a colorless oil identified as extremely clean 1-*tert*-butyl-3-chloro-2-azetidinone (**2a**).

In a similarly fashion *cis*-1-*tert*-butyl-3-chloro-4-methyl-2-azetidinone (**2b**) was treated with antimony pentafluoride–sulfur dioxide. The nmr spectra was recorded as above, and work-up of the solution with sodium methoxide in methanol yielded only extremely clean *cis*-1-*tert*-butyl-3-chloro-4-methyl-2-azetidinone (**2b**).

Reduction of 1-*tert*-Butyl-3-chloro-2-azetidinone (2a) with Zinc. Zinc dust (2.5 g, 30 mmol), activated by stirring for 2 min in concentrated hydrochloric acid, washing four times with distilled water and four times with acetone (reagent grade), and drying *in vacuo* for 15 min, was added to a solution of 1-*tert*-butyl-3-chloro-2-azetidinone (**2a**, 0.40 g, 2.49 mmol) in ethanol. The heterogeneous mixture was then refluxed for 10 days, cooled, filtered, and evaporated to an oil. The oil was distilled to give 0.13 g (41%) of 1-*tert*-butyl-2-azetidinone, bp 90–100° (25 mm).

1-*tert*-Butyl-2-azetidinone. Triethylamine (3.55 g, 35.0 mmol) was added to a slurry of 3-*tert*-butylaminopropionic acid (**11**, 1.3 g, 9.0 mmol) in dry tetrahydrofuran (10 ml). A solution of thionyl chloride (1.4 g, 12 mmol) in tetrahydrofuran (10 ml) was slowly added to the stirred slurry. The resulting yellow mixture was stirred at room temperature for 14 hr, then filtered through a filter cell, and the filtrate was evaporated to a dark brown sludge. The sludge was washed through 5% alumina with chloroform, and the eluent was evaporated to 0.085 g (7%) of a yellow oil identical with the 1-*tert*-butyl-2-azetidinone prepared by reduction of 1-*tert*-butyl-3-chloro-2-azetidinone (**2a**): ir (liquid film) 2900 (CH) and 1740 cm^{-1} (C=O); nmr (CCl_4) δ 1.28 (s, 9, *tert*-butyl), 2.68 (m, 2, CH_2), and 3.12 (m, 2, CH_2); mol wt 127.

Anal. Calcd for $C_7H_{13}NO$: C, 66.11; H, 10.30; N, 11.01. Found: C, 66.02; H, 10.46; N, 10.92.

Reaction of 1-*tert*-Butyl-3-chloro-2-azetidinone (2a) with Sodium Methoxide. In a drybox 1-*tert*-butyl-3-chloro-2-azetidinone 1.2 mmol) was stirred with a solution of sodium hydroxide (0.06 g, 1.5 mmol) in water (5 ml) for 2 hr. The mixture was then refluxed for 3 hr. The resulting solution was cooled, and solvent was removed by evaporation to give 0.245 g (94%) of a pale yellow powder in which the sole organic species present was identified as sodium 1-*tert*-butyl-2-aziridinecarboxylate (**1a**) by comparison of the ir and nmr spectra with spectra of an authentic sample.

Reaction of 1-*tert*-Butyl-3-chloro-2-azetidinone (2a) with Sodium Methoxide. In a dry box 1-*tert*-butyl-3-chloro-2-azetidinone (**2a**, 0.31 g, 1.8 mmol) was added to a solution of sodium methoxide (0.16 g, 3.0 mmol) in methanol (2.5 ml) and left at room temperature for 2 days. The reaction mixture was poured into benzene (15 ml), washed with water, dried ($MgSO_4$), and evaporated to 0.14 g (48%) of an oil identified as methyl 1-*tert*-butyl-2-aziridinecarboxylate by comparison of ir and nmr spectra with the spectra of an authentic sample.

Reaction of *cis*-1-*tert*-Butyl-3-chloro-4-methyl-2-azetidinone (2b) with Sodium Hydroxide. The azetidinone (**2b**, 0.30 g, 1.7 mmol) was dissolved in dioxane (1 ml), and the resulting solution was added to a solution of sodium hydroxide (0.16 g, 40.0 mmol) in water (2 ml). More water was added until the mixture became clear, and the solution was left at room temperature for 30 days. It was then washed with ether and evaporated to 0.38 g (83%) of a white powder identified as sodium *cis*-1-*tert*-butyl-3-methyl-2-az-

iridinecarboxylate (**1b**) by comparison of the ir and nmr spectra with the spectra of a known sample.

Reaction of *trans*-1-*tert*-Butyl-3-chloro-4-methyl-2-azetidinone (2c) with Sodium Hydroxide. The azetidinone (**2c**, 0.30 g, 1.7 mmol) was dissolved in dioxane (1 ml), and the resulting solution was added to a solution of sodium hydroxide (0.18 g, 45.0 mmol) in water (2 ml). Water was added until the mixture became clear, and the resulting solution was left at room temperature for 21 days. It was washed with chloroform and evaporated to a white solid. Nmr observation showed that about 30% of the solid consisted of sodium *trans*-1-*tert*-butyl-3-methyl-2-aziridinecarboxylate (**1c**). The other components of the mixture were not characterized.

Registry No.—**1a**, 24719-64-0; **1b**, 50562-57-7; **1c**, 50562-58-8; **2a**, 23120-47-0; **2b**, 50562-60-2; **2c**, 50562-61-3; **3b**, 50562-62-4; **3c**, 50562-63-5; **4b**, 50562-64-6; **4c**, 50562-65-7; **11**, 574-45-8; methyl *cis*-1-*tert*-butyl-3-methyl-2-aziridinecarboxylate, 34863-28-0; methyl *trans*-1-*tert*-butyl-3-methyl-2-aziridinecarboxylate, 34856-93-4.

Supplementary Material Available. Nmr spectra of representative key compounds described in this paper (*e.g.*, **2a**, **2b**, **2c**, **3b**, **3c**, and **4a**) will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-902.

References and Notes

(1) (a) A portion of these results was presented as a Communication: J. A. Deyrup and S. C. Clough, *J. Amer. Chem. Soc.*, **91**, 4590 (1969). (b) Support of the National Science Foundation (Grant GP 17642) is gratefully acknowledged.
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The Reaction of 6-Amino- and 6-Hydrazinopyrimidines with Diethyl Azodicarboxylate. A New Method for Carbon-5 Functionalization of Pyrimidines[1]

Edward C. Taylor* and Frank Sowinski

Department of Chemistry, Princeton University, Princeton, New Jersey 08540

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6-Amino- and 6-hydrazinopyrimidines are shown to react with diethyl azodicarboxylate to give 5-(1,2-dicarbethoxyhydrazino) derivatives. The synthetic potential of this simple method for the direct introduction of nitrogen into the 5 position of the pyrimidine ring is illustrated by a synthesis of 1,3-dimethyluric acid from 1,3-dimethyl-6-aminouracil by reaction with diethyl azodicarboxylate, reduction to 1,3-dimethyl-5-carbethoxyamino-6-aminouracil, and thermal ring closure.

6-Aminopyrimidines unsubstituted at position 5 react with a wide variety of electrophiles (NO^+, NO_2^+, X^+, $RC{=}O^+$, etc.) to give 5-substituted derivatives which number among the most versatile and useful of pyrimidine intermediates.[2] We have now examined the reaction of a number of 6-amino- and 6-hydrazinopyrimidines with diethyl azodicarboxylate and have found that the products are 5-(1,2-dicarbethoxyhydrazino)pyrimidines.[3] These Michael adducts, which possess a reduced nitrogen substituent at position 5, have proved to be versatile synthetic intermediates. The present paper describes this new procedure for C-5 functionalization of pyrimidines;[4] subsequent papers will report the conversion of these adducts to 6- and 7-azapteridines, including the antibiotics fervenulin[4] and 2-methylfervenulone (MSD-92).[5]

Our results are summarized in Tables I and II. The reaction proceeds with remarkable ease when run in suspension in hot dichlorobenzene. Under these conditions the reactants slowly dissolve, and the product then generally crystallizes directly from the hot reaction solution. Electron-withdrawing substituents which reduce the nucleophilicity of the pyrimidine ring towards electrophilic reagents (*e.g.*, **5**), not surprisingly, retard the reaction. Furthermore, the reaction is either retarded or inhibited with 6-hydrazinopyrimidines if the proton adjacent to the ring is substituted by an alkyl group (*e.g.*, **13** and **15**). This observation suggests that the diethyl azodicarboxylate–6-amino- (or 6-hydrazino-) pyrimidine reaction may involve a cyclic transition state similar to that proposed for the reaction of diethyl azodicarboxylate with olefins,[6] where a concerted mechanism with little or no charge development is involved. Proton abstraction from the allylic position of the olefin would thus have its counterpart in the present case in N–H abstraction from the 6 substituent. When such a cyclic transition state is not feasible

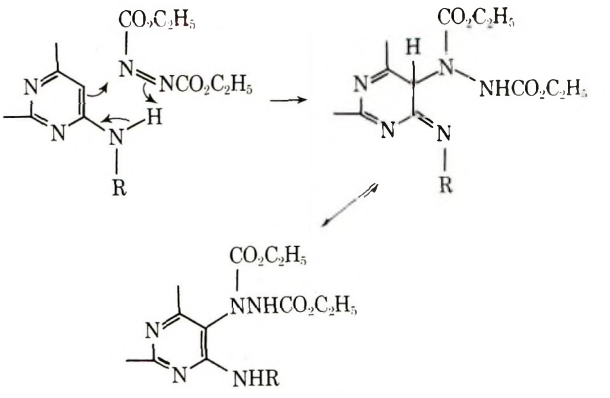
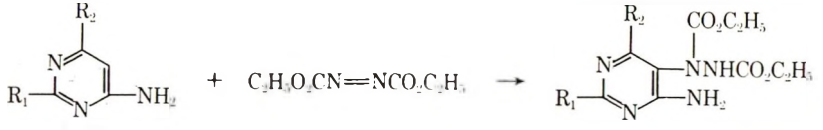


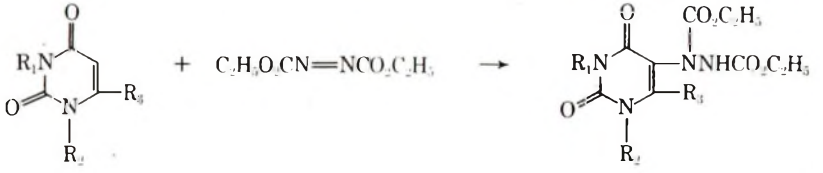
Table I
Formation of 5-(1,2-Dicarbethoxyhydrazino)pyrimidines from 6-Aminopyrimidines and Diethyl Azodicarboxylate



Compd no.	R_1	R_2	Reaction solvent	Temp, °C	Time	Yield, %	Mp, °C, dec	Product formula[f]	Analysis: Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
1	H	OH	DMF	125	2 hr	67[a]	230–231	$C_{10}H_{15}N_5O_5$	42.10	5.31	24.55	41.91	5.31	24.36
2	NH_2	NH_2	DMA	120	0.5 hr	37[b]	240–241	$C_{10}H_{17}N_7O_4$	40.13	5.72	32.76	40.02	5.84	32.58
3	NH_2	$NHC_6H_4CH_3(p)$	ClC_6H_5	40[c]	10 min	90[a]	221–222	$C_{17}H_{22}N_7O_4$	52.43	5.95	25.18	52.34	6.11	25.03
4	$(CH_3)_2N$	NH_2	ClC_6H_5	110	1 min	90[a]	237–238	$C_{12}H_{21}N_7O_4$	44.02	6.46	29.96	44.01	6.41	30.01
5	NH_2	Cl	ClC_6H_5	Reflux	3.5 hr	22[d]	202–203	$C_{10}H_{15}ClN_6O_4$	37.69	4.74	26.37	38.05	4.88	26.21
6	NH_2	OH	ClC_6H_5	135	5 min	74[a]	250–252	$C_{10}H_{16}N_6O_5$	39.99	5.37	27.99	40.08	5.30	28.03
7	SCH_3	NH_2	ClC_6H_5	123	5 min	67[e]	245–246	$C_{11}H_{18}N_6O_4S$	39.98	5.49	25.40	39.94	5.73	25.15

[a] Recrystallized from ethanol. [b] Purified by extraction with hot ethanol, evaporation of the solvent, dissolution of the residue in hot acetonitrile, and cooling. [c] The reaction is exothermic at this temperature and heating is therefore stopped at this point. [d] Recrystallized from 1-propanol. [e] Recrystallized from acetonitrile. [f] Registry no. are, respectively, 49810-27-7, 49810-28-8, 49809-99-6, 49810-00-6, 49810-01-7, 49810-02-8, 49810-03-9.

Table II
Formation of 5-(1,2-Dicarbethoxyhydrazino)uracils from 6-Amino- (or Hydrazino-) uracils and Diethyl Azodicarboxylate

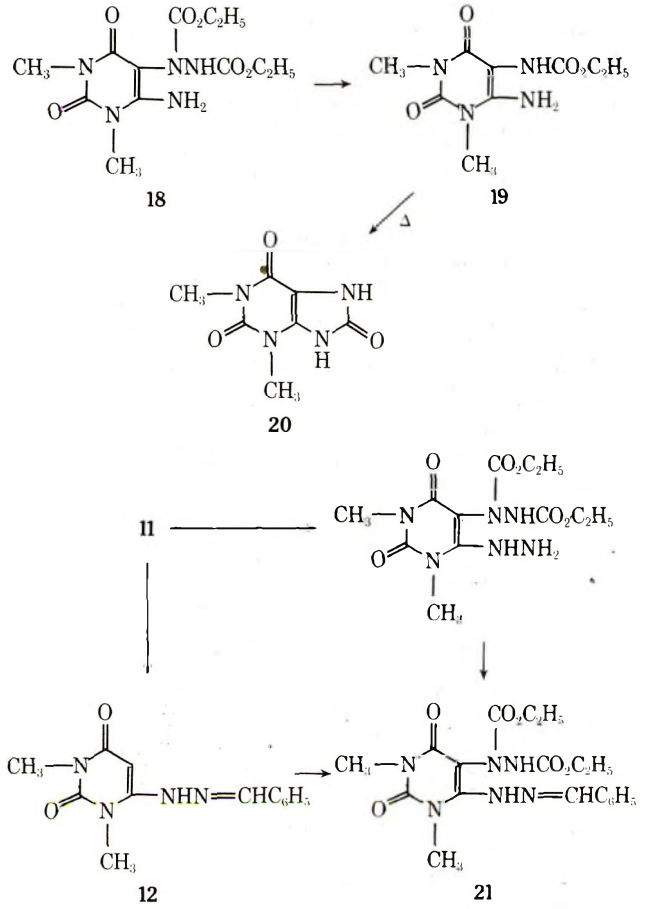


Compd no.	R_1	R_2	R_3	Reaction solvent	Temp, °C	Time	Yield, %	Mp, °C	Product formula[g]	Analysis: Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
8	H	H	NH_2	DMA	140	50 min[a]	61[b]	259–260 dec	$C_{10}H_{15}N_5O_6$	39.86	5.02	23.25	39.58	5.16	23.41
9	CH_3	CH_3	NH_2	[c]			77[b]	146–148	$C_{12}H_{19}N_5O_6$	43.77	5.81	21.26	43.54	5.87	21.35
10	CH_3	CH_3	$NHCH_3$	ClC_6H_5	Reflux	15 min	90[b]	129–131	$C_{13}H_{21}N_5O_6$	45.48	6.16	20.40	45.61	6.33	20.18
11	CH_3	CH_3	$NHNH_2$	DMF	[d]		60[b]	204–205 dec	$C_{12}H_{20}N_6O_6$	41.86	5.86	24.41	42.03	5.83	24.32
12	CH_3	CH_3	$NHN{=}CHC_6H_5$	DMF	Reflux	5 min	73[b]	193–195	$C_{19}H_{24}N_6O_6$	52.77	5.60	19.44	53.07	5.75	19.42
13	CH_3	CH_3	$N(CH_3)NH_2$	ClC_6H_5	Reflux	5 min	6[b]	175–176	$C_{13}H_{22}N_6O_6$	43.57	6.19	23.45	43.70	6.32	23.60
14	CH_3	CH_3	$N(CH_3)NHCHO$	DMF	125	2 hr	57[b]	159–160 dec	$C_{14}H_{22}N_6O_7$	43.52	5.74	21.75	43.34	5.65	21.51
15	CH_3	H	$N(CH_3)NH_2$												
16	CH_3	H	$N(CH_3)N{=}CH\text{-}C_6H_4OCH_3(p)$	DMF	120	2 hr	67[b]	221–222 dec	$C_{20}H_{26}N_6O_7$	51.94	5.66	18.17	51.93	5.73	17.92
17	CH_3	H	$N(CH_3)NHCH_3$	ClC_6H_5	120	5 min	71[e]	111–112[f]	$C_{13}H_{21}N_6O_6 \cdot 0.5C_6H_6$	48.48	6.10	21.20	48.81	6.09	21.30

[a] After the initial exothermic reaction (at 140°) had subsided, three successive additional portions (0.1 equiv each) of diethyl azodicarboxylate were added at 10-min intervals. [b] Recrystallized from ethanol. [c] See Experimental Section. [d] 1 equiv of diethyl azodicarboxylate was added dropwise to a suspension of the pyrimidine in DMF at such a rate that the temperature of the reaction mixture did not rise above 50° (1.5 hr). Stirring was then continued for 2 hr at room temperature. [e] Recrystallized from benzene. [f] Solvate with 0.5 mol of benzene. [g] Registry no. are, respectively, 49810-12-0, 18969-87-4, 49810-14-2, 18969-82-9, 49810-16-4, 49810-17-5, 49810-18-6, 49810-19-7, 49810-20-0.

(*e.g.*, **13**, **15**), competing tetrazene formation[7] may intervene, although no attempt was made to isolate and identify these sensitive materials. It is interesting to note that elimination of this potentially competitive pathway by conversion of the $-N(CH_3)NH_2$ substituent to a benzylidene (**12**, **16**), formyl (**14**), or N_1,N_2-disubstituted derivative (**17**) leads again to successful Michael addition at position 5 of the pyrimidine ring, although yields are decreased and more drastic conditions appear to be necessary.

The structures of the 5-(1,2-dicarbethoxyhydrazino)pyrimidine Michael adducts were confirmed in every case by nmr spectroscopy (disappearance of the characteristic pyrimidine C-5 aromatic proton resonance), and, in the case of 1,3-dimethyl-5-(1,2-dicarbethoxyhydrazino)-6-aminouracil (**18**), by chemical evidence as well. Thus, Raney nickel or Leuckart (formic acid) reduction of **18** resulted in cleavage of the N–N bond to give 1,3-dimethyl-5-carbethoxyamino-6-aminouracil (**19**), identical with an authentic sample prepared by the reaction of 1,3-dimethyl-5,6-diaminouracil with ethyl chloroformate.[8] Furthermore, heating of **19** resulted in ring closure to 1,3-dimethyluric acid (**20**), identical with an authentic sample. This latter reaction comprises a new synthetic approach to purines involving the direct introduction into position 5 of the pyrimidine ring of a reduced nitrogen substituent capable of eventual incorporation into the imidazole ring of the final purine.



Most of the 6-aminopyrimidines examined were well-known, commercially available intermediates. 1,3-Dimethyl-6-hydrazino- (**11**) and 1,3-dimethyl-6-(1-methylhydrazino)uracil (**13**) were prepared by treatment of 1,3-dimethyl-6-chlorouracil[9] with hydrazine and methylhydrazine, respectively, using chloroform as solvent rather than excess hydrazine solution as previously described.[9] The requisite 1,3-dimethyl-6-chlorouracil was prepared by chlorination of 1,3-dimethylbarbituric acid, which we found to be more conveniently prepared by acid hydrolysis of 1,3-dimethyl-6-aminouracil than by condensation of malonic acid with 1,3-dimethylurea.[10]

The structures of the 6-(1-methylhydrazino)uracils **13** and **15** and of 1,3-dimethyl-6-hydrazinouracil (**11**) followed from the observation that they formed benzylidene derivatives with aromatic aldehydes. The product (**12**) of the reaction of **11** with benzaldehyde reacted with diethyl azodicarboxylate to give an adduct (**21**) identical with that formed by reaction of benzaldehyde with the initial adduct formed from diethyl azodicarboxylate with **11**.

3-Methyl-6-(1-methylhydrazino)uracil (**15**)[11] and 3-methyl-6-(1,2-dimethylhydrazino)uracil (**17**) were similarly prepared from 3-methyl-6-chlorouracil and methylhydrazine or 1,2-dimethylhydrazine, respectively.

Experimental Section

Formation of 5-(1,2-Dicarbethoxyhydrazino)-6-amino- (or hydrazino-) pyrimidines. General Procedure. To a suspension of the 6-amino- (or hydrazino-) pyrimidine in the appropriate solvent was added 1 equiv of diethyl azodicarboxylate, and the mixture was heated as specified in Tables I and II. Depending on the solubility of the product in the solvent employed, the 5-(1,2-dicarbethoxyhydrazino) derivative was either isolated by filtration, or the solvent was evaporated under reduced pressure and the residue recrystallized (see Tables I and II).

1,3-Dimethyl-5-(1,2-dicarbethoxyhydrazino)-6-aminouracil (18). A stirred suspension of 108.5 g (0.7 mol) of 1,3-dimethyl-6-aminouracil (**9**) in a mixture of 122.0 g (0.7 mol) of diethyl azodicarboxylate and 300 ml of chlorobenzene was heated to reflux in an oil bath maintained at 150–160°. A vigorous reaction accompanied by considerable foaming occurred, and it became necessary to remove the heat source. The reaction continued spontaneously for several minutes and, after it had subsided, heating was resumed for an additional 20 min. The reaction mixture was then filtered, the filtrate cooled, and the copious crop of ivory-colored crystals collected by filtration, washed with benzene followed by ether, and dried; yield (product solvated with chlorobenzene) 290 g, mp 66–70°. Repeated recrystallization of a small sample from benzene resulted in exchange of benzene for chlorobenzene of solvation: mp 88–90°; nmr ($CDCl_3$) 1.26 (t, 6, CH_3CH_2O), 3.30 (s, 3, CH_3N), 3.39 (s, 3, CH_3N), 4.21 (m, 4, CH_3CH_2O), 6.37 (s, 2, NH_2), 7.35 (s, 6, C_6H_6), and 7.98 ppm (s, 1, NH). The remainder of the product (solvated with chlorobenzene) was dissolved in 1500 ml of boiling water and the solution heated briefly until steam distillation of the chlorobenzene was complete. The solution was then decolorized with charcoal, filtered, and cooled, and the colorless crystals which separated were collected by filtration: yield 165 g (70%) of the hemihydrate, mp 142–144° dec.

Anal. Calcd for $C_{12}H_{19}N_5O_6 \cdot 0.5H_2O$: C, 42.60; H, 5.96; N, 20.70. Found: C, 42.33; H, 5.85; N, 20.75.

The anhydrous material, mp 146–148° dec, was prepared by recrystallization from absolute ethanol followed by drying *in vacuo* at 65° for 24 hr.

Anal. Calcd for $C_{12}H_{19}N_5O_6$: C, 43.77; H, 5.81; N, 21.26. Found: C, 43.54; H, 5.87; N, 21.35.

1,3-Dimethyl-5-carbethoxyamino-6-aminouracil (19). Method A. To a suspension of 390 g of Raney nickel (Grace no. 28, freed of excess water by draining with slight suction on a Büchner funnel followed by repeated washing with absolute ethanol) in 750 ml of absolute ethanol was added 25.0 g of 1,3-dimethyl-5-(1,2-dicarbethoxyhydrazino)-6-aminouracil (**18**) hemihydrate. The mixture was stirred and heated under reflux for 30 min, the nickel allowed to settle, and the solution decanted. The residual nickel was stirred four times with 500-ml portions of hot absolute ethanol, and the combined decantations were evaporated to 250 ml, filtered, and cooled to give 13.4 g (75%) of **19**, mp 212–213° (lit.[8] mp 206–207°; mixture melting point with authentic material prepared by the literature procedure[8] was 212–213°).

Anal. Calcd for $C_9H_{14}N_4O_4$: C, 44.62; H, 5.83; N, 23.13. Found: C, 44.32; H, 5.90; N, 22.93.

Method B. A solution of 5.4 g of 1,3-dimethyl-5-(1,2-dicarbethoxyhydrazino)-6-aminouracil in 17 ml of 97–100% formic acid was heated under reflux for 1 hr and concentrated to dryness under reduced pressure. The residue was dissolved in 25 ml of water and again concentrated to dryness. This process was repeated, and the residue was triturated with 1:1 ethanol–ether to give 1.62 g (47%) of crude **19**. Drying and recrystallization from ethanol gave material identical with that prepared by method A.

1,3-Dimethyluric Acid (20). 1,3-Dimethyl-5-carbethoxyamino-6-aminouracil (**19**) (500 mg) was placed in a test tube, in which a slight positive pressure of nitrogen was maintained, which was immersed in an oil bath preheated to 175°. The temperature of the heating bath was then raised to 235° over a period of 45 min. The contents of the reaction vessel were cooled, powdered, recrystallized from water, and dried: yield 0.38 g (93%) of colorless crystals, mp 412–415° (lit.[12] mp 408–410° dec; mixture melting point with authentic material 412–415°).

Anal. Calcd for $C_7H_8N_4O_3$: C, 42.63; H, 4.11; N, 28.56. Found: C, 42.70; H, 4.35; N, 28.60.

1,3-Dimethyl-6-methylaminouracil (10). 1,3-Dimethyl-6-chlorouracil was prepared by the procedure of Pfleiderer and Schündehütte[9] except that it was found more convenient to take up the crude product in chloroform, and to use the resulting solution (dried and filtered) directly. Thus, to 500 ml of a stirred chloroform solution containing 50.9 g (0.30 mol) of 1,3-dimethyl-6-chlorouracil was added over a 20-min period a mixture of 250 ml of ethanol and 93.0 g of a 40% aqueous solution (37.4 g, 1.2 mol) of methylamine. After 24 hr the reaction mixture was concentrated *in vacuo* and the residue washed with cold ethanol, acetone, and then ether to give 67.0 g (quantitative) of the hydrochloride monohydrate, mp 204–205° dec. A 37.4-g (0.182 mol) portion of this material was dissolved in 200 ml of boiling water, cooled slightly, and treated in small portions with 15.1 g (0.182 mol) of solid sodium bicarbonate. Cooling and filtering then gave 28.8 g (quantitative) of the free base of **10**, mp 240–241° dec.

Anal. Calcd for $C_7H_{11}N_3O_2$: C, 49.69; H, 6.55; N, 24.84. Found: C, 49.69; H, 6.36; N, 24.75.

1,3-Dimethyl-6-hydrazinouracil (11). To a stirred solution of 131.0 g (0.75 mol) of 1,3-dimethyl-6-chlorouracil in 1 l. of chloroform was added dropwise over a period of 2 hr a solution of 120.0 g (2.03 mol) of 85% aqueous hydrazine hydrate in 200 ml of ethanol. The reaction mixture was maintained at room temperature overnight and concentrated under reduced pressure, and the residue was triturated with 250 ml of ethanol. Filtration then gave 108.1 g (84%) of **11**, mp 239–240° dec. The analytical sample, recrystallized from ethanol, melted at 240–241° dec (lit.[9] mp 216–218°).

Anal. Calcd for $C_6H_{10}N_4O_2$: C, 42.34; H, 5.92; N, 32.92. Found: C, 42.60; H, 6.08; N, 33.13.

1,3-Dimethyl-6-(benzylidinehydrazino)uracil (12). To a solution of 1.70 g (0.01 mol) of 1,3-dimethyl-6-hydrazinouracil (**11**) in 75 ml of hot aqueous ethanol (2:1) was added a solution of 1.1 g (0.01 mol) of benzaldehyde. The voluminous solid which formed immediately was collected by filtration and recrystallized from ethanol to give 2.35 g (91%) of colorless crystals, mp 270–271° (lit.[9] mp 253°).

Anal. Calcd for $C_{13}H_{13}N_4O_2$: C, 60.68; H, 5.09; N, 21.78. Found: C, 60.50; H, 5.24; N, 21.54.

1,3-Dimethyl-6-(1-methylhydrazino)uracil (13). To a solution of 83.5 g (0.475 mol) of 1,3-dimethyl-6-chlorouracil in 1.5 l. of chloroform was added slowly, over a period of 30 min, a solution of 65.8 g (1.425 mol) of methylhydrazine in 500 ml of chloroform. After stirring for 48 hr at room temperature, the mixture was filtered and the filtrate evaporated to dryness under reduced pressure. Trituration of the residue with 100 ml of cold ethanol followed by filtration gave 71.0 g (81%) of colorless crystals of **13**, mp 133–134°. The melting point was not changed upon recrystallization from ethanol.

Anal. Calcd for $C_7H_{12}N_4O_2$: C, 45.64; H, 6.56; N, 30.42. Found: C, 45.54; H, 6.08; N, 30.21.

1,3-Dimethyl-6-(3,4,5-trimethoxybenzylidene-1-methylhydrazino)uracil was prepared in 92% yield as described above for the preparation of **12**, mp 177–178°.

Anal. Calcd for $C_{17}H_{22}N_4O_5$: C, 56.34; H, 6.12; N, 15.47. Found: C, 56.62; H, 5.96; N, 15.25.

1,3-Dimethyl-6-(2-formyl-1-methylhydrazino)uracil (14). To a mixture of 22.5 g (0.22 mol) of acetic anhydride and 150 ml of formic acid, maintained at 0°, was added gradually 32.0 g (0.20 mol) of 1,3-dimethyl-6-(1-methylhydrazino)uracil (**13**). The mixture was stirred at 0° until solution was complete and then heated at 50–55° for 1 hr. Concentration of the resulting solution under reduced pressure, trituration of the residual oil with cold ethanol, and filtration then gave 23.6 g (55%) of colorless crystals of **14**, mp 169–170°.

Anal. Calcd for $C_8H_{12}N_4O_3$: C, 45.28; H, 5.71; N, 26.41. Found: C, 45.10; H, 5.71; N, 26.25.

3-Methyl-6-(1-methylhydrazino)uracil (15). To a stirred solution of 23.0 g (0.5 mol) of methylhydrazine in 100 ml of ethanol was gradually added a hot solution of 16.1 g (0.1 mol) of 3-methyl-6-chlorouracil[13] in 300 ml of dioxane. After 16 hr at room temperature, 5.4 g (0.1 mol) of sodium methoxide in 100 ml of methanol was added, the mixture filtered from precipitated sodium chloride, and the filtrate concentrated to give 14.0 g (76%) of colorless crystals of **15**, mp 205–207° (lit.[11] mp 207–209°).

3-Methyl-6-(*p*-anisylidene-1-methylhydrazino)uracil (16) was prepared in the usual manner from 3-methyl-6-(1-methylhydrazino)uracil and *p*-anisaldehyde in hot ethanol: yield 92%, mp 227–228° dec.

Anal. Calcd for $C_{14}H_{15}N_4O_3$: C, 58.52; H, 5.26; N, 19.50. Found: C, 58.32; H, 5.47; N, 19.27.

3-Methyl-6-(1,2-dimethylhydrazino)uracil (17). A stirred, ice-cooled solution of 13.3 g (0.10 mol) of 1,2-dimethylhydrazine dihydrochloride in 25 ml of water was treated with 8.0 g (0.20 mol) of solid sodium hydroxide, the mixture was filtered, and the filtrate was added to a solution of 4.0 g (0.025 mol) of 3-methyl-6-chlorouracil[13] in 300 ml of hot ethanol. The reaction mixture was heated under reflux for 4.5 hr and filtered, and the filtrate was concentrated under reduced pressure. The residual solid was extracted with 100 ml of hot ethanol, and the extract was filtered and again concentrated under reduced pressure. This time the residual solid was extracted with 10 ml of hot acetonitrile and the extract (after filtration) concentrated and cooled to give 3.5 g (76%) of colorless crystals of **17**, mp 179–181°.

Anal. Calcd for $C_7H_{12}N_4O_4$: C, 45.64; H, 6.56; N, 30.42. Found: C, 45.67; H, 6.72; N, 30.40.

Registry No.—**1**, 1193-22-2; **2**, 1004-38-2; **3**, 49753-53-9; **4**, 49810-25-5; **5**, 156-83-2; **6**, 56-06-4; **7**, 1005-39-6; **8**, 873-83-6; **9**, 6642-31-5; **10**, 5770-42-3; **11**, 40012-14-4; **12**, 25774-97-4; **13**, 4318-53-0; **14**, 49810-09-5; **16**, 42748-18-5; **17**, 49810-11-9; **19**, 49810-21-1; **20**, 944-73-0; diethyl azodicarboxylate, 1972-28-7; 1,3-dimethyl-6-chlorouracil, 6972-27-6; 1,3-dimethyl-6-(3,4,5-trimethoxybenzylidene-1-methylhydrazino)uracil, 49810-23-3.

References and Notes

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Mobile Keto Allyl Systems. XV.[1] Reaction of Amines with α-(Bromomethyl)benzalacetone and Synthesis of an Acetylazetidine

Michael C. Eagen and Norman H. Cromwell*

Department of Chemistry, University of Nebraska, Lincoln, Nebraska 68508

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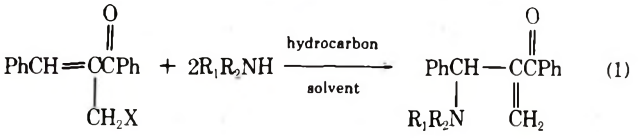
The synthesis and reaction of α-(bromomethyl)benzalacetone (2) with *tert*-butylamine, morpholine, and piperidine in hydrocarbon solvent is reported. Substitution-rearrangement products 3 were obtained for all amines. The morpholine and piperidine reactions gave 3 as well as normal substitution products 4. The formation of compounds 3 and 4 is discussed in terms of a variant of an S_N2' mechanism. The synthesis and structure determination of *trans*-1-*tert*-butyl-2-phenyl-3-acetylazetidine is described.

Although primary allyl halides react with amines to yield mainly normal substitution products,[2] Cromwell and Rebman observed rearrangement-substitution products (II) upon treating *tert*-butylamine, cyclohexylamine, morpholine, or piperidine with *trans*-α-(bromomethyl)chalcone (Ia) in hydrocarbon solvent.[3] Kinetic studies showed a retardation in the reaction rate of Ia with increasing bulk at the α-carbon atom of the attacking amine.[4] The ratios of reactivities of the bromide Ia and the chloride Ib with cyclohexylamine and triethylcarbinylamine were 3.6 and 5.7, respectively. This small leaving group effect suggested that the reaction of amines with Ia or Ib involved a rate-limiting transition state in which there is only a small extension of the carbon-halogen bond.[4]

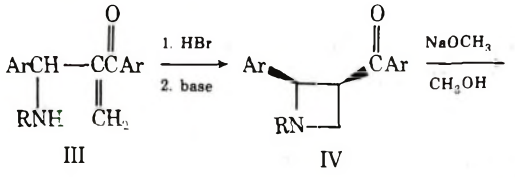


(1)

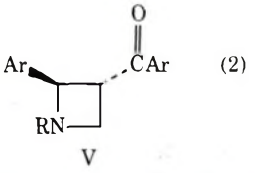
Ia, X = Br
b, X = Cl

II

The β-benzoylallyl amines III are precursors to the high yield synthesis of azetidinyl ketones.[5] A variety of amino derivatives of type III gave the cis azetidine IV, exclusively, in nearly quantitative yield. The cis compounds were readily epimerized to the trans isomers V with sodium methoxide in methanol.



III IV



(2)

V

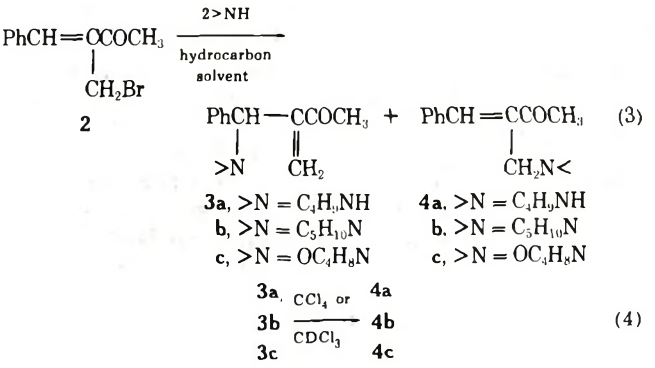
We were interested in studying the reaction of amines with α-(bromomethyl)benzalacetone (2) in hydrocarbon solvent and in utilizing the above procedure for the synthesis of an acetylazetidine.

Results

trans-α-(Methyl)benzalacetone (1) was synthesized in satisfactory yield by the hydrogen chloride catalyzed condensation of benzaldehyde with butanone. Bromination of 1 with *N*-bromosuccinimide in refluxing carbon tetrachloride containing a catalytic amount of benzoyl peroxide yielded *trans*-α-(bromomethyl)benzalacetone (2). Compound 2 was sufficiently soluble in pentane to undergo reaction with amines.

Careful treatment of 2 with a 2 mol equiv of *tert*-butylamine in pentane at room temperature produced 2-[α-(*tert*-butylamino)benzyl]-1-buten-3-one (**3a**), exclusively. Upon dissolving **3a** in carbon tetrachloride, slow isomerization to 1-(*tert*-butylaminomethyl)benzalacetone (**4a**) was observed by pmr. Both **3a** and **4a** were characterized as their hydrohalide salts.

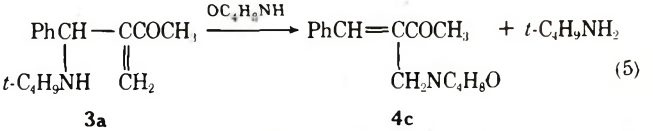
When 2 was treated with a 2 mol equiv of morpholine or piperidine in hexane solvent at room temperature, both rearrangement-substitution (**3b** and **3c**) and substitution (**4b** and **4c**) products were observed. Upon dissolving the reaction mixtures in chloroform-*d*, slow isomerization to the thermodynamically more stable isomers was complete (**3b** to **4b** and **3c** to **4c**). The lower spectrum in Figure 1[6] is for the products from the reaction of 2 with piperidine after filtering off a 95.3% yield of piperidine hydrobromide. The 6.19- and 6.27-ppm resonances were assigned to the vinylic protons and the 4.49-ppm resonance to the benzyl proton in **3b**. The top spectrum in Figure 1 resulted from allowing the product mixture **3b** and **4b** to stand at room temperature for several days in chloroform-*d*. The 3.32-ppm resonance was assigned to the vinyl methylene protons in **4b**. All of the amino ketones (3 and 4) were heat-sensitive oils whose hydrohalide salts were hygroscopic. They were analyzed as their picrates. Attempts to purify the product mixtures on a Florisil chromatography column resulted in decomposition of the compounds.



(3)

(4)

The amino ketone **3a** reacted with morpholine in pentane solvent to produce **4c**. No evidence for a 1,3-diamino ketone was obtained.

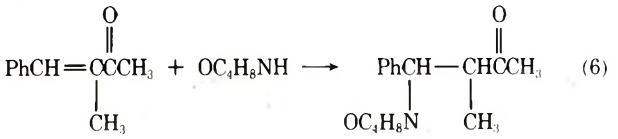


(5)

3a 4c

A 20-fold excess of morpholine was allowed to react neat with 1 at room temperature for 13 days. Pmr analysis of the reaction mixture showed unreacted 1 and an 8:1 ratio of the diastereomers of the Michael adduct 5. The diaste-

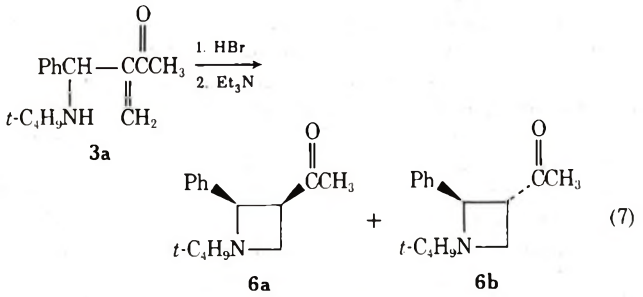
reomers of **5** were readily identified by the α methyl resonances ($CHCH_3$) appearing as doublets centered at 0.80 and 1.28 ppm. The predominant diastereomer was fractionally crystallized from ether–pentane, mp 90.5–91.5°. When this reaction was carried out for 3.5 months, the diastereomers were present in equal amounts with 30% unreacted starting material remaining.



(6)

1 **5**

The amino ketone **3a** was dissolved in chloroform saturated with hydrogen bromide at 0° and allowed to reach room temperature after standing several days. Careful neutralization of the reaction mixture with excess triethylamine and subsequent work-up provided a 70% yield of azetidinyl ketones **6a** and **6b** in a 6:1 ratio, respectively (estimated by integration of pmr signals), and some starting material (**3a**).



(7)

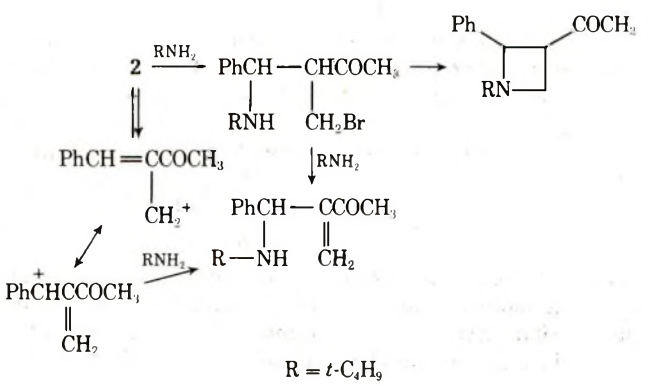
3a **6a** **6b**

The reaction mixture was eluted with ether–benzene on a silica gel chromatography column. The first band eluted was identified by pmr as **6b** (Figure 2).[6] No other azetidinyl product was collected. Unidentified material was eluted after **6b** and considered to be degradation products of **3a** and **4a.** Compound **6b** was a clear stable oil. Upon treatment with sodium methoxide in methanol-d_1 the acetyl methyl protons and the 3-H ring proton were readily exchanged. The 2-H ring proton signal collapsed from a doublet to a singlet centered at δ 4.39.

Discussion

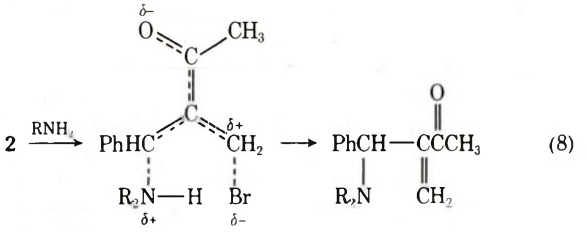
Ionization of the β-carbo allyl bromide **2** and subsequent nucleophilic attack by amine in a nonpolar solvent is not likely.[7] The reaction of **1** in neat morpholine was very slow and incomplete even after 3 months. These data argue against the formation of a 1,4-Michael adduct followed by rapid elimination of hydrogen bromide. If this elimination step was sufficiently slow, then azetidine formation (with *tert*-butylamine) should have been observed since the two reactions are competitive (Scheme I).

Scheme I



$R = t\text{-}C_4H_9$

The formation of rearrangement-substitution products from the reaction of amines with **2** in hydrocarbon solvent is best described by a variant of an S_N2' mechanism. The amine attacks the electron deficient γ-carbon atom of the allyl system with the carbonyl group oxygen atom accepting much of the developing negative charge. The carbon–nitrogen bond formation proceeds ahead of the carbon–bromine bond breakage. The approach of the amine could be aided by hydrogen bonding with the carbonyl oxygen atom[8] or with the bromine atom resulting in a cis orientation of the amine and bromine (eq 8). A cis geometry for the attacking nucleophile to the leaving group was proved for the reaction of piperidine with *trans*-6-alkyl-2-cyclohexen-1-yl-2,6-dichlorobenzoates.[9] We envisage structure A for the transition state of the reaction of amines with **2.**



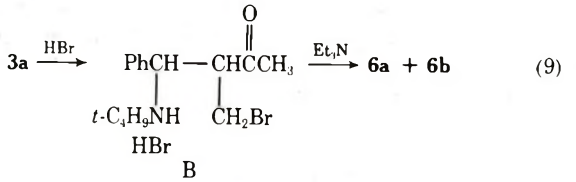
(8)

A

The normal substitution products **4b** and **4c** were obtained from reaction of piperidine with **3b** and morpholine with **3c,** respectively, or by self-rearrangement of **3b** and **3c.** The possibility of the former process was demonstrated when **3a** reacted with morpholine to produce **4c** (eq 5).[10] The self-rearrangement process is very slow in pentane or hexane and requires solvents of higher polarity to become important (eq 4).

The formation of **4b** and **4c** in hydrocarbon solvent was not expected in view of the reaction of morpholine and piperidine with Ia to produce only abnormal substitution products under the conditions of eq 1 and 3. We rationalize that compounds **3b** and **3c** are able to compete with **2** for unreacted amine while II cannot compete with Ia. It is known that the reactivity of amines toward Ia and II is influenced by the bulkiness of the attacking amine and, for Ia, interaction between substituents at the α-carbon atom of the attacking amine and the γ-phenyl ring of the allyl system.[3,10] It now appears necessary to consider the substituent on the β-carbonyl group of the allyl system as a product controlling factor.

The addition of hydrogen bromide to **3a** probably formed a γ-bromo amine B which cyclized to the cis azetidinyl ketone **6a.**[5a] Approximately 30% of unchanged starting material was observed by pmr (Figure 2)[6] and was considered to arise from elimination of hydrogen bromide from B rather than incomplete addition of hydrogen bromide to **3a.**[11] The reaction is further complicated by the production of a small amount of the trans azetidinyl ketone **6b.**



(9)

B

The cis azetidine **6a** results from a stereospecific intramolecular nucleophilic displacement of halogen by nitrogen from the erythro form of B.[5] The trans azetidine **6b** is derived from the threo form of B or by epimerization of **6a** in the presence of excess triethylamine.

Configuration assignments were based on pmr spectra and were compared with known 3-carbo azetidines.[5] Ex-

amination of the spectra in Figure 2[6] shows the C-2 benzyl doublet of **6b** (J = 6.6 Hz) centered at 4.39 ppm compared to 4.69 ppm for **6a** (J = 8.3 Hz).

The benzyl proton of trans 3-carbo azetidines (V) typically resonate at higher field than in the cis isomer (IV).[5c] Also, the trans isomers of V show a smaller coupling constant for the benzyl proton than the cis compounds IV. Lastly, the relative chemical shifts of the acetyl methyl protons in **6a** and **6b** suggest that the assignments were correct. For **6a**, the acetyl methyl protons are cis to the phenyl ring and resonate at 1.37 ppm. In **6b**, a trans configuration exists and the singlet now resonates at lower field at 1.91 ppm.

Experimental Section

Melting points were determined from a Mel-Temp or a Hoover capillary tube device and are uncorrected. The infrared spectra were recorded on Perkin-Elmer Models 237 and 621 spectrophotometers and a Beckman IR-18. The pmr spectra were obtained from Varian Models A-60, A-60D, and HA-100 spectrometers utilizing tetramethylsilane as an internal standard. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, Ill.

trans-α-**(Methyl)benzalacetone (1).**[12] A 53-g (0.5 mol) sample of benzaldehyde and 36 g (0.5 mol) of butanone were stirred magnetically at 0° while anhydrous hydrogen chloride was bubbled in until saturated. The mixture was stirred overnight to leave a red oil followed by evaporation of water and hydrogen chloride *in vacuo* with heating. The resulting mass was taken up in 400 ml of 95% ethanol containing 70 g (0.5 mol) of K_2CO_3 and 49 g (0.5 mol) of KOAc and refluxed 4 hr. The solvent was evaporated and the residue taken up in ether and filtered, and the ether evaporated to leave a yellow oil. The oil was distilled through a 6-in. Vigreux column collecting 48 g (60%): bp 80–93° (~1 mm); pmr (CCl_4) δ 7.1–7.4 (m, 6, C_6H_5CH), 2.33 (s, 3, $COCH_3$), and 1.96 (d, 3, J = 1.5 Hz, vinyl CH_3); $\nu_{C=O}$ (CCl_4) 1670 cm^{-1}.

trans-α-**(Bromomethyl)benzalacetone (2).** A 48-g (0.30 mol) sample of **1** dissolved in 500 ml of CCl_4 containing 53.4 g (0.30 mol) of *N*-bromosuccinimide and a catalytic amount (*ca.* 0.05 g) of benzoyl peroxide were refluxed 14 hr, cooled to room temperature, and filtered; the solvent evaporated *in vacuo* to leave an oil. The oil was dissolved in 100 ml of ether–hexane (1:1, v/v) and cooled for crystallization of 54.6 g (76%) of **2**. Upon recrystallization it showed mp 49–50°; pmr (CCl_4) δ 7.1–7.6 (m, 6, C_6H_5CH), 4.22 (s, 2, CH_2Br), and 2.38 (s, 3, $COCH_3$); $\nu_{C=O}$ (CCl_4) 1686 cm^{-1}.

Anal. Calcd for $C_{11}H_{11}BrO$: C, 55.23; H, 4.68; Br, 33.44. Found: C, 55.18; H, 4.82; Br, 33.29.

2-[α-(*tert*-Butylamino)benzyl]-1-buten-3-one (3a). A 4.78-g (0.02 mol) sample of **2** dissolved in 400 ml of pentane was treated with 3.00 g (0.04 mol) of *tert*-butylamine in 20 ml of the same solvent. The contents were stirred 43 hr while stoppered at room temperature and filtered to remove 2.95 g (96.4%) of *tert*-butylamine hydrobromide. The pentane was evaporated *in vacuo* at room temperature to leave **3a** as an oil: pmr (CCl_4) δ 7.15–7.5 (m, 5, C_6H_5), 6.15 and 6.4 (m, 1 each, $C{=}CH_2$), 5.06 (m, 1, C_6H_5CH), 2.2 (s, 3, CH_3), and 1.05 (s, 10, NH and *t*-C_4H_9); $\nu_{C=O}$ ($CHCl_3$) 1673 cm^{-1}; hydrobromide (methanol–ether) mp 191.5–192.5°.

Anal. Calcd for $C_{15}H_{22}BrNO$: C, 57.68; H, 7.13; Br, 25.58; N, 4.48. Found: C, 57.86; H, 7.25; Br, 25.36; N, 4.40.

1-(*tert*-Butylaminomethyl)benzalacetone (4a). A small amount (*ca.* 0.1 ml) of **3a** was dissolved in *ca.* 0.3 ml of CCl_4 at room temperature. After 2 days isomerization of **3a** to **4a** was quantitative: pmr (CCl_4) δ 7.17–7.7 (m, 6, C_6H_5CH), 3.4 (s, 2, CH_2N), 2.5 (s, 3, $COCH_3$), 1.28 (NH), and 1.13 (s, 9, *tert*-C_4H_9); $\nu_{C=O}$ ($CHCl_3$) 1657 cm^{-1}; hydrochloride (methanol–ether) mp 157–158°.

Anal. Calcd for $C_{15}H_{22}ClNO$: C, 70.45; H, 9.34; Cl, 10.95; N, 4.32. Found: C, 70.35; H, 9.37; Cl, 11.02; N, 4.32.

2-[α-(Piperidino)benzyl]-1-buten-3-one (3b) and 1-(Piperidinomethyl)benzalacetone (4b). A 1.20-g (0.005 mol) sample of **2** dissolved in 100 ml of hexane was treated with 0.85 g (0.01 mol) of piperidine in 50 ml of hexane. The contents were stirred 23 hr while stoppered at room temperature and filtered to remove 0.79 g (95.3%) of piperidine hydrobromide. The hexane was evaporated to *ca.* 3 ml and the solution analyzed by pmr to show **3b** and **4b** in a 1:1 ratio. Upon standing in $CDCl_3$ slow isomerization of **3b** to **4b** was quantitative: **3b** pmr, δ 6.27 and 6.19 (s, 1 each, $C{=}CH_2$), and 4.49 (s, 1, C_6H_5CH); **4b**, δ 7.25–7.7 (m, 6, C_6H_5CH), 3.32 (s, 2, CH_2N), 2.43 (s, 3, $COCH_3$), 2.20–2.55 (m, 4, CH_2NCH_2), and 1.3–1.7 [m, 6, $(CH_2)_3$]; $\nu_{C=O}$ ($CHCl_3$) 1668 cm^{-1}; picrate (ethanol) mp 146–147°.

Anal. Calcd for $C_{22}H_{24}N_4O_8$: C, 55.93; H, 5.12; N, 11.86. Found: C, 55.83; H, 5.05; N, 12.06.

2-[α-(Morpholino)benzyl]-1-buten-3-one (3c) and 1-(Morpholinomethyl)benzalacetone (4c). A 1.20-g (0.005 mol) sample of **2** dissolved in 100 ml of hexane was treated with 0.87 g (0.01 mol) of morpholine in 50 ml of hexane. The contents were stirred 23 hr while stoppered at room temperature and filtered to remove 0.78 g (92.9%) of morpholine hydrobromide. The hexane was evaporated to *ca.* 3 ml, and the solution was analyzed by pmr to show **3c** and **4c** in a 2:1 ratio, respectively. Upon standing in $CDCl_3$ slow isomerization of **3c** to **4c** was quantitative: **3c** pmr, δ 6.22 and 6.33 (s, 1 each, $C{=}CH_2$) and 4.47 (s, 1, C_6H_5CH); **4c**, δ 7.0–7.6 (m, 6, C_6H_5CH), 3.5–3.7 (m, 4, CH_2OCH_2), 3.38 (s, 2, CH_2N), 2.47 (s, 3, $COCH_3$), and 2.2–2.5 (m, 4, CH_2NCH_2); $\nu_{C=O}$ ($CHCl_3$) 1670 cm^{-1}; picrate (ethanol) mp 186–187°.

Anal. Calcd for $C_{21}H_{22}N_4O_9$: C, 53.16; H, 4.67; N, 11.81. Found: C, 53.16; H, 4.64; N, 11.98.

2-Acetyl-1-morpholino-1-phenylpropane (5). A 3.20-g (0.02 mol) sample of **1** was dissolved in 34.8 g (0.4 mol) of morpholine at room temperature and stirred magnetically for 13 days. The morpholine was evaporated under a stream of nitrogen (2 days) to leave a yellow residue. Pmr analysis showed a 1:8 ratio of the diastereomers of **5**. The mixture was crystallized from 50 ml of ether–pentane (1:1, v/v) to yield 2.22 g (45%) of the diastereomer in greater yield: mp 90.5–91.5°; pmr ($CDCl_3$) δ 6.9–7.4 (m, 5, C_6H_5), 3.1–3.8 (m, 6, CH_2OCH_2 and C_6H_5CHCH), 2.1–2.5 (m, 4, CH_2NCH_2), 1.9 (s, 3, $COCH_3$), and 1.28 (d, 3, J = 6.2 Hz, CCH_3); $\nu_{C=O}$ ($CHCl_3$) 1709 cm^{-1}; picrate (ethanol) mp 171–171.5°.

Anal. Calcd for $C_{21}H_{24}N_4O_9$: C, 52.94; H, 5.08; N, 11.76. Found: C, 52.98; H, 4.95; N, 11.58.

In another experiment 3.20 g (0.02 mol) of **1** was dissolved in 1.74 g (0.02 mol) of morpholine at room temperature. The contents stood for 3.5 months and were analyzed by pmr (CCl_4) to show a 1:1 ratio of the diastereomers of **5**: CCH_3, δ 1.20 (d, J = 6 Hz) and 0.80 (d, J = 6 Hz). Approximately 30% of **1** was unreacted.

trans-**1-*tert*-Butyl-2-phenyl-3-acetylazetidine (6b).** A 4.78-g (0.02 mol) sample of **2** was dissolved in 350 ml of pentane followed by treatment with 2.92 g (0.04 mol) of *tert*-butylamine. The contents were stirred magnetically at room temperature while tightly stoppered for 31.5 hr, and filtered to remove *tert*-butylamine hydrobromide; the solvent evaporated *in vacuo* to leave an oil which was dissolved in 125 ml of $CHCl_3$ saturated with anhydrous HBr at 0°. The reaction was tightly stoppered and allowed to stand while warming to room temperature over a period of 13 days. Excess HBr and solvent were removed *in vacuo* with warming to leave a solid, which was taken up in 60 ml of $CHCl_3$ followed by slow addition (30 min) of 25 ml of Et_3N, and then filtered. The solvent and Et_3N were removed to leave a residue which was taken up in boiling pentane and filtered; the pentane was evaporated to leave an oil analyzed by pmr to show 70% of **6a** and **6b** (6:1 ratio, respectively) and **3a**. A portion of the product mixture was chromatographed on a silica gel column using ether–benzene (1:1, v/v) as eluent. The first band eluted was **6b** and the only azetidinyl product collected: pmr ($CDCl_3$) 7.1–7.7 (m, 5, C_6H_5), 4.39 (d, J = 6.6 Hz, 1, C_6H_5CH), 2.9–3.5 (m, 3, $CHCH_2$), 1.91 (s, 3, CH_3), and 0.88 (s, 9, *t*-C_4H_9); $\nu_{C=O}$ 1712 cm^{-1} (CCl_4); picrate (ethanol) mp 165.5–166.5°.

Anal. Calcd for $C_{21}H_{24}N_4O_8$: C, 54.78; H, 5.25; N, 12.17. Found: C, 54.52; H, 5.31; N, 12.23.

The Reaction of 2-[α-(*tert*-Butylamino)benzyl]-1-buten-3-one (3a) with Morpholine. Approximately 1.2 g (0.005 mol) of **3a** in 25 ml of hexane was treated with 1.5 g (0.015 mol) of morpholine. The contents stood at room temperature several days followed by complete evaporation of solvent and excess amine. The resulting oil was analyzed by pmr to show only **4c**.

Acknowledgment. We gratefully acknowledge financial support from Grant No. CA-02931 of the National Cancer Institute, U. S. Public Health Service, and the University of Nebraska Damon Runyon Memorial Fund for Cancer Research.

Registry No.—**1**, 42968-14-9; **2**, 42967-97-5; **3a**, 42967-98-6; **3a** HBr, 42967-99-7; **3b**, 42968-00-3; **3c**, 42968-01-4; **4a**, 42968-02-5; **4a** HCl, 42968-03-6; **4b**, 42968-04-7; **4b** picrate, 42968-05-8; **4c**, 42968-06-9; **4c** picrate, 42968-07-0; **5** isomer A, 42968-08-1; **5** iso-

mer B, 42968-09-2; **5** picrate, 42968-10-5; **6a**, 42968-11-6; **6b**, 42968-12-7; **6b** picrate, 42968-13-8; benzaldehyde, 100-52-7; 2-butanone, 78-93-3; *tert*-butylamine, 78-81-9; piperidine, 110-89-4; morpholine, 110-91-8.

Supplementary Material Available. Full nmr data in Figures 1 and 2 will appear following this article 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 the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-911.

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Synthetic Applications of Trimethylsilyl Cyanide. An Efficient Synthesis of β-Aminomethyl Alcohols

David A. Evans,*[1] Gary L. Carroll, and Larry K. Truesdale

Contribution No. 3220 from the Department of Chemistry, University of California, Los Angeles, California 90024

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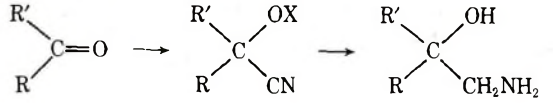
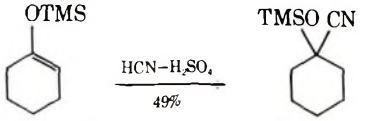
The use of trimethylsilyl cyanide (TMSCN) as a reagent for the direct formation of trimethylsilyl cyanohydrin ethers **3** from ketones is reported. The advantages in using TMSCN as opposed to hydrogen cyanide are illustrated by the formation of cyanohydrin ethers of ketones that do not form stable cyanohydrins. The reduction of derivatives **3** with lithium aluminum hydride is reported to afford β-aminomethyl alcohols **4** in good yield. The combined carbonyl derivatization–reduction sequence should afford a general synthesis of **4** useful in executing ring expansion reactions.

A great deal of attention has been devoted to the conversion of ketones to β-aminomethyl alcohols **4**. Interest in these derivatives has largely centered around their use in the Tiffeneau–Demjanov ring expansion of cycloalkanones.[2] The major difficulty in this general homologation process has been associated with the lack of reliable routes to β-aminomethyl alcohols.

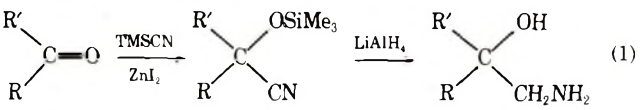


1 **2**, X = H; **3**, X = $SiMe_3$ **4**

The two classical methods for effecting this transformation have involved the formation and subsequent reduction of either ketone cyanohydrins[3] **2** or β-nitromethyl alcohols.[4] Both procedures have suffered from lack of generality and low overall yields for the desired transformation.[5] For the more widely used homologation sequence proceeding through ketone cyanohydrins, the yield of β-amino alcohol **4** is directly dependent upon the stability of the cyanohydrin **2**, the formation of which is highly dependent upon the steric and strain factors in the ketone.[6] Recently Parham and coworkers have shown that cyanohydrin ethers can be prepared by the acid-catalyzed addition of HCN to both alkyl[7a] and trimethylsilyl enol ethers,[7b,c] and that the resultant cyanohydrin derivatives can be reduced with $LiAlH_4$ to the desired β-amino ethers or alcohols. Although this approach results in the synthesis of derivatives of unstable cyanohydrins, the sequence requires the synthesis of the appropriate enol derivative, thus lengthening as well as restricting the homologation sequence to those systems for which enol ethers are easily prepared.



In conjunction with our interest[8] in exploring the utility of trimethylsilyl cyanide (TMSCN)[9] as a useful reagent in organic synthesis, we would like to report on its advantages in effecting carbonyl aminomethylation *via* the α-silyloxy nitriles **3** (eq 1).

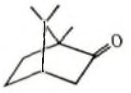


(1)

1 **3** **4**

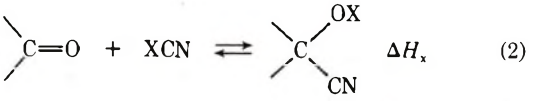
Our previous studies have shown that, in contrast to the substrate sensitivity of HCN–carbonyl addition reactions, the addition of TMSCN to both ketones and aldehydes is a general, high-yield process.[8] Apparently this is a consequence of the alteration in the ΔH for the carbonyl addi-

Table I
Synthesis of β-Aminomethyl Alcohols 4

1			3			4			
Registry no.	Structure	Identification	Registry no.	Yield, %[a]	Bp, °C (mm)	Registry no.	Yield, %[b]	Mp or bp,[d] °C (mm)	Ref
108-94-1		a	24731-36-0	94	72 (1.0)	19968-85-5	86	206–208	3e
502-49-8		b	50361-50-7	94.5	47 (0.03)	50361-56-3	55	217	3a, 3f
830-13-7		c	50361-51-8	94.5	80 (0.03)	50361-57-4 832-29-1	59.4	199–200 (124–126)[c]	3h
76-22-2		d[14]	50361-52-9	>95[e]		50361-59-6	89.2	258–261	
529-34-0		e	50361-53-0	>95[e]		50361-60-9	64[c]	100 (0.003)	
565-62-8		f	40326-22-5	91.5	69 (2.0)	50529-56-1	57.2[c]	30 (0.03)	
98-86-2	$PhCOCH_3$	g	25438-38-4	>95[e]		50361-61-0	84.4	138–140	20

[a] Yields were of isolated product except where noted. [b] Amine isolated as the hydrochloride salt except where noted. [c] Isolated as the free amine. [d] Melting points are those of amine hydrochloride; boiling points are for the amino alcohols. [e] Yield determined by glc.

tion reaction when changing from proton to silicon (X = H, SiR_3; eq 2).



(2)

Although calculations of ΔH_{Si} *vs.* ΔH_H for eq 2 are quite inaccurate owing to the unknown value of the Si–CN bond dissociation energy and the apparent discrepancies in the reported H–C bond dissociation energy in hydrogen cyanide (111 kcal/mol,[10a] 129 kcal/mol[10b]), one may calculate a $\Delta H_{Si} - \Delta H_H$ value of −31 to −49 kcal/mol if a Si–CN bond energy value of 76 kcal.mol is used.[11] Although this calculation is optimistic,[12,13] it is suggestive that the addition of silyl cyanides to carbonyl groups should be energetically more favorable than the corresponding addition reactions of HCN. This prediction has been clearly borne out by experiment.

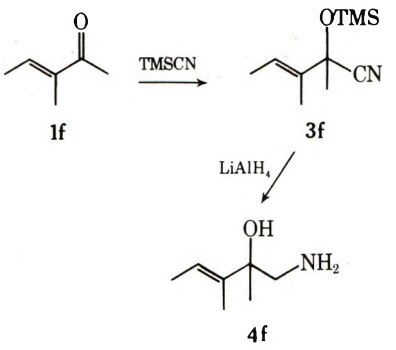
As shown in Table I, the advantage of employing TMSCN in the direct formation of cyanohydrin derivatives **3** is evident. In spite of the reported inability to form cyanohydrins of both camphor[14] and α-tetralone,[6a] we have found that the corresponding trimethylsilyl cyanohydrins **4** may be formed in excellent yields. These results are not surprising in light of our similar observations[8a] with other systems such as benzophenone and 1-indanone, which are also resistant to cyanohydrin formation.[6a] Another unusual property of TMSCN is its regiospecificity in reactions with α,β-unsaturated carbonyl derivatives.[8a,b] For example, 3-methyl-3-penten-2-one (**f**) reacts with TMSCN to give *exclusively* the 1,2 adduct. Direct carbonyl insertion has also been observed to be the exclusive mode of reaction of TMSCN with *p*-quinones.[8b] These observations are in marked contrast to the base-catalyzed addition of hydrogen cyanide with similar substrates. With the exception of the TMSCN–camphor adduct **30**, which exhibited partial reversion to starting materials on distillation, the trimethylsilyl cyanohydrins could be readily distilled without decomposition.

As we have previously reported, the addition of TMSCN to ketones and aldehydes is dramatically catalyzed by both Lewis acids as well as nucleophiles such as cyanide ion.[8c] The choice of zinc iodide as a cyanosilylation catalyst in the present study was arbitrary, and, in systems that are particularly acid labile, other modes of catalysis should work equally well.

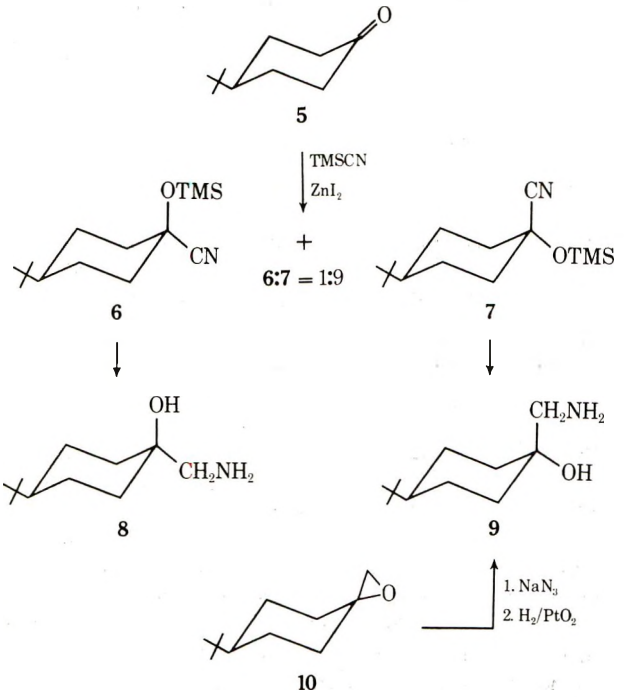
Reduction of the trimethylsilyl cyanohydrins **3** to the desired β-aminomethyl alcohols was carried out with lithium aluminum hydride according to the procedure of Amundsen and Nelson.[15] In most routine ketone aminomethylations the ketone may be simply mixed with 1–1.2 equiv of TMSCN in the presence of a small amount (*ca.* 1–3 mg) of anhydrous zinc iodide in the absence of solvent. With the exception of highly hindered ketones such as camphor where heating (100°, 2 hr) is required, the reaction to form the trimethylsilyl cyanohydrin **3** is exothermic. The cyanohydrin derivatives may be reduced directly to the amino alcohols **4** without purification. For the cases cited in Table I the ketones were cyanosilylated and reduced without isolation of the trimethylsilyl cyanohydrin.

The use of TMSCN for the aminomethylation of α,β-unsaturated ketones should be particularly useful. The desired transformation, illustrated by the conversion of enone **1f** to amino alcohol **4f**, is not possible *via* either the classical cyanohydrin[3] or nitromethane[4] procedures owing to the problems associated with preferential 1,4 addition.

To ascertain the stereochemical course of TMSCN addition to a relatively unhindered but conformationally locked ketone, 4-*tert*-butylcyclohexanone (**5**) was treated with 1.05 equiv of TMSCN in the presence of zinc iodide. The mixture of adducts **6** and **7** formed in a ratio of 1:9 in



97% yield was reduced to the amino alcohols **8** and **9** in 96% yield.[16] Proof that the major diastereoisomer was **9** was confirmed by independent synthesis from the epoxide **10** of known stereochemistry.[17] It appears that the observed isomer ratio of 90:10 for **7:6** is a consequence of kinetic rather than thermodynamic control. Although the ratio of **7:6** remains unchanged after 24 hr at 25° in the presence of the zinc iodide catalyst, equilibrium can be established at this tempterature with a catalytic amount of potassium cyanide 18-crown-6 complex.[8c] The observed equilibrium ratio of **7:6** of 78:22 is in accord with the calculated equilibrium ratio of approximately 72:28 based on the conformational *A* values reported for $-OSiMe_3$[18] and $-CN$.[19]



Conclusions

Trimethylsilyl cyanide is an excellent reagent for the direct formation of ketone cyanohydrin ethers. The transformation proceeds in excellent yield in a variety of systems. Even hindered ketones which prove to be unreactive toward hydrogen cyanide addition readily form adducts. The reduction of cyanohydrin ethers can be carried out efficiently with lithium aluminum hydride, affording good yields of β-aminomethyl alcohols.

Experimental Section[21]

Trimethylsilyl Cyanide (TMSCN). Procedure A is a modification of that reported by MacDiarmid and coworkers.[9] Procedure B was developed by us as a more economical route for large-scale preparations.

A. A dry, foil-wrapped, 1-l, round-bottom flask, equipped with a mechanical stirrer, was charged with 269.8 g (2.01 mol) of silver cyanide followed by 730 ml (6 mol) of chlorotrimethylsilane.[22] The mixture was mechanically stirred for 3 days. The solution was filtered, yielding a clear organic layer and solid, which was subsequently washed with anhydrous ether and the filtrate and ether washes were combined. Careful distillation using a 60-cm vacuum-jacketed fractionating column produced 158.5 g (1.60 mol, 79.6%) of trimethylsilyl cyanide: bp 114–117° (760 mm); nmr (CCl_4, with $CHCl_3$ as an internal standard) δ 0.4 [s, $Si(CH_3)_3$]; ir (neat) 2210 cm^{-1} (-CN).

B. A dry, 1-l, three-necked reaction vessel equipped with a mechanical stirrer, a spiral reflux condenser, and a Dry Ice condenser protected with a NaOH trap was charged with 500 ml of anhydrous ether and 15.9 g (2.0 mol) of granular lithium hydride. Approximately 150 ml (3.8 mol) of hydrogen cyanide,[23] distilled slowly through a calcium chloride trap maintained at 50–60°, was introduced into the stirred reaction vessel through the spiral condenser inlet over a 2-hr period. The reaction mixture was externally cooled with an ice bath sufficiently to maintain a slow steady reflux at the Dry Ice condenser. Upon completion of the hydrogen cyanide addition, the light brown reaction mixture was stirred for 1 hr at 25°, the spiral reflux condenser was removed, and 250 ml of technical (98%) chlorotrimethylsilane[22] was added over a 30-min period. Stirring was continued for 18 hr at 25°, the Dry Ice condenser was removed, and the solution was heated at reflux (1 hr) to remove excess hydrogen cyanide. The reaction mixture was filtered, the solid residue was rinsed with anhydrous ether, and the combined filtrate was distilled as in procedure A to give 153 g of trimethylsilyl cyanide, bp 117–118°. In several different runs yields of 71–84% based on lithium hydride were obtained.

General Synthesis of Trimethylsilyl Cyanohydrins 3. To 1 equiv of ketone, contained in a dry, one-necked reaction vessel fitted with a serum cap, a static nitrogen head for pressure equilibration, and a magnetic stirring bar, was added *via* syringe 1.1 equiv of trimethylsilyl cyanide containing a catalytic amount of anhydrous zinc iodide with stirring. Approximately 1–10 mg of catalyst is ample for reactions carried out on a 0.1-*M* scale. For unhindered ketones the reaction is exothermic and external cooling may be necessary, while for hindered ketones warming may be required. Although solvents were not used in this study even with solid ketones, the option of employing solvents such as chloroform or benzene has been exercised with no change in yield. The crude yields of adduct are nearly quantitative. In the present study the cyanohydrin ether was either distilled directly from the reaction flask through a 6-in. Vigreux column or used without further purification.

Cyclohexanone cyanohydrin ether (3a)[24] (94%) had bp 72–74° (1 mm); ir (neat) 1246, 838, 750 cm^{-1} ($SiCH_3$); nmr (CCl_4) δ 0.15 (s, 9, CH_3).

Anal. Calcd for $C_{10}H_{19}NOSi$: C, 60.86; H, 9.70. Found: C, 60.78; H, 9.61.

Cyclooctanone cyanohydrin ether (3b) (94.5%) had bp 47° (0.03 mm, molecular distillation); nmr (CCl_4) δ 0.1 [s, 9, $Si(CH_3)_3$], 1.5 (m, 14, CH_2).

Anal. Calcd for $C_{12}H_{23}NOSi$: C, 63.94; H, 10.29. Found: C, 63.76; H, 10.44.

Cyclododecanone cyanohydrin ether (3c) (94.5%) had bp 80° (0.03 mm, molecular distillation); nmr (CCl_4) δ 0.1 [s, 9, $Si(CH_3)_3$], 1.3 (s, 22, ring CH_2); ir (neat) no CN.

Anal. Calcd for $C_{16}H_{31}NOSi$: C, 68.29; H, 11.10. Found: C, 68.39; H, 10.95.

3-Methyl-3-penten-2-one cyanohydrin ether (3f) (91.5%) had bp 68–70° (2 mm); ir (neat) 1665 cm^{-1} (no CN); nmr (CCl_4) δ 0.1 [s, 9, $Si(CH_3)_3$], 1.4, 1.48 (broad s, 9, 3 CH_3), 5.66 (m, 1, =CH).

Anal. Calcd for $C_{10}H_{19}NOSi$: C, 60.86; H, 9.70. Found: C, 61.01; H, 9.90.

β-Aminomethyl Alcohols 4a–g. The general conditions for reduction are similar to that reported by Amundsen.[15] A dry, nitrogen-purged, 100-ml, three-necked flask equipped with a mechanical stirrer, reflux condenser, and Hershberg addition funnel was charged with a suspension of 1.53 g (40.4 mmol) of lithium aluminum hydride in 30 ml of anhydrous ether. To this suspension was added a solution of 36 mmol of unpurified cyanohydrin ether **3** in 10 ml of ether dropwise at a rate which maintained gentle reflux of the reaction mixture. Stirring was continued for 1 hr after the addition had been completed. Destruction of the excess lithium aluminum hydride was completed by cautious dropwise addition of 1.5 ml of water followed by dropwise addition of 1.5 ml of 15% NaOH and subsequent addition of 4.5 ml of water. Stirring was

continued until a granular white precipitate was formed. Filtration yielded a clear ether solution which was dried over anhydrous sodium sulfate. The amino alcohol **4** may be isolated as the free amine by removing the ether under reduced pressure or, as the amine hydrochloride salt, by bubbling HCl gas through the ether solution to precipitate the amine hydrochloride salt.

1-Aminomethyl-1-cyclohexanol (4a) was isolated as the amine hydrochloride (86%), mp 206–208° (reported[3c] mp 211°).

Anal. Calcd for $C_7H_{16}NOCl$: C, 50.75; H, 9.74. Found: C, 50.84; H, 9.59.

1-Aminomethyl-1-cyclooctanol (4b) was isolated as the amine hydrochloride (55.3%), mp 217° (reported[3a] mp 230°), nmr (DMSO-d_6) δ 1.5 (s, 14, ring CH_2), 2.7 (m, 2, NCH_2), 3.4 (m, 1, OH), 8.0 (m, 3, NH_3).

1-Aminomethyl-1-cyclododecanol (4c) was isolated as the amine hydrochloride (59.4%), mp 199–200° (reported[3h] mp 217°), or as the amine, mp 124–125° (reported[3h] mp 126.6–127.7°), nmr (DMSO-d_6) on amine salt δ 1.30 (s, 22, CH_2), 2.64 (s, 2, CH_2N), 8.04 (m, 3, NH_3).

2-(Aminomethyl)-2-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptane (4d) was isolated as the amine hydrochloride salt (89.2%), mp 258–261°, nmr (DMSO-d_6) δ 2.8 (s, 2, CH_2N), 4.74 (s, 1, OH), 8.0 (m, 3, NH_3).

Anal. Calcd for $C_{11}H_{22}NOCl$: C, 60.12; H, 10.09. Found: C, 59.96; H, 9.80.

1-(Aminomethyl)-1,2,3,4-tetrahydro-1-naphthol (4e) was isolated as the amine (64%), bp 100° (0.003 mm, molecular distillation), nmr ($CDCl_3$) δ 2.0, 2.2, 2.87, 2.97 (s, CH_2N), 7.2 (m, 4, aromatic H).

Anal. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53. Found: C, 74.53; H, 8.56.

2-(Aminomethyl)-3-methyl-3-penten-2-ol (4f) was isolated as the amine (57.2%), bp 30° (0.03 mm), nmr ($CDCl_3$) δ 1.2 (s, 3, CH_3), 1.6 (m, 6, CH_3), 1.7 (m, 3, NH_2, OH), 2.6 (q, J = 12 Hz, 2, CH_2N), 5.6 (m, 1, C=CH).

Anal. Calcd for $C_7H_{15}NO$: C, 65.07; H, 11.70. Found: C, 65.22; H, 11.59.

α-(Aminomethyl)-α-methyl benzyl alcohol (4g) was isolated as the amine hydrochloride salt (84.8%), mp 138–140°, nmr (DMSO-d_6) δ 1.5 (s, 3, CH_3), 3.0 (s, 2, CH_2N), 5.9 (m, 1, OH), 7.4 (m, 5, aromatic H), 8.05 (m, 3, NH_3).

Anal. Calcd for $C_9H_{14}NOCl$: C, 57.60; H, 7.52. Found: C, 57.50; H, 7.40.

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Registry No.—TMSCN, 7677-24-9.

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Alkylation of Alkylidenebis(dialkylamines) with Alkyl Dihalides

Charles F. Hobbs* and Harold Weingarten

Monsanto Company, Corporate Research Department, St. Louis, Missouri 63166

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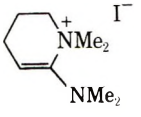
Alkylidenebis(dialkylamines) (enediamines), **1**, undergo C-alkylation with alkyl dihalides, $X(CH_2)_nX$, to give linear diamidinium salts, **2**, and cycloalkylamidinium salts, **3**. The latter predominate when n = 2, 4, and 5. 1,3-Diiodopropane (n = 3) and **1** afforded the novel tetrahydropyridinium salt **6** by both C- and N-alkylation. Evidence for N-alkylation with other dihalides is presented. Although alkylation of the simplest bis(enediamine) **16** with methylene iodide gave the expected cyclopropanedicarboxamidinium salt **17**, bis(enediamines) **18–21** gave complex product mixtures. Formation of *N,N,N′,N′*,2-pentamethylacrylamidinium salt **14** from enediamine **10b** and *N,N,N′,N′*-tetramethylcyclopentene-1,2-dicarboxamidinium salt **22** from enediamine **21** indicates incursion of the oxidation–reduction processes in these cases.

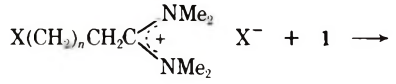
In a previous paper[1] we discussed the alkylation of alkylidenebis(dialkylamines) (enediamines) with alkyl halides. In this paper we report the extension of this work to the alkylation of enediamines and bis(enediamines) with alkyl dihalides.[2]

Our interest in this area was generated by the observation that vinylidenebis(dimethylamine) (**1**) gave an excellent yield of the glutaramidinium salt **2** (n = 1, X = I) with methylene iodide. With longer chain dihalides, however, cycloalkylation (route b, Scheme I) became predominant, giving the amidinium salts **3** and **4**, the latter being the conjugate acid of **1**. The cyclization products **3**, which were observed by nmr spectroscopy, were not isolated; rather, the reaction mixtures were hydrolyzed to obtain the cycloalkaneamides **5**. The yields of products from the two modes of reaction, a and b, are summarized in Table I.[3] In the case of 1,3-diiodopropane, none of the cyclobutane derivative (**3**, n = 3, X = I) was observed. Instead, the novel tetrahydropyridinium salt **6** was isolated in good yield.

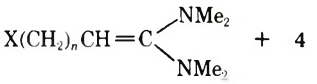


6

Presumably, the monoadducts **7** are common intermediates in all of these reactions. Displacement of halide by a second molecule of enediamine affords the linear product **2**, whereas proton abstraction by the strongly basic starting enediamine yields a new enediamine, **8**. Normally, **8**



7

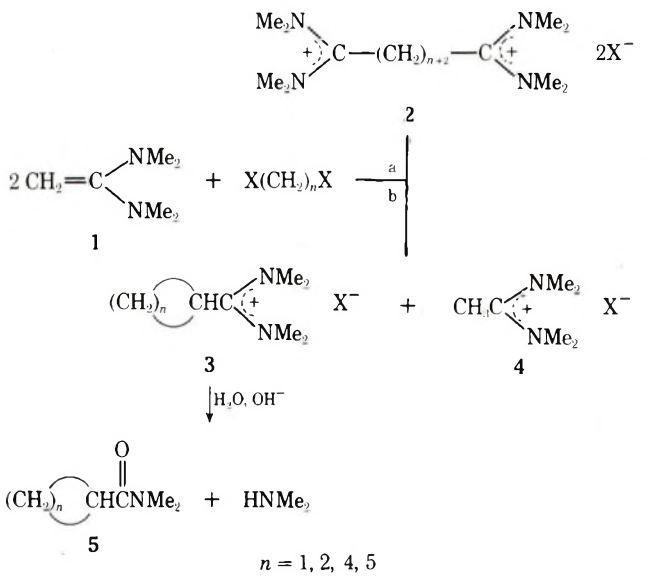


8

undergoes intramolecular displacement by carbon to give **3**. In the 1,3-diiodopropane case, however, **8** (n = 3) cyclizes at nitrogen rather than carbon, giving **6**. Thus, the characteristic tendency of the enediamines to alkylate at carbon with formation of the charge-stabilizing amidinium grouping[1] is overshadowed in this case by the more favorable energetics of formation of a six-membered rather than a four-membered ring.

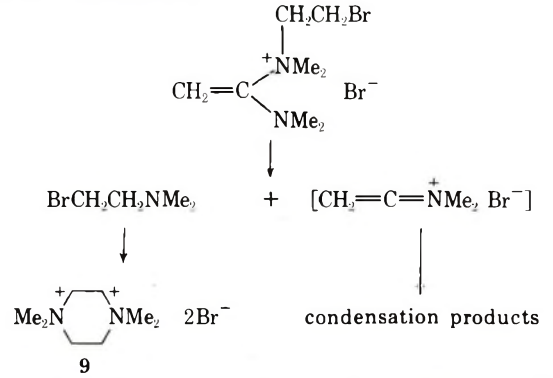
It is likely that N-alkylation occurred to some extent with the other halides as well, although we would not expect to observe the initial products because of their instability.[1] In the case of 1,2-dibromoethane, however, we were able to isolate tetramethylpiperazinium bromide (**9**),

Scheme I



n = 1, 2, 4, 5

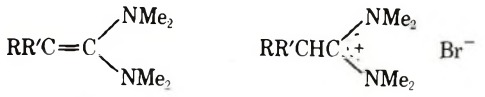
which could be formed by initial N-alkylation of the enediamine, elimination to give the ketenimmonium salt[1,4] and 2-dimethylaminoethyl bromide, and subsequent dimerization[5] of the latter.



9

Extension of the above reactions to enediamines substituted at the vinyl carbon met with only limited success. Reaction of the propenylidenediamine **10a** with 1,2-dibromoethane gave only 8% of *N,N*,1-trimethylcyclopropanecarboxamide after hydrolysis compared to 34% of the cyclopropanecarboxamide obtained from **1**. The main product was the conjugate acid, **11a**, indicating that elimination of hydrogen bromide from dibromoethane had taken place. With **10b** and 1,2-dibromoethane, only elimination to give **11b** was observed.

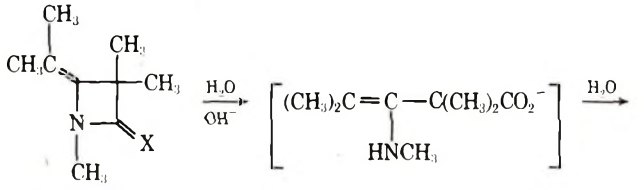
Enediamine **10b** with methylene iodide gave a complex mixture of products, two components of which were shown to be the isobutyramidinium salt **11b** and the methac-



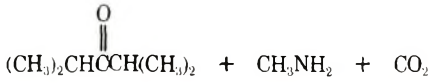
10 11

a, R = CH_3; R′ = H
b, R = R′ = CH_3

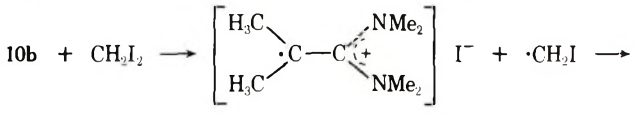
rylamidinium salt **14** by comparison of the nmr spectrum of the mixture with authentic samples.[1,6] Mild hydrolysis of the mixture yielded tetramethylammonium iodide, *N,N*-dimethylisobutyramide, *N,N*-dimethylpivalamide, *N,N*,2-trimethylacrylamide, and the β-lactam **12a**. The remainder of the product consisted of high-boiling residue. The structure of the novel β-lactam was elucidated by nmr, infrared, and mass spectral analysis, and by basic hydrolysis to methylamine and the expected diisopropyl ketones.



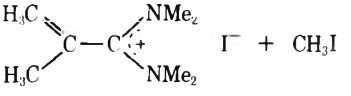
12a, X = O
b, X = NMe_2^+



The isolation of tetramethylammonium iodide and the pivalamide indicates that methylation has taken place, while the appearance of the methacrylamide suggests the incursion of an oxidation–reduction process. Both processes can be explained by oxidation of the electron-rich enediamine **10b** by methylene iodide to give radical cation **13**[6] and iodomethyl radical.



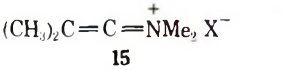
13



14

The latter abstracts hydrogen from **13** to give **14** and methyl iodide, which in turn methylates **10b** to afford the pivalamidinium salt.[1,7] Some disproportionation of radical cation **13** to **14** and isobutyramidinium salt probably also occurs.[6]

The origin of β-lactam **12a**, or its most probable precursor **12b**, is not clear although we believe that N-alkylation followed by elimination to give the ketenimmonium salt **15**[1,4] is involved. Thus, the reaction of methylene iodide



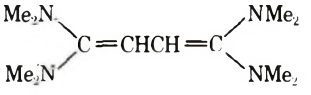
15

with ketenimmonium salt **15** (X = Cl), prepared independently,[4b] gave a mixture of salts which afforded, after hydrolysis, a low yield of lactam **12a** in addition to high-boiling residues. The mechanistic course of this reaction remains obscure.

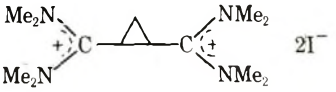
In view of the marked steric hindrance to alkylation observed in the substituted enediamines, we were surprised to find that 1,1,4,4-tetrakis(dimethylamino)-1,3-butadiene (**16**) reacted smoothly with methylene iodide to give 58% of the cyclopropane derivative **17**. Substitution of 1,2-dibromoethane for methylene iodide, however, gave a complex mixture of products in which none of the expected cyclobutane products could be detected.

Table I
Product Yields from Reaction of Vinylidenebis(dimethylamine) and Alkyl Dihalides

$X(CH_2)_nX$		Yield, %	
n	X	2	5
1	I	84	
2	Br		34
4	I	20	55
5	I	20	39



16

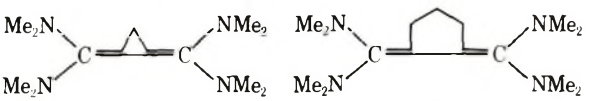


17

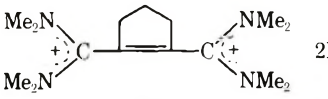
In contrast to **16**, the bis(enediamines) **18**–**20** yielded with methylene iodide or methylene bromide complex mixtures in which the major products were the conjugate acids[8] of the bis(enediamines). Tetramethylammonium ion also was detected in the reaction mixtures. Hydrolysis afforded the diamides corresponding to the starting bis(enediamines) as well as considerable high-boiling residue; we could not detect any of the expected cycloalkylated products. It is possible that the expected products were formed in small yield but did not survive under the reaction conditions.

Reaction of compound **21** with methylene iodide likewise gave a complex mixture of amidinium salts.

18, *n* = 1
19, *n* = 2

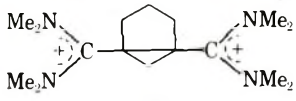


20 **21**

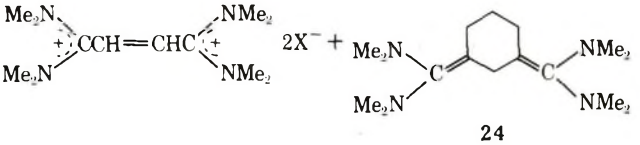


22

Hydrolysis afforded small yields of *N,N,N′,N′*-tetramethylcyclopentane-1,2-dicarboxamide and *N,N,N′,N′*-tetramethylcyclopentene-1,2-dicarboxamide, the latter being predominant. This result indicates that **21** was oxidized[6,9] to **22** (X = I) in the reaction. The oxidizing agent is not known for certain, but may be either methylene iodide, as in the case of **10b**, or the expected alkylation product **23**, as shown by an ancillary experiment. Thus, when **23** (X = PF_6)[6,9] was treated with the bis(enedi-



23



24

amine) **16**[10] in acetonitrile, nmr spectroscopy revealed the disappearance of **23** within 5–10 min and the appearance of new peaks identical with those of **24**.[6,9] This suggests that **23** may have been formed in the reaction of **21** with methylene iodide but underwent reductive ring opening[11] by **21** to yield **22** and **24**. The latter would be expected to react further with methylene iodide and hence would not be observed in this case.

Experimental Section[12]

***N,N,N′,N′*-Tetramethylcyclopropane-1,2-dicarboxamide.** Dimethyl cyclopropane-1,2-dicarboxylate[13] and dimethylamine, heated at 60° for 5 days in a pressure bottle, yielded 60% of *cis*- and *trans*-*N,N,N′,N′*-tetramethylcyclopropane-1,2-dicarboxamide, bp 123–143° (0.35 mm). Fractional crystallization afforded the pure cis isomer: mp 103–104.5°; nmr ($CDCl_3$) τ 6.86 (s) and 7.11 (s) [total 12, $(CH_3)_2NC{=}O$], 7.87 (m, 2, CHC=O), 8.5 (m, 1, ring methylene), and 8.9 (m, 1, ring methylene).

Anal. Calcd for $C_9H_{16}N_2O_2$: C, 58.67; H, 8.75; N, 15.21; mol wt, 184. Found: C, 58.41; H, 8.63; N, 14.77; mol wt, 184.

***N,N,N′,N′*-Tetramethylcyclopentane-1,2-dicarboxamide.** Cyclopentane-1,2-dicarboxylic acid[14] was converted (94% yield) to its dimethylamide *via* the acid chloride by standard procedures. The product had bp 129–130° (11 mm), $n^{25}D$ 1.5020.

Anal. Calcd for $C_{11}H_{20}N_2O_2$: C, 62.23; H, 9.50; N, 13.20. Found: C, 62.22; H, 9.32; N, 13.40.

1,2-Bis[bis(dimethylamino)methylene]cyclopropane (20). Treatment of *N,N,N′,N′*-tetramethylcyclopropanedicarboxamide with tetrakis(dimethylamino)titanium[15] at 0° in tetrahydrofuran gave 58% of **20**: bp 98–100° (0.85 mm); $n^{25}D$ 1.5656; nmr (C_6D_6) τ 7.26 (s) and 7.32 (s) [total 24, $(CH_3)_2N$–] and 8.25 (s, 2, ring methylene). Extreme sensitivity to moisture and oxygen precluded elemental analysis.

1,2-Bis[bis(dimethylamino)methylene]cyclopentane (21). Reaction of *N,N,N′,N′*-tetramethylcyclopentane-1,2-dicarboxamide with tetrakis(dimethylamino)titanium[15] for 3 days at 90° gave *3.0 g (15%) of* ***21****: mp 94.5–95.0° (CH_3CN)*; mol wt, *266* (mass spectroscopy); nmr (C_6D_6) τ 7.36 (s, 12, $CH_3NC{=}C$), 7.60 (s, 12, $CH_3NC{=}C$), and ~8.0 (m, 6, ring protons). Extreme atmospheric sensitivity precluded elemental analysis.

Vinylidenebis(dimethylamine) with Methylene Iodide. A solution of 2.28 g (0.02 mol) of vinylidenebis(dimethylamine) (**1**),[15] 2.68 g (0.01 mol) of methylene iodide, and 4 ml of dry acetonitrile was allowed to stand at room temperature for 40 hr. The solid product was collected by filtration and recrystallized from acetonitrile to obtain 4.2 g (84%) of *N,N,N′,N′,N″,N″,N‴,N‴*-octamethylglutaramidinium diiodide (**2**, n = 1, X = I), mp 233–234°.

Anal. Calcd for $C_{13}H_{30}I_2N_4$: *C, 31.47; H, 6.09; I, 51.15;* N, 11.29. Found: C, 31.14; H, 5.94: I, 51.31; N, 11.01.

The bis(tetraphenylborate) salt had mp 250–252°; nmr (CD_3CN) τ ~2.9 *(m, 40, phenyl)*, 7.03 (s, 24, $^+NCH_3$), 7.4 *(m, 6,* $-CH_2-$).

Vinylidenebis(dimethylamine) with 1,2-Dibromoethane. A mixture of 11.4 g (0.1 mol) of **1**, 9.4 g (0.05 mol) of 1,2-dibromoethane, and 60 ml of dry acetonitrile was heated to 70° for 24 hr. The mixture then was cooled and filtered to remove crystalline precipitate. The crystalline product, 0.1 g (1.3%), was recrystallized from aqueous ethanol to give *N,N,N′,N′*-tetramethyl-1,4-piperazinium dibromide (**9**): mp 355° dec; nmr (CF_3CO_2H) τ 5.78 (s, 8, CH_2N^+), 6.37 (s, 12, CH_3N^+). The nmr spectrum was identical with that of an authentic sample;[16] the mixture melting point was 356° dec.

The original filtrate was freed of solvent at the rotary evaporator and the resulting solid was hydrolyzed in the cold with 100 ml of 2 *N* sodium hydroxide solution. Extraction with ether, followed by distillation of the extract, afforded a mixture of *N,N*-dimethylacetamide and *N,N*-dimethylcyclopropanecarboxamide, mole ratio 2.3:1. Redistillation afforded 1.9 g (34%) of *N,N*-dimethylcyclopropanecarboxamide: bp 75–78° (10 mm); $n^{25}D$ 1.4673; nmr (CCl_4) τ 6.8 (s, broad, 6, $OCNCH_3$), ~8.15 (m, 1, CHCO), ~9.25 (m, 4, ring protons). The product was identical (ir, nmr, and vpc) with an authentic sample prepared from cyclopropanecarboxylic acid chloride and dimethylamine.

Only 13% of the cyclopropanecarboxamide was obtained when dimethylformamide was substituted for acetonitrile as solvent.

Vinylidenebis(dimethylamine) with 1,3-Diiodopropane. A solution of 11.4 g (0.10 mol) of **1**, 14.8 g (0.05 mol) of 1,3-diiodopropane, and 20 ml of dry acetonitrile was allowed to stand at room temperature for 3 days. The solution was concentrated in an inert atmosphere and then filtered to obtain 8.9 g (63%) of 6-dimethylamino-1,1-dimethyl-1,2,3,4-tetrahydropyridinium iodide (**6**): mp 195–196° dec; nmr (CD_3CN) τ 4.04 (m, 1, HC=C), 6.13 (m, 2, CH_2N^+), 6.71 (s, 6, CH_3N^+), 7.36 (s, 6, CH_3N), and 7.8 (m, 4, CCH_2CH_2C). Addition of trifluoroacetic acid caused the disappearance of peaks at τ 4.04 and 7.36 and the appearance of two new singlets at τ 5.92 and 6.04, ratio 1:1 [$=N(CH_3)_2^+$].

Anal. Calcd for $C_9H_{19}IN_2$: C, 38.31; H, 6.79; N, 9.93. Found: C, 38.45; H, 6.80; N, 9.98.

Compound **6** was dissolved in excess dilute hydrochloric acid and allowed to stand for 5 days. The solution was basified with 50% sodium hydroxide in the cold and continuously extracted with ether. Distillation of the ether extract afforded 4.7 g (55%) of 5-dimethylamino-*N,N*-dimethylpentanamide: bp 68° (0.25 mm) [lit.[17] bp 107–108° (2 mm)]; $n^{25}D$ 1.4601; nmr (C_6D_6) τ 7.25 (s) and 7.32 (s) [6 total, $OCN(CH_3)_2$], 7.91 [s + m, 10, $(CH_3)_2N$, CH_2N, and CH_2CO], and 8.4 (m, 4, CCH_2CH_2C).

Anal. Calcd for $C_9H_{20}N_2O$: C, 62.75; H, 11.70; N, 16.26; mol wt, 172. Found: C, 62.65; H, 11.76; N, 16.40; mol wt, 172.

Vinylidenebis(dimethylamine) with 1,4-Diiodobutane. A solution of 9.12 g (0.08 mol) of **1**, 12.4 g (0.04 mol) of 1,4-diiodobutane, and 20 ml of dry acetonitrile was allowed to stand for 4 days. The mixture was filtered to remove 4.4 g (20%) of crystals, a small sample of which was recrystallized from acetonitrile to give *N,N,N′,N′,N″,N″,N‴,N‴*-octamethyloctanediamidinium diiodide (**2**, n = 4, X = I): mp 265–267°; nmr (CF_3CO_2H) τ 6.70 (s, 24, $^+NCH_3$), 7.2 (m, 4, $^+CCH_2$), and 7.70 (m, 8, CCH_2CH_2C).

Anal. Calcd for $C_{16}H_{36}I_2N_4$: C, 35.70; H, 6.74; I, 47.15; N, 10.41. Found: C, 35.77: H, 6.76; I, 47.11; N, 10.34.

The filtrate and the remainder of the crystals were recombined and treated with 60 ml of 2 *N* sodium hydroxide solution. The aqueous solution was continuously extracted with ether and the ether extract was distilled to obtain 3.1 g (55%) of *N,N*-dimethylcyclopentanecarboxamide: bp 94–95° (7 mm); $n^{25}D$ 1.4765 [lit.[18] bp 64° (0.5 mm); $n^{25}D$ 1.4759]; nmr (CCl_4) τ 6.97 (s), 7.14 (s) and ~7.1 (m) (7 total, $O{=}CNCH_3$ and CHC=O), and ~8.34 (m, 8, ring protons).

Anal. Calcd for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92; mol wt, 141. Found: C, 67.92; H, 10.76; N, 10.07; mol wt, 141.

The pot residue from the above distillation was recrystallized from tetrahydrofuran to obtain 0.5 g (5%) of *N,N,N′,N′*-tetramethylsuberamide: mp 86–87°; nmr (CCl_4) τ 7.01 (s) and 7.11 (s) [12 total, $O{=}CN(CH_3)_2$], 7.78 (t, 4, $O{=}CCH_2$), and 8.48 (m, 8, CCH_2C).

Anal. Calcd for $C_{12}H_{24}N_2O_2$: C, 63.12; H, 10.59; N, 12.27; mol wt, 228. Found: C, 62.88; H, 10.48; N, 12.02; mol wt, 228.

Vinylidenebis(dimethylamine) with 1,5-Diiodopentane. A solution of 11.4 g (0.1 mol) of **1** and 16.2 g (0.05 mol) of 1,5-diiodopentane in 20 ml of acetonitrile was kept at room temperature for 2 days. The reaction mixture was cooled in ice and then filtered to obtain 5.6 g (20%) of crude *N,N,N′,N′,N″,N″,N‴,N‴*-octamethylnonanediamidinium diiodide (**2**, n = 5, X = I): analytical sample mp 171.5–172°; nmr (CD_3CN) τ 6.78 (s, 24, $^+NCH_3$), 7.26 (m, 4, $^+CCH_2$), and 8.54 [m, 10, $C(CH_2)_5C$].

Anal. Calcd for $C_{17}H_{38}I_2N_4$: C, 36.97; H, 6.93; I, 45.95; N, 10.14. Found: C, 37.38; H, 6.81; I, 45.85; N, 10.06.

The filtrate and crystals, except for the analytical sample, were recombined and hydrolyzed with 75 ml of 2 *N* sodium hydroxide to obtain 3.0 g (39%) of *N,N*-dimethylcyclohexanecarboxamide and 1.7 g (14%) of *N,N,N′,N′*-tetramethylnonanedicarboxamide.

N,N-Dimethylcyclohexanecarboxamide exhibited the following properties: bp 107–108° (7 mm) [lit.[19] bp 158° (44 mm)]; nmr (C_6H_6) τ 7.30 (s, broad, 6, OCNCH), 7.7 (m, 1, HCCO), and 8.5 (m, 10, ring protons).

Anal. Calcd for $C_9H_{17}NO$: C, 69.63; H, 11.04; N, 9.02; mol wt, 155. Found: C, 69.62; H, 11.42; N, 9.11; mol wt, 155.

N,N,N′,N′-Tetramethylnonanedicarboxamide had bp 175–177° (0.3 mm); mp 36–37° [lit.[20] mp 40–41°]; nmr (C_6H_6) τ 7.25 and 7.46 (singlets, 12 total, $OCNCH_3$), 7.96 (m, 4, $OCCH_2$), and 8.5 [m, 10, $C(CH_2)_5C$].

Anal. Calcd for $C_{13}H_{26}N_2O_2$: C, 64.42; H, 10.81; N, 11.56; mol wt, 242. Found: C, 64.54; H, 10.75; N, 11.56; mol wt, 242.

Propenylidenebis(dimethylamine) (10a) with 1,2-Dibromoethane. A solution of 12.8 g (0.10 mol) of **10a**[15] and 9.4 g (0.05 mol) of 1,2-dibromoethane in 40 ml of dry acetonitrile was heated at 70° for 5 days. The acetonitrile was removed at the rotary evaporator and the residue was treated with 75 ml of 2 *N* sodium hydroxide. The aqueous solution was continuously extracted with ether and the ether extract was distilled to obtain, after a large forerun of *N,N*-dimethylpropanamide, 0.5 g (8%) of

crude *N,N*,1-trimethylcyclopropanecarboxamide: bp 105° (13 mm); nmr (C_6H_6) τ 7.19 [s, 6, O=CN(CH_3)$_2$], 8.84 (s, 3, CCH_3), 9.15 (m, 2, ring protons), and 9.58 (m, 2, ring protons); mass spectrum (70 eV) *m/e* 127, 112, 83, 72, 55, 44. A satisfactory element analysis was not obtained.

2-Methylpropenylidenebis(dimethylamine) (10b) with Methylene Iodide. A solution of 13.4 g (0.05 mol) of methylene iodide and 14.2 g (0.10 mol) of **10b**[15] in 25 ml of dry acetonitrile was heated at reflux for 7 days. *N,N,N',N'*,2-Pentamethylpropionamidinium iodide (**11b**) and *N,N,N',N'*,2-pentamethylacrylamidinium iodide (**14**) were identified in the mixture by comparison of the nmr spectra with those of authentic samples.[1,6] The mixture was filtered to obtain 9.7 g (0.048 mol) of crude tetramethylammonium iodide. The tetraphenylborate had mp 370–375°; nmr (acetone-d_6) τ 2.80 (m, 20, phenyl) and 6.67 (s, 12, CH_3N^+).

Anal. Calcd for $C_{28}N_{32}BN$: C, 85.47; H, 8.21; N, 3.56. Found: C, 85.55; H, 8.23; N, 3.66.

The filtrate from above was stripped of solvent at reduced pressure and the residue was treated with cold 2 *N* sodium hydroxide. The hydrolysis mixture was extracted with ether and the extract was distilled to obtain, besides 8 g of tar, 1.7 g of a 4:1:1 mixture of *N,N*-dimethylisobutyramide, *N,N*-dimethylpivalamide (identified by vpc and mass spectroscopy), and *N,N*,2-trimethylacrylamide, respectively. The latter was identified by comparison of vpc retention times and nmr spectrum with those of an authentic sample prepared by hydrolysis of the corresponding amidinium salt:[6] nmr (CCl_4) τ 4.84 (m, 1, HC=C), 5.03 (m, 1, HC=C), 7.02 (s, 6, O=CNMe_2), and 8.09 (m, 3, CH_3C=).

In addition, 0.8 g (10%) of the β-lactam, 4-isopropylidene-*N*,3,3-trimethyl-2-azetidinone (**12a**), was obtained: bp 100–105° (17–20 mm); nmr (CCl_4) τ 6.96 (s, 3, CH_3NC=O), 8.23 (s, 3, CH_3C=C), 8.39 (s, 3, CH_3C=C), and 8.73 [s, 6, $(CH_3)_2C$]; mass spectrum (70 eV) *m/e* (rel intensity) 153 (1), 152 (3), 96 (10), 83 (12), 82 (10), 81 (37), 69 (4), 68 (11), 67 (4), 56 (6), 55 (6), 54 (4), 53 (7), 42 (45), 41 (37), 28 (100); ir (CCl_4) 1704 and 1790 (C=O) and 1645 cm^{-1} (>C=C<). A satisfactory element analysis could not be obtained.

Hydrolysis of the lactam, carried out in alcoholic sodium hydroxide overnight at 80°, afforded methylamine, identified by its nmr spectra, and diisopropyl ketone, identified by comparison of vpc retention times and nmr spectrum with those of an authentic sample.

1-Chloro-*N,N*,2-trimethylpropenylamine (15) with Methylene Iodide. A mixture of 20 g (0.15 mol) of 1-chloro-*N,N*,2-trimethylpropenylamine,[4] 20 g (0.075 mol) of methylene iodide, and 20 ml of dry acetonitrile was heated for 72 hr at 70° under a nitrogen atmosphere. The bulk of the acetonitrile was removed by distillation under reduced pressure, the dark red residue was taken up in water, and the solution was extracted with ether. Distillation of the ether extract afforded 4.8 g of recovered methylene iodide. The water solution was made basic with 6 *N* sodium hydroxide and extracted with ether, and the extract was distilled to obtain 0.8 g of β-lactam **12a**, shown by vpc and infrared and nmr spectroscopy to be identical with that obtained from the reaction of **10b** and methylene iodide. The remainder of the product consisted of high-boiling residue which could not be identified.

1,1,4,4-Tetrakis(dimethylamino)butadiene (16) with Methylene Iodide. A solution of 11.3 g (0.05 mol) of **16**[15] in 10 ml of dry acetonitrile and a solution of 13.4 g (0.05 mol) of methylene iodide in 10 ml of dry acetonitrile were added simultaneously in a dropwise manner at room temperature to 20 ml of acetonitrile over a period of 18 hr. The mixture was allowed to stand for 2 days, then was concentrated to one-half the original volume and filtered to obtain 14.34 g (58%) of *trans-N,N,N',N',N'',N'',N''',N'''*-octamethyl-1,2-cyclopropanedicarboxamidinium diiodide (**17**): analytical sample mp 252–254° dec; nmr (CF_3CO_2H) τ 6.60 [s, 24, $^+N(CH_3)_2$], 7.11 (m, 2, $^+$CCH), and 7.84 (m, 2, cyclopropane methylene).

Anal. Calcd for $C_{13}H_{28}I_2N_4$: C, 31.59; H, 5.71; I, 51.36; N, 11.34. Found: C, 31.77; H, 5.83; I, 51.16; N, 11.35.

The crystals were recombined with the filtrate and the entire reaction mixture was hydrolyzed with 60 ml of 2 *N* sodium hydroxide. The aqueous solution was continuously extracted with ether, and the ether extract was distilled to obtain 3.7 g (40%) of *trans-N,N,N',N'*-tetramethyl-1,2-cyclopropanedicarboxamide: bp 110–111° (0.3 mm); mp 57–60° (lit.[21] mp 56–58°); nmr (CCl_4) τ 6.80 and 7.10 [singlets, 12 total, OCN$(CH_3)_2$], 7.78 (m, 2, OCCH), and 8.83 (m, 2, cyclopropane methylene).

Anal. Calcd for $C_9H_{16}N_2O_2$: C, 58.67; H, 8.75; N, 15.21; mol wt, 184. Found: C, 58.50; H, 8.69; N, 15.19; mol wt, 184.

1,2-Bis[bis(dimethylamino)methylene]cyclopentane (21) with Methylene Iodide. A solution of 3.11 g (0.013 mol) of **21**[6] and 3.40 g (0.013 mol) of methylene iodide in 50 ml of acetonitrile was allowed to stand at room temperature for 10 days. The acetonitrile was evaporated under vacuum and the residue was treated with 2 *N* sodium hydroxide. The mixture was continuously extracted with ether and the ether extract was distilled to obtain 0.6 g of material, bp 110–115° (0.15 mm), consisting of 72% of *N,N,N',N'*-tetramethylcyclopent-1-ene-1,2-dicarboxamide and 20% of *N,N,N',N'*-tetramethylcyclopentane-1,2-dicarboxamide. The two amides were separated by preparative vpc and the former was identified by comparison of its mass spectrum, vpc retention time, and nmr spectrum with those of an authentic sample prepared by silver nitrate oxidation[6,9] of **21** to *N,N,N',N',N'',N'',N''',N'''*-octamethylcyclopent-1-ene-1,2-dicarboxamidinium iodide **22**, X = I) followed by basic hydrolysis: nmr (C_6D_6) τ 7.34 [s, 12, O=CN$(CH_3)_2$], 7.49 (2 d, 4, J = 7 and ~1 Hz, CH_2CH_2C=C), and 8.32 (2 t, 2, J = 7 and ~1 Hz, $CH_2CH_2CH_2$); mass spectrum (70 eV) *m/e* 210, 182, 167.

Acknowledgment. We thank Mrs. J. S. Wager and Mr. D. E. McMackins for certain preparations.

Registry No.—**1**, 815-62-3; **2** (*n* = 1, X = I), 50483-83-5; **2** (*n* = 1, X = Ph_4B), 50477-43-5; **2** (*n* = 4, X = I), 50483-84-6; **2** (*n* = 5, X = I), 50483-85-7; **6**, 50483-86-8; **9**, 24996-75-6; **10a**, 815-67-8; **10b**, 10596-50-6; **11b**, 16487-61-9; **12a**, 50483-91-5; **14**, 50483-92-6; **15**, 26189-60-6; **16**, 10596-53-9; **17**, 50486-74-3; **20**, 50483-95-9; **21**, 50483-96-0; *cis-N,N,N',N'*-tetramethylcyclopropane-1,2-dicarboxamide, 50486-75-4; *trans-N,N,N',N'*-tetramethylcyclopropane-1,2-dicarboxamide, 22299-29-2; dimethyl cyclopropane-1,2-dicarboxylate, 702-28-3; *N,N,N',N'*-tetramethylcyclopentane-1,2-dicarboxamide, 50483-98-2; cyclopentane-1,2-dicarboxylic acid, 50483-99-3; methylene iodide, 75-11-6; 1,2-dibromoethane, 106-93-4; *N,N*-dimethylcyclopropanecarboxamide, 17696-23-0; 1,3-diiodopropane, 627-31-6; 5-dimethylamino-*N,N*-dimethylpentanamide, 22041-47-0; 1,4-diiodobutane, 628-21-7; *N,N*-dimethylcyclopentanecarboxamide, 50484-00-9; *N,N,N',N'*-tetramethylsuberamide, 3644-93-7; 1,5-diiodopentane, 628-77-3; *N,N*-dimethylcyclohexanecarboxamide, 17566-51-7; *N,N,N',N'*-tetramethylnonanedicarboxamide, 13424-87-8; *N,N*,1-trimethylcyclopropanecarboxamide, 50484-04-3; tetramethylammonium tetraphenylborate, 15525-13-0; *N,N*,2-trimethylacrylamide, 6976-91-6; *N,N,N',N'*-tetramethylcyclopent-1-ene-1,2-dicarboxamide, 50484-06-5.

References and Notes

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(2) Reported in part by C. F. Hobbs and H. Weingarten, *J. Amer. Chem. Soc.*, **91**, 780 (1969).
(3) The main course of reaction between 1 and 1,2-dibromoethane was elimination by the strongly basic enediamine to yield vinyl bromide and **4**.
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(7) A careful check of the methylene iodide showed no detectable methyl iodide, eliminating it as a source of the methylation observed.
(8) The conjugate acids were identified in the mixture by comparison of the nmr spectra with those of authentic samples prepared by addition of trifluoroacetic acid to acetonitrile solutions of the bis (enediamines).
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(10) Compound **16** rather than **21** was used in order to simplify the nmr analysis; the results should be analogous.
(11) This is the reverse of oxidative coupling of **24** to give **23**.[6,9]
(12) Melting points are corrected; boiling points are uncorrected. Molecular weights were determined by mass spectroscopy. All reactions, manipulations, and distillations involving enediamines were performed in an atmosphere of dry nitrogen.
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Abnormal Behavior in the Reaction of Trialkyl Phosphite Esters with *N*-Haloimides

Daniel J. Scharf

Hooker Chemical Corporation, Research Center, Grand Island, New York 14072

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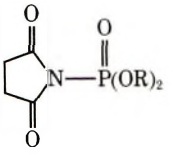
Characteristic of *N*-haloimides is the electropositive nature of halogen (X) induced by the strong electron-withdrawing polarization of the N-X bonds. Prior investigators have reported that phosphite esters react with *N*-haloimides *via* nucleophilic attack at halogen (X = Cl, Br), followed by collapse of the resultant phosphonium ion intermediate to normal Michaelis–Arbusov product, which bears an *N*-dialkylphosphonyl radical. For those esters, $P(OR)_3$, where R = *n*-alkyl but larger than methyl, the observation of normal Arbusov product produced in near-quantitative yield has been confirmed. However, when R = methyl or alkyl branched at the α carbon, the Arbusov product is observed as a minor component. N-Methylation and β elimination, respectively, are observed as the major processes. Further, minor deoxygenation by the branched alkyl systems and enhanced alkylation where R = CH_3 are processes influenced by the reaction's mode of addition. Extended mechanistic interpretations to rationalize these results are presented in terms of internal rotations within the initially formed intermediate followed by ancillary processes.

As part of a project to assess flame-retardant ability of a wide variety of phosphorus-containing compounds, syntheses of several *N*-(dialkylphosphonyl)succinimides (**1**) were attempted. In accordance with existent procedures,[1-3] whereby a trialkyl phosphite ester reacts with an *N*-haloimide, the desired compounds were obtained in good to excellent yields where R is *n*-alkyl (*e.g.*, C_2H_5, *n*-C_4H_9) or alkyl branched beyond the α carbon (*i*-C_4H_9). However, when R is methyl (CH_3) or alkyl branched at the α carbon (*i.e.*, oxygen-bearing carbon in phosphite ester, *e.g.*, *i*-C_3H_7, *sec*-C_4H_9, *t*-C_4H_9), Arbusov product (**1**)[4,5] is produced in low yield. The major products consist



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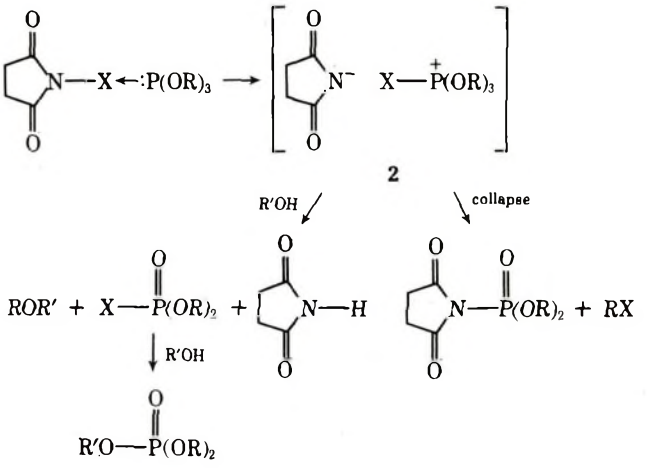
of *N*-methylsuccinimide and dimethyl phosphorohalidate, and succinimide and dialkyl phosphorohalidate for R = CH_3 and R = α-branched alkyl, respectively. Results are summarized in Table I.

By virtue of the polarizability of the N-X bond (Scheme I) nucleophilic attack on *N*-halosuccinimide by a phosphite ester has been proposed to occur at halogen in lieu of nitrogen.[1,6,7]

Characterization of the product mix from conducting the reaction in the presence of a proton source (ROH) offers convincing support for the intermediacy of the ion pair **2**.[1] In view of this mechanism, a consideration of the data in Table I notes definitive 1:1 ratios existing for Arbusov product and alkyl halide and for succinimide (*N*-methyl for R = CH_3) and dialkyl phosphorohalidate, $(RO)_2P(=O)X$. The former product ratio is expected on the basis of the established mechanism for the Arbusov reaction, but the latter correlation can be drawn only if an additional R group can be accounted for in those cases where R $\neq$ CH_3. More careful investigation employing low-temperature trapping and an additional phosphite ester bearing an alkyl radical of lower volatility revealed the complemental component existing as an olefin. Relative ratios of pertinent products to the correlation being discussed are listed in Table II. Mechanistically, the following extension (Scheme II) to the original scheme proposed by McEwen, *et al.*, is consistent with the observed results.

Scheme I



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Scheme II

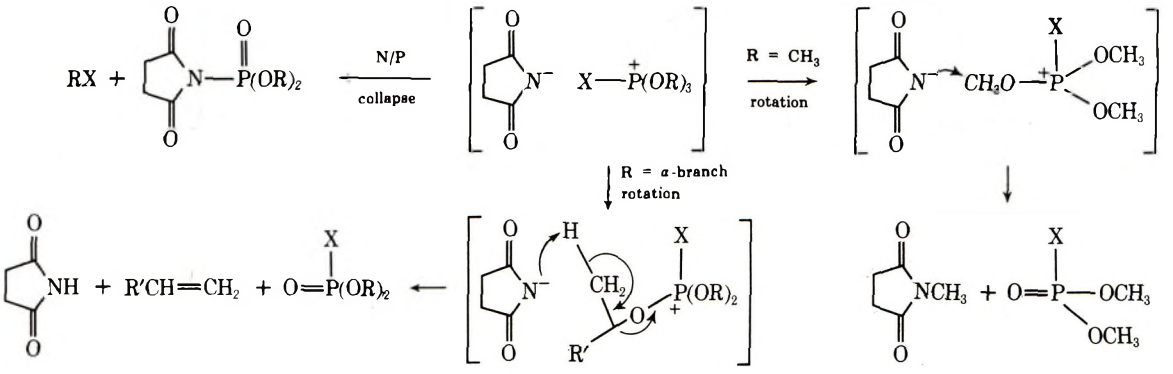
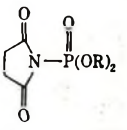
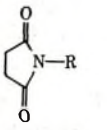
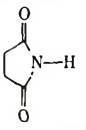
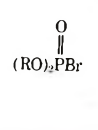


Table I
Product Distribution from the Reaction of Trialkyl Phosphites [$P(OR)_3$] with *N*-Bromosuccinimide (NBS)[a]

R	Reactants, mol[b]		Products, mol				
	NBS[c]	$P(OR)_3$				RBr	
CH_3	0.10	0.10	0.044	0.046		>0.04	0.049
	(0.10)	(0.20)[d]	(0.027)	(0.065)		(>0.02)	(0.061)
	0.10	0.20	0.043	0.053		>0.04	0.045
C_2H_5	0.10	0.10	0.092		<0.01	0.093	<0.01
	(0.10)	(0.10)	(0.081)		(0.01)	(0.075)	(0.01)
n-C_4H_9	0.10	0.10	0.095		0.00	0.089	0.00
	(0.10)	(0.10)	(0.083)		(0.015)	(0.080)	(0.012)
i-C_4H_9	0.10	0.10	0.091		0.00	0.086	0.00
	(0.10)	(0.10)	(0.078)		(0.018)	(>0.07)	(0.015)
sec-C_4H_9	0.10	0.10	0.033		0.064	0.029	0.066
	(0.10)	(0.10)	(0.022)		(0.060)	(0.020)	(0.063)
t-C_4H_9	0.10	0.10			0.096		0.091
i-C_3H_7	0.10	0.10	0.056		0.041	0.050	0.040
	(0.10)	(0.10)	(0.037)		(0.048)	(>0.03)	(0.045)

[a] All runs were conducted in CS_2 at 1 *M* concentrations under nitrogen at 0–5°. [b] Numbers in parentheses refer to inverse addition, *i.e.*, addition of *N*-haloimide to phosphite ester. [c] The reaction with *N*-chlorosuccinimide gave close to identical results. [d] Excess required to effect total conversion.

For the system where R is simple alkyl but not methyl, ion-pair collapse is the favored process due to facile attack of nitrogen on phosphorus. Where R is methyl, sterically unencumbered attack on methyl by the nucleophilic succinimidyl anion apparently competes favorably with ion-pair collapse. Note is made further that formation of a stable pentavalent phosphorus component provides driving force for this process. In the case where R is α-branched alkyl, the succinimidyl anion performs primarily as a proton-abstracting base. Here again, driving force is provided by the formation of a phosphorus double bond oxygen producing stable pentacovalent phosphorous. This latter ability is clearly dependent on the degree of steric inhibition to attack on phosphorus. An examination of Dreiding models for the system where R = cyclohexyl demonstrates decided secondary interactions of the approaching succinimidyl moiety with ring protons that are not present in the acyclic radicals. These added steric requirements apparently contribute appreciably to almost exclusive olefin formation in this system.[8] Similar mechanistic rationale has been proposed by Harpp and Orwig for the desulfurization–alkylation reaction of sulfenimides with tris(dimethylamino)phosphine.[9]

Alternative to the E2-elimination process is the possibility of initial dissociation *via* an E1 mechanism, followed by loss of a proton to succinimidyl anion. Precedent for this pathway is found in the Arbusov reactions of certain phosphite esters with alkyl halides where halide attack on the intermediate phosphonium ion (3) alkoxy group is hindered.[10,11] No facility for dissociative behavior exists for primary alkyl groups such that the S_N2 mechanism depicted for R = CH_3 seems likely.

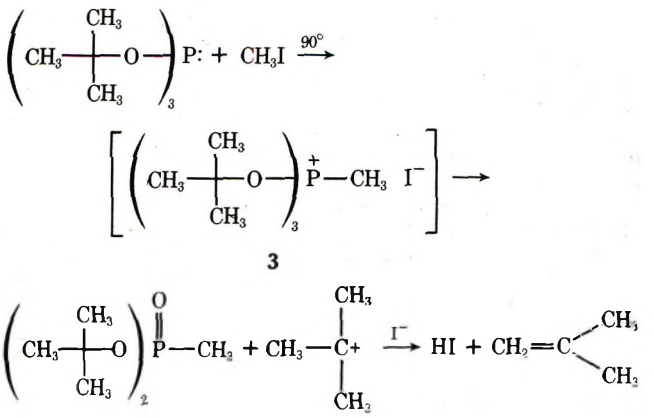


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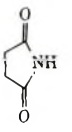
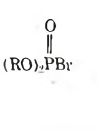
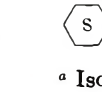
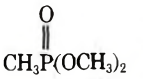
Table II
Ratio of Non-Arbusov Products

R			Olefin
sec-C_4H_9	1.0	1.0	Butenes[a] 0.9
t-C_4H_9	1.0	1.0	Isobutene[a] 1.0
	1.0	1.0	Cyclohexene 1.0

[a] Isolated and characterized as dibromides from bubbling into Br_2–CCl_4. [b] This distribution comprised *ca.* 85–90% of the product mix. A small (5–8%) quantity of Arbusov product was observed.

As indicated in Table I, experiments conducted wherein inverse addition of *N*-haloimide to the phosphite ester was made gave somewhat higher yields of products from competing processes at the expense of Arbusov product. An influential effect by phosphite ester in excess is apparent. This is borne out most dramatically for R = CH_3. When trimethyl phosphite (TMP) was employed as solvent (50-fold excess), minimal Arbusov product was produced, an 80% yield of *N*-methylsuccinimide was isolated, and copious dimethyl methylphosphonate (4) was observed. When conditions of high dilution (0.1 *M*) in an inert solvent ($CHCl_3$) were employed where 1 equiv of TMP was added to *N*-bromosuccinimide, the Arbusov product has been observed in as high as 70% yield. The following mechanistic refinement (Scheme III) is consistent with these observations.



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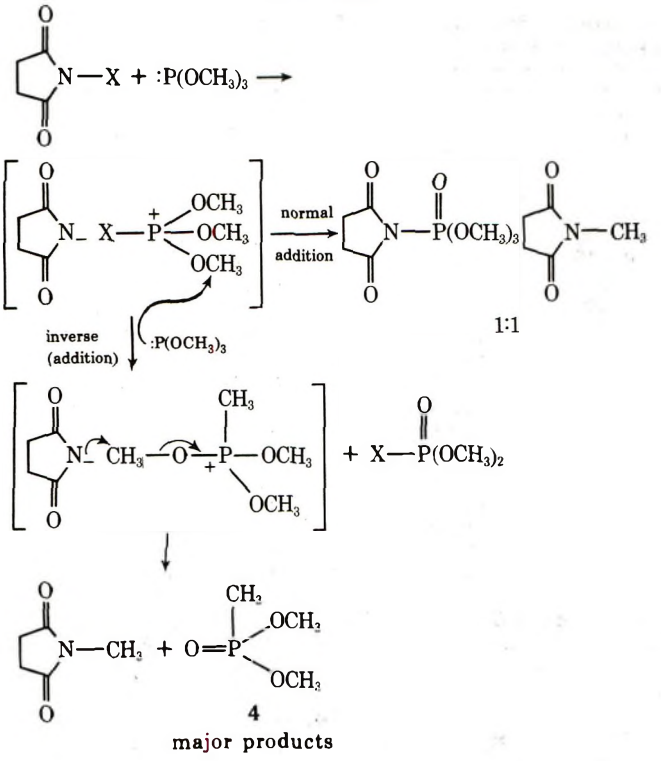
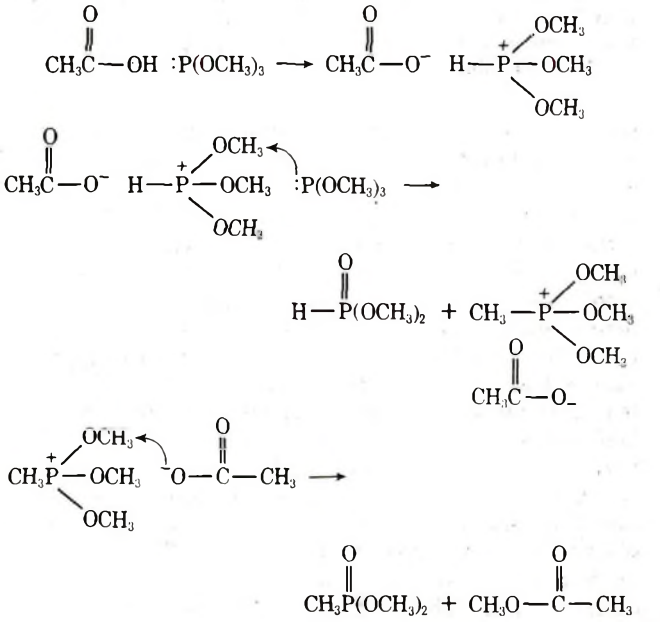
The depicted dealkylation–alkylation sequence has support from an independent study wherein alkyl dialkyl phosphonate ester is observed as a side product in deoxy-

Scheme III



genation reactions by phosphite esters.[12] Further, a similar mechanism has been proposed for the rearrangement of TMP to dimethyl methylphosphonate (4) when reaction is carried out with acetic acid.[13] Little, if any, alkylation–dealkylation behavior is thought to be operative for the higher alkyl phosphites owing to steric considerations and the failure to detect the respective dialkyl alkylphosphonate esters.



Small quantities of trialkyl phosphate (5–10%) were isolated from all experiments in which the inverse mode of addition was utilized. This component is attributed to minor deoxygenation of the succinimidyl moiety. Note is made that this process is dominant for cyclic anhydrides.[12]

Further investigation of this reaction in this laboratory will proceed in the direction of isolating and further characterizing a stable intermediate (1). Reactivity with alkylating and acylating agents and other chemistry will be explored.

Experimental Section

Materials. *N*-Bromosuccinimide (mp 181–183°) and *N*-chlorosuccinimide (mp 147–149°) were purchased from Matheson Coleman and Bell. Methyl, ethyl, and isopropyl trialkyl phosphite esters were purchased from Aldrich Chemical Co., Inc., and were fractionally distilled through a 12-in. glass helices column several times before use. The preparation of *tert*-butyl,[11] *n*-butyl, isobutyl, *sec*-butyl, and cyclohexyl[14] trialkyl phosphites was according to known procedures. All reaction solvents were dried over sodium and distilled directly into the reaction flask.

Instruments. All nmr spectra were recorded on Varian Models T-60 and HA-100 MHz spectrometers. Ir spectra were obtained on a Perkin-Elmer Model 337 spectrophotometer. All melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. For quantification of product distributions, gas–liquid chromatography on a Hewlett-Packard 402 high efficiency gas chromatograph employing 4 ft × 6 mm o.d. × 3 mm i.d. columns was used. Two column systems of 20% SE-30/80–100 mesh Chromosorb W and Carbowax 20M were used for the determination. (See Analyses section.)

General Procedure. All reactions were carried out in a 250-ml three-neck flask, equipped with a stirring bar/Mag-Mix stirrer, gas inlet tube, addition funnel, and gas evolution tube connected to a trap immersed in Dry Ice–acetone. Carbon disulfide (100 ml) was distilled from sodium into the preflamed reaction flask. *N*-Bromosuccinimide (0.1 mol) was suspended in the CS_2, the flask was immersed in an ice–water bath,[15] and agitiation was begun. After temperature equilibration (5–10 min) a slow stream of nitrogen was passed through the CS_2 suspension and the trialkyl phosphite (0.1 mol) was added neat over 10–15 min. When addition was complete, the system was allowed to warm to room temperature and stir for an additional 1 hr. During this period, Arbusov product and/or succinimide separated from the reaction medium. The flask contents were allowed to stand, the clear CS_2 solution was decanted, and the oily to solid residue was extracted with several portions of CS_2. The combined CS_2 solutions, trap contents, and CS_2-insoluble residue were analyzed according to the method under Analyses. *Note:* The inverse addition reactions were identical in every respect except that *N*-halosuccinimide was added as a solid to phosphite ester in CS_2 solution.

Analyses. Except for methyl bromide (bp 3.5°) which was isolated and determined from the tared Dry Ice–acetone trap, ethyl chloride and bromide, and isopropyl chloride, determined exclusively by nmr of CS_2 reaction medium, all alkyl halide yields were estimated by vpc comparison against benzene as an internal standard (column temperature 90°) coupled with ^1H nmr comparison of halide *vs.* remaining components. The dialkyl phosphorobromidates and -chloridates were quantified by vpc against naphthalene as an internal standard (column temperature 150–190°); identification of these last components was made on the basis of peak enhancement (vpc) with authentic materials prepared according to known methods.[16,17] Further identification was made by conversion of the halo phosphates to the respective dialkyl methyl phosphates. These latter materials were produced by treating the product mix from the CS_2 fraction with methanol. Nmr ($POCH_3$ doublet, 3.75 ppm, J = 12 Hz) and the vpc peak enhancement technique with authentic materials was definitive for these components.

All Michaelis–Arbusov products, *N*-(dialkylphosphonyl)succinimide, as well as succinimide, were isolated by exhaustive stripping of the reaction mix followed by column chromatography on silica gel; benzene–$CHCl_3$ was used as elution solvent. Identification was made on the basis of ^1H nmr and combustion analyses. Quantification was based on a proton nmr determination of the crude product, since some deterioration on the column was noted. Data pertinent to these latter materials are given below for each system.

***N*-(Dimethylphosphonyl)succinimide** was isolated from silica gel chromatography (44% N.A., 27% I.A.)[18] as a light yellow to amber viscous oil unstable to distillation: ir ν_{max} (film) 1750 (C=O), 1290, 1180, 1125, 1045, 850, 820, 780, 660, 550 cm^{-1}; nmr δ_{TMS} ($CDCl_3$) 2.82 (singlet, 4 H, succinimidyl ring), 3.93 (doublet, J = 12 Hz, 6 H, phosphorous ester methyls).

Anal. Calcd for $C_6H_{10}NO_5P$: C, 34.80; H, 4.84; P, 14.98; N, 6.77. Found: C, 34.68; H, 4.87; P, 14.76; N, 6.55.

N-Methylsuccinimide (46% N.A., 65% I.A.) was obtained from

this experiment as white, crystalline needles, mp 68–70° (lit.[19] mp 68–70°).

N-(**Diethylphosphonyl**)**succinimide.** This material separated from solution (92% N.A., 81% I.A.) during reaction as a white solid which was purified by recrystallization from methanol: mp 57–60° (lit.[2] mp 60–62°); ir ν_{max} (Nujol) 1730 (C=O), 1295, 1250, 1125, 1030, 815, 755, 665, 555 cm^{-1}; nmr δ_{TMS} ($CDCl_3$) 3.20 (triplet, J = 8 Hz, 6 H, CH_3's), 2.80 (singlet, 4 H, succinimidyl ring), 4.32 (quintet, J = 8 Hz, 4 H, ethyl CH_2's).

N-(**Diisopropylphosphonyl**)**succinimide** was obtained as a dark red oil from silica gel (56% N.A., 37% I.A.): ir ν_{max} (film) 1725 (C=O), 1280–1290, 1100–1140, 1000, 750, 650, 560 cm^{-1}; nmr δ_{TMS} ($CDCl_3$) 1.43 (doublet, J = 6 Hz, 12 H, isopropyl CH_3's), 2.80 (singlet, 4 H, succinimidyl ring), 4.85 (septet, J = 6 Hz, 2 H, isopropyl methines).

Anal. Calcd for $C_{10}H_{18}NO_5P$: C, 45.65; H, 6.85; N, 5.33; P, 11.78. Found: C, 45.57; H, 6.68; N, 4.96; P, 11.83.

N-(**Di-*n*-butylphosphonyl**)**succinimide.** This material was isolated from exhaustive stripping of product mix followed by recrystallization from chloroform. Melting point (45–47°) and spectral data were identical with those reported previously.[1]

N-(**Diisobutylphosphonyl**)**succinimide.** Solids (dark red) that separated from CS_2 solution during reaction at 5° were collected by suction filtration. Nmr (see below) indicated the crude material to be 90% of the title compound. Purification by recrystallization from ethyl ether (slow evaporation) yielded wheat-white needles: mp 94–97°; ir ν_{max} (Nujol) 1735 (C=O), 1275, 1130, 1030, 880, 820, 660, 545 cm^{-1}; nmr δ_{TMS} ($CDCl_3$) 0.98 (doublet, J = 6 Hz, 12 H, ester CH_3's), 2.0 (multiplet, broad, 2 H, butyl methine), 2.80 (singlet, 4 H, succinimidyl ring), 4.1 (doublet of doublets, J_{PCH_2} = 8 Hz, J_{CH_2CH} = 6 Hz, 4 H, $POCH_2$).

Anal. Calcd for $C_{12}H_{22}NO_5P$: C, 49.50; H, 7.56; N, 4.81; P, 10.65. Found: C, 49.36; H, 7.42; N, 4.54; P, 10.59.

N-(**Di-*sec*-butylphosphonyl**)**succinimide.** This material was obtained from silica gel chromatography as a light red oil not analytically pure. Spectral evidence is offered as proof of structure: ir ν_{max} (film) 1740 (C=O), 1280, 1180, 1120, 1040, 815, 770, 660, 550 cm^{-1}; nmr δ_{TMS} ($CDCl_3$) 0.95 (triplet, J = 8 Hz, 6 H, γ methyls on butyl group), 1.30 (doublet, J = 6 Hz, 6 H, α methyls on butyl group), 1.65 (multiplet, 4 H, butyl methylenes), 2.80 (singlet, 4 H, succinimidyl ring), 4.45 (sextet, J = 6 Hz, OCH methines).

Acknowledgment. Appreciation is afforded Hooker Chemical Corp. for permission to conduct and publish this work under its auspices.

Registry No.—1 (R = CH_3), 39843-52-2; 1 (R = C_2H_5), 2737-05-5; 1 (R = *i*-C_3H_7), 50599-95-6; 1 (R = *i*-C_4H_9), 50599-96-7; 1 (R = *sec*-C_4H_9), 50599-97-8; $P(OR)_3$ (R = CH_3), 121-45-9; $P(OR)_3$ (R = C_2H_5), 122-52-1; $P(OR)_3$ (R = *n*-C_4H_9), 102-85-2; $P(OR)_3$ (R = *i*-C_4H_9), 1606-96-8; $P(OR)_3$ (R = *sec*-C_4H_9), 7504-61-2; $P(OR)_3$ (R = *t*-C_4H_9), 15205-62-6; $P(OR)_3$ (R = *i*-C_3H_7), 116-17-6; *N*-bromosuccinimide, 128-08-5; *N*-chlorosuccinimide, 128-09-6.

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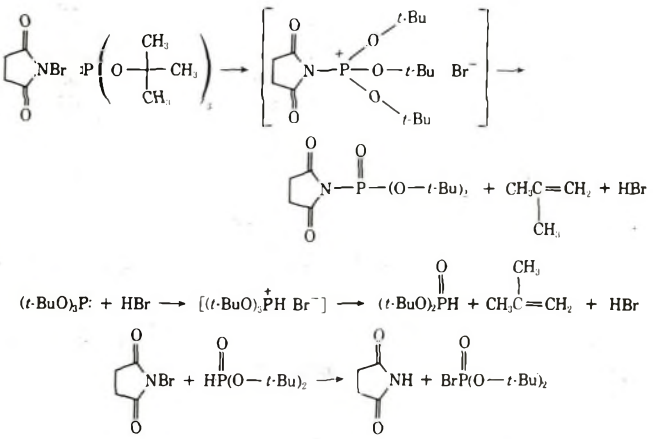

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Studies of Chemical Exchange by Nuclear Magnetic Resonance. IX. Rotation about the Amide Bond in *N,N*-Dimethylformamide[1,2]

Robert C. Neuman, Jr.,* and Violet Jonas

Department of Chemistry, University of California, Riverside, California 92502

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Activation parameters have been determined for rotation about the amide bond in pure *N,N*-dimethylformamide-d_1: E_a, 24.3 ± 0.2 kcal/mol; log A, 14.6 ± 0.1; ΔS^*, +6.3 ± 0.4 eu; ΔF^*_{298}, 21.8 kcal/mol. Kinetic data were obtained by total line shape analysis of the nmr spectra. The activation parameters are contrasted with previous values obtained using different techniques and a structure-reactivity correlation for amide rotation is discussed. These results are also compared with data for unsubstituted and *N*-methylformamide in an attempt to assess the importance of alkyl substitution on nitrogen on the C–N rotational barrier.

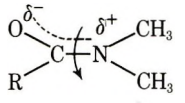
Rotation about the partial double bond of *N,N*-dimethylamides (1) has been extensively studied in part because these systems are the simplest models for the peptide bond in proteins.[1,3-10] Early studies gave inaccurate activation parameters for C–N rotation because approximate procedures were used to derive rate constants. Now

Table I
Kinetic Data for Rotation about the C–N Bond in *N,N*-Dimethylformamide-d_1 (3) in the Pure Liquid

Temp, °C	τ, sec[a]	$\delta\nu_\infty$, Hz[b]
107.3 ± 0.2	0.115	9.05
108.9 ± 0	0.0950	9.02
111.5 ± 0.2	0.0780	9.00
113.0 ± 0	0.0660	8.98
115.6 ± 0.2	0.0540	8.98
117.4 ± 0	0.0475	8.93
119.7 ± 0	0.0398	8.93
121.1 ± 0	0.0338	8.85
123.8 ± 0.2	0.0286	8.85
124.8 ± 0.1	0.0261	8.85
125.4 ± 0	0.0245	8.95
127.6 ± 0.2	0.0212	8.81
129.0 ± 0.2	0.0191	8.79
130.0 ± 0.1	0.0181	8.78
132.1 ± 0.1	0.0155	8.75
132.6 ± 0	0.0140	8.75
135.7 ± 0.2	0.0116	8.71
137.7 ± 0.2	0.0107	8.69
139.7 ± 0.1	0.00875	8.66
140.7 ± 0	0.00810	8.65
142.1 ± 0.3	0.00720	8.63
143.5 ± 0.2	0.00670	8.62
145.1 ± 0	0.00625	8.60

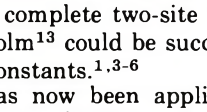
[a] The unimolecular rotational rate constant k(sec)$^{-1}$ is equal to $1/(2\tau)$. [b] $\delta\nu_\infty$ is the chemical shift between the two NCH_3 groups which would exist in the absence of rotation about the C–N bond.

it is generally recognized that total analysis of the NCH_3 high-resolution pmr line shape is required to obtain the most accurate rate constants.[6-8,11,12]



1

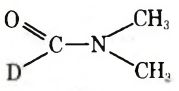
Spin coupling between R and the two NCH_3 groups must either be eliminated or taken into account in the line shape equations.[5,6,8] In our studies of amides and related derivatives of the general structure 2, we found that



2

the deuterium substitution shown minimized coupling to the extent that the complete two-site exchange equations of Gutowsky and Holm[13] could be successfully used to extract accurate rate constants.[1,3-6]

This approach has now been applied to the simplest member of the series, *N,N*-dimethylformamide-d_1 (3), and the data are presented here. At least 14 studies on DMF have been reported,[7,11,13,14] but their results have been inconsistent. Only two used reliable procedures for rate-constant determination and none of these included a total line shape study where spin coupling was eliminated by deuterium substitution.[11,14j] Several years ago we demonstrated that amide barriers appeared to be correlated by a linear free energy equation of the form $\rho^*\sigma^* + SE_S$ (Figure 1).[5,12] We hoped that new data might improve the correlation for the R = H system and this was a major motivation for the study of 3.



3

Experimental Section

N,N-Dimethylformamide-d_1 was synthesized by reaction of DCO_2H with dimethylamine in benzene.[15] Dimethylamine was bubbled into 95 ml of benzene for 45 min, during which time the solution volume increased to 110 ml. To this solution cooled in an ice bath were added dropwise 15 g of DCO_2H (Stohler Isotope Chemicals; 98% deuterium labeled). The resultant mixture was stirred for an additional 0.5 hr, removed from the ice bath, and refluxed. Water generated during the reflux was collected in a Dean-Stark trap. When no more water was produced, the benzene was evaporatively distilled and the crude $DCONMe_2$ was purified by vacuum distillation (74°, 65 mm). The second fraction, constituting the majority of the reaction product, shown to be pure and *ca.* 98% deuterated by nmr, was used for the variable-temperature experiments. Nmr of DMF-d_1 (neat, TMS internal reference) showed two equal-area singlets at δ 2.79 and 2.96 and a trace singlet visible at high amplitude at δ 8.03; commercial DMF (neat, TMS internal reference) showed two equal-area multiplets at δ 2.79 and 2.95 and a broad singlet at δ 8.02; relative areas 3:3:1.

Variable-temperature spectra were recorded for the NCH_3 doublet at a sweep width of 50 Hz using a Varian A-60D nmr spectrometer. Several spectra were recorded at each temperature to assure reproducibility. The sweep width was continuously calibrated and tuning of the spectrometer was checked before and after each spectrum using the signal of the internal standard hexamethyldisilane present in low concentration. The two NCH_3 peaks coalesced at 124.5° and the ambient temperature (41°) value of $\delta\nu_\infty$ was 9.85 Hz.[16]

Temperatures were determined before and after each spectrum using the Varian ethylene glycol standard and the equation T(°C) = 193.5 − 1.693 $\delta\nu_e$ where $\delta\nu_e$ is the chemical shift in hertz between the CH_2 and OH protons.[16]

Line shape analyses were carried out using the complete Gutowsky–Holm equations modified for different T_2 values for the two NCH_3 signals.[14c] The T_2 values were different for each peak owing to the incomplete spin decoupling and were determined from the line widths of the NCH_3 signals. The best-fit analyses were carried out as previously described and the final step involved visual matching between the experimental and computer-generated spectra of the NCH_3 protons. The kinetic data are presented in Table I.[16]

Results and Discussion

Rotational Barrier for DMF. The ambient temperature NCH_3 spectrum of 3 is compared with its undeuterated analog in Figure 2. Most of the asymmetry arising from spin coupling has been eliminated. An Arrhenius plot of the rotational kinetic data (Table I) is shown in Figure 3 and gives the activation parameters E_a, 24.3 ± 0.2 kcal/mol; log A, 14.6 ± 0.1; ΔS^*, +6.3 ± 0.4 eu; ΔF^*_{298}, 21.8 kcal/mol.

Table II
Activation Parameters for C–N Rotation in Pure *N,N*-Dimethylformamide

Entry	Method	E_a, kcal/mol	Log A	ΔS^*, eu	ΔF^*_{25}, kcal/mol	Ref
1	TLS	24.3	14.6	+6.3	21.8	This work
2	TLS	20.5	12.7	−2.3	20.6	14j
3	TLS	20.8		0.0	20.2	11
4	SE	21.6		+1.0	20.7	11
5	COMB	22.0	13.0	−1.0	21.7	14i
6	COMB	26.0	15.0	+8.1	23.0	14k
7	COMB	26.0	16.0	+12.8	21.6	14d
8	COMB	27.4	16.0	+12.8	23.0	14i

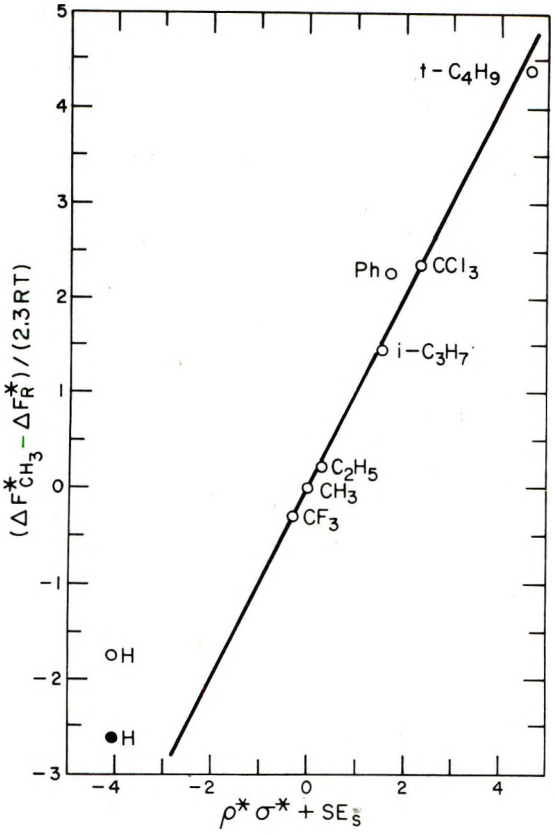


Figure 1. Linear free energy correlation for rotation about the central C–N bond for neat amides of the general structure $RC(O)NMe_2$; $\rho^* = -1.25$ and $S = -2.76$. The theoretical line has a slope of one and a zero intercept. Solid point for R = H represents new data from this study.

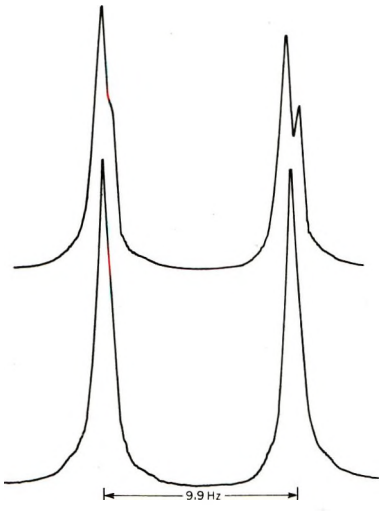


Figure 2. NMe_2 proton line shapes for neat *N,N*-dimethylformamide (top) and neat *N,N*-dimethylformamide-d_1 (bottom).

The most striking aspect of a comparison of these results with those from previous studies is that they are more similar to some of the data from studies using a combination of *approximate* methods (COMB) than to those obtained using the supposedly more reliable total line shape analysis (TLS) and spin-echo (SE) methods (Table II). Those listed as entries 2 and 3 were obtained using undeuterated DMF and it was necessary to try to correct for the spin coupling in the analysis equations. The data in the fourth entry were obtained using deuterated DMF (3), but there has been some indication that spin-echo studies lead to low activation parameters.

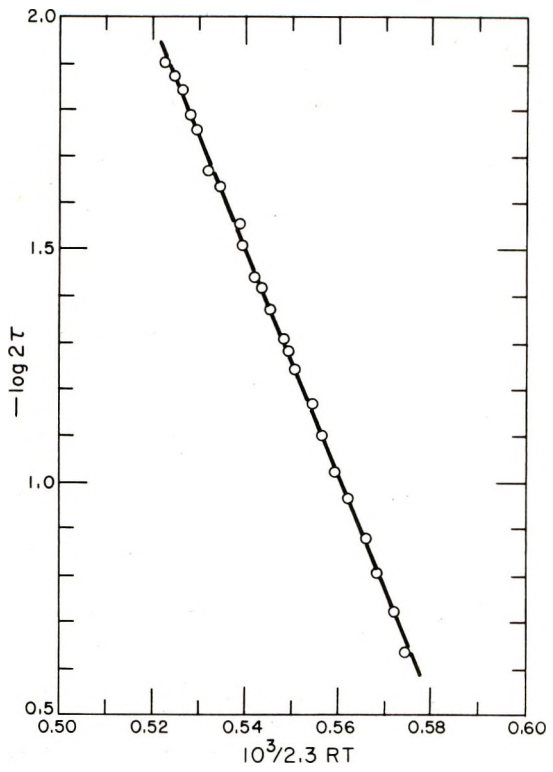


Figure 3. Arrhenius plot of the kinetic data for rotation about the central C–N bond in DMF-d_1.

Among the data in entries 5–8, only the latter set were obtained using deuterated DMF (3) to reduce asymmetry in the NCH_3 line shape. However, double irradiation of the formyl proton, an alternative way to eliminate the interfering coupling, was utilized to obtain the results listed as entry 5.

It seems unlikely that substitution of deuterium for protium on the formyl carbon of DMF would lead to a measurable change in the activation parameters. The linear free energy correlation for rotation in *N,N*-dimethylamides (Figure 1) shows that the barriers depend to similar extents on electronic and steric effects associated with R (1).[5,12] The difference in polar effects between H and D can be estimated from the relative ionization constants of DCO_2H and HCO_2H.[5,17,18] This difference is very small and is predicted to cause the rotational barrier for 3 to be 0.03 kcal/mol less than that for undeuterated DMF.[19]

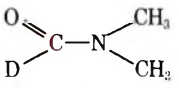
The difference in steric effects could be calculated using data for the isotope effect on base-catalyzed hydrolysis of methyl or ethyl formate.[5,18] However, we have been unable to locate such data in the literature. It seems unlikely, however, that the "steric sizes" of H and D differ enough to have any significant effect on the rotational barrier. In particular it should be noted that the rotational process in DMF does not lead to rehybridization at the carbonyl carbon and that an isotope effect from rehybridization of the (D)H–CO bind is thus precluded.

From a parochial point of view we favor our data over the others in Table II. Care was taken to obtain many high-quality and reproducible spectra, to minimize asymmetry in the NCH_3 line shape, to accurately determine the temperatures at which spectra were recorded, and to obtain many data points over a reasonably large temperature range. The small positive entropy of activation (ΔS^*) is reasonable for C–N rotation of an *N,N*-dimethylamide in the pure liquid reflecting the expected increase in freedom owing to desolvation in the rotational transition state. Values of ΔS^* have often served as the primary gauge of the "goodness" of rotational barrier data because

of the notorious insensitivity of values of ΔF^* to the experimental methods used to obtain the data.[1,3-6] In the case of DMF, however, the spread in values of ΔF^* seems unusually large and we do not have an explanation for this.

Our value of ΔF^* for DMF fits the linear free energy correlation[5] better than that[14j] previously used (Figure 1). However, a value above 23 kcal/mol would be required to obtain a perfect fit. While one or more of the other data points might be in error, it seems more likely that some special problem exists in fitting the R = H (1) substituent to the plot. We have noted that the chemical shift of the HCO proton for DMF remains relatively constant from below 0.1 *M* to almost 6 *M* DMF in carbon tetrachloride, but then it appears to shift downfield at higher concentrations.[20] No such change is observed for the CH_3CO protons in DMA.[20] This probably indicates some sort of special solvation interaction (perhaps hydrogen bonding) which would of course reach an extreme in the pure liquid. In this regard, it is perhaps fortuitous that any free-energy correlation exists for C–N rotation in the pure liquid *N,N*-dimethylamides. While the amide molecules are probably self-associated as dimers in each case,[20] the nature of this self-solvation cannot be identical.

A Comparison with Other Formamides. The formamide system is unique because rotational activation parameters are now available for the series of N-substituted compounds **3–6**. The data for isomers **4** and **5** were recent-



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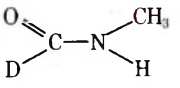
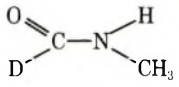


4

	3	**4**
E_a	24.3	23.6
Log *A*	14.6	14.0
ΔF^*	21.8	22.0



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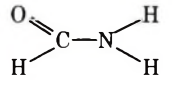
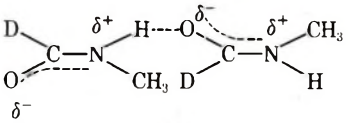


6

	5	**6**
E_a	23.7	19.2
Log *A*	15.0	13.9
ΔF^*	20.7	17.8

ly determined by us,[1a] while those for **6** were reported by another group.[21] However, these must be compared with care because major differences in intermolecular interactions must exist between these systems.

Dimethylformamide molecules probably exist mainly as dimers held together by dipolar attraction.[20] *N*-Methylformamide molecules are probably connected in short polymeric chains *via* hydrogen bonding as shown in **7**,[1]



7

and the formamide molecules are hydrogen bonded to 2-butanone, the solvent used in that study. It is possible that the extent of hydrogen bonding of **4** may be different from that of **5**; however, it should be noted that the effective solvent for both **4** and **5** is the same (90% **4** and 10% **5**).[1a]

We suggest that the NH hydrogen bonding of formamide (**6**) to 2-butanone has relatively little effect on the C–N rotational barrier because the carbonyl group of the amide is not involved. Thus the reported ΔF^* (*ca.* 18 kcal/mol) may be close to that of "monomeric" formamide. Studies carried out by us and others suggest that rotational ΔF^* values for self-associated amides (*e.g.*, neat DMF) are about 1 kcal/mol greater than those of the corresponding monomer,[14j,22] in which case the latter would be a little less than 21 kcal/mol. Finally, the interaction shown as **7** is similar to that proposed for *N,N*-dimethylacetamide in the solvent formamide, where we have estimated that the C–N rotational barrier is about 2 kcal/mol greater than that for monomeric DMA. This would indicate that monomeric **4** and **5** might have ΔF^* values of 20 and 19 kcal/mol, respectively. In summary, the inherent rotational barriers for **3–6** can be approximated as 21, 20, 19, and 18 kcal/mol, respectively.[23]

Registry No.—*N,N*-Dimethylformamide, 68-12-2.

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Studies of Chemical Exchange by Nuclear Magnetic Resonance. X. The Inherent C-N Rotational Barriers in Amides, Thioamides, and Amidinium Ions[1,2]

Robert C. Neuman, Jr.,* and Violet Jonas

Department of Chemistry, University of California, Riverside, California 92502

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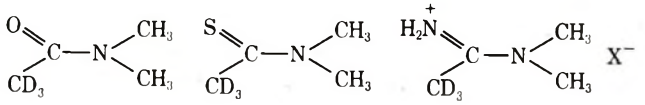
Activation parameters have been determined for C-N rotation in compounds of the general structure $CD_3C(X)NMe_2$ at low concentrations in nonpolar media. The resulting data follow [X, solvent, concentration (mole per cent), E_a (kilocalories/mole), log A, ΔF^* (25°, kilocalories/mole), ΔS^* (eu)]: O, CCl_4, 1.7, 18.3 ± 0.2, 13.5, 17.4, +1.1; O, isooctane, 2.6, 18.0 ± 0.3, 13.3, 17.3, +0.5; S, decalin, 1.6, 21.1 ± 0.2, 13.4, 20.3, +0.6; $NH_2^+NO_3^-$, 1,1,2,2-tetrachloroethane, 0.4, 24.0 ± 0.3, 14.2, 22.1, +4.6; $NH_2^+Cl^-$, TCE, 0.4, 22.8 ± 0.3, 13.6, 21.7, +1.9. These are compared with data obtained for the same systems in different solvents. Solute-medium interactions are discussed and it is proposed that these new data represent the "inherent" C-N rotational barriers for these systems. In contrast with earlier results, the values of ΔF^* now correlate with values of J (^{13}CH) for the NCH_3 protons.

Activation parameters for rotation about the partial double C-N bond in amides and derivatives are influenced by solute-solute and solute-solvent interactions.[1,3-6] Amides and thioamides exist as self-association dimers in the pure liquids or in high-concentration solutions of noninteracting solvents. In dipolar solvents such as dimethyl sulfoxide, a molecule of amide or thioamide is presumed to associate strongly with a solvent molecule in a similar pairwise dipolar association. However, in a solvent such as formamide, hydrogen-bonding interactions appear to replace the dipolar association complexes. In any event, we and others have shown that the medium has a marked influence on rotational barriers.

Recently, we reported a study of the three systems shown below in the common solvent dimethyl sulfoxide-



1 2 3

d_6.[3] The types of intermolecular interactions of 1 and 2 with the medium were the same as mentioned above, but the experimental data, and common sense, indicated that the amidinium ion 3 interacted with DMSO-d_6 *via* hydrogen bonding. Thus, the results were not directly comparable, even though all three systems were studied in a common solvent. It was necessary to try to analyze the contributions of the different interactions to attempt to compare rotational barriers.

We have now been able to obtain rotational activation parameters for the solutes 1-3 in nonpolar media at low concentrations. The results give a different ordering of the relative rotational barriers for these compounds than previously observed.[3] This order O < S < NH_2^+ conforms to the relative values of the ^{13}CH coupling constants for the NCH_3 protons in 1-3, a correlation which we had proposed early in our studies of the comparative barriers of amides, thioamides, and amidinium salts. We suggest that the data presented here are close approximations to the "inherent" barriers to C-N rotation in these compounds, and this report concludes the series "Studies of Chemical Exchange by Nuclear Magnetic Resonance."

Results and Discussion

The nonexchanging chemical shift ($\delta\nu_\infty$) between the two NCH_3 resonance signals reflects the extent of aggregation of amide molecules in noninteracting media.[7] The concentration dependence of $\delta\nu_\infty$ for DMA-d_3 in isooctane at 5° is shown in Figure 1 and from these data a dimerization constant of 2.3 (mole fraction)$^{-1}$ was calculated for the equilibrium shown in eq 1.[8] This compares favorably with

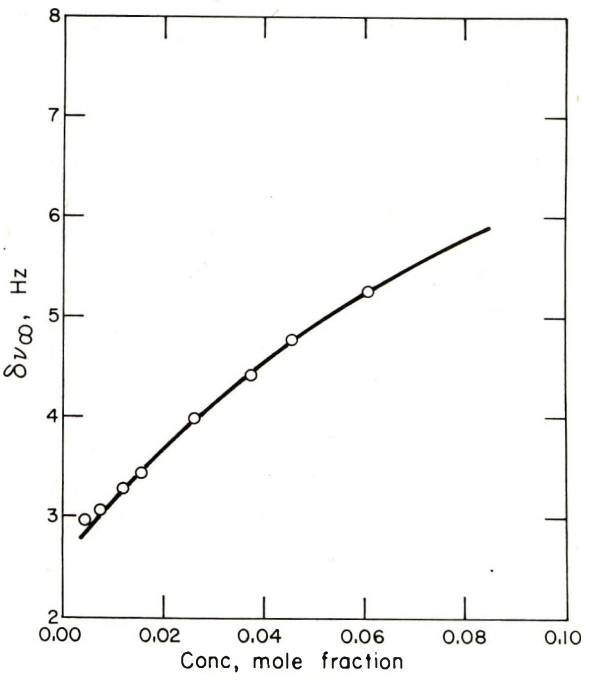


Figure 1. Concentration dependence of the chemical shift ($\delta\nu_\infty$) between the two NCH_3 groups which would exist in the absence of rotation about the C-N bond; solvent, isooctane.

$$2\text{DMA-}d_3 \rightleftharpoons (\text{DMA-}d_3)_2 \quad (1)$$

a previous value of 3.8 (mole fraction)$^{-1}$ determined for DMA-d_3 in CCl_4 (37°).[7] From the data in isooctane, it is possible to extract values of $\delta\nu_\infty$ for monomeric and dimeric DMA. The values 2.6 and 17.0 Hz are different from those obtained in CCl_4, which are 7.3 and 13.8 Hz, but this is not unexpected owing to the possible medium effects on the relative magnetic environments of the NCH_3 groups.

Careful kinetic studies of C-N rotation in DMA-d_3 in isooctane (0.026 mole fraction) and carbon tetrachloride (0.017 mole fraction) were carried out. Under these conditions, DMA-d_3 exists primarily, but not exclusively, in the monomeric state (isooctane, 95% monomer; CCl_4, 94% monomer). Lower concentrations would have been desirable, but were not feasible owing to low amplitude of the nmr signals. The activation parameters in these two solvents are reported in Table I (see Figure 2) along with

Table I
Activation Parameters for C–N Rotation in $CD_3C(X)N(CH_3)_2$

X	Solvent	Concn, mol %	E_a, kcal/mol	Log A	ΔF^* (25°), kcal/mol	ΔS^*, eu	Ref
O	CCl_4	1.7	18.3 ± 0.2	13.5	17.4	+1.1	This work
	Isooctane	2.6	18.0 ± 0.3	13.3	17.3	+0.5	This work
	Neat	100.0	19.6 ± 0.3	13.8	18.2	+2.9	*a*
	DMSO-d_6	9.5	20.3 ± 0.3	14.1	18.5	+4.1	*b*
	Formamide	9.8	21.3 ± 0.6	14.2	19.4	+4.4	*a*
	D_2O	2.0	21.0 ± 0.9	13.9	19.5	+3.0	*c*
S	Decalin	1.6	21.1 ± 0.2	13.4	20.3	+0.6	This work
	o-DCB	33.3	(21.0 ± 0.3)	(12.6)	21.3	(−3.0)	*d*
	DMSO-d_6	8.1	25.9 ± 0.9	14.6	23.4	+6.3	*b*
$NH_2^+NO_3^-$	TCE	0.4	24.0 ± 0.3	14.2	22.1	+4.6	This work
	DMSO-d_6	3.1	21.3 ± 0.3	12.7	21.5	−2.6	*b*
$NH_2^+Cl^-$	TCE	0.4	22.8 ± 0.3	13.6	21.7	+1.9	This work
	DMSO-d_6	7.4	22.8 ± 0.7	13.5	21.8	+1.4	*b*

[a] See ref 4. [b] See ref 3. [c] P. A. Temussi, T. Tancredi, and F. Quadrifoglio, *J. Phys. Chem.*, **73**, 4227 (1969). [d] Determined using an approximate analysis method; see ref 10.

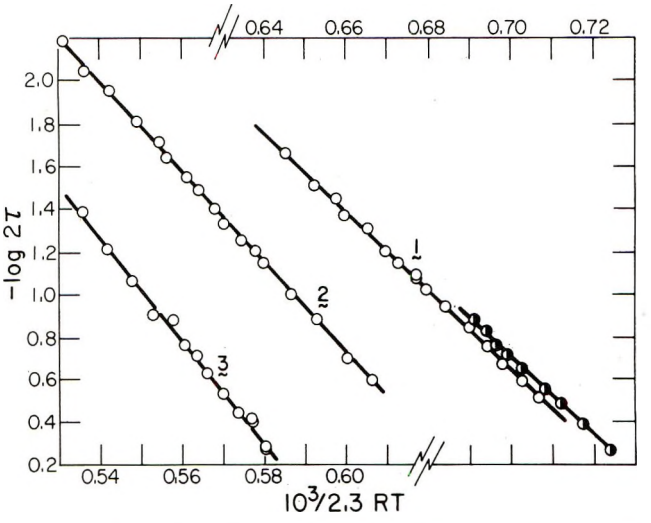


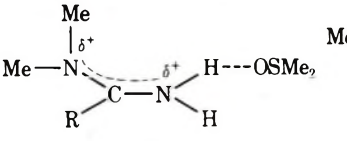
Figure 2. Arrhenius plots of the kinetic data for rotation about the central C–N bond in **1**, ◑, solvent, isooctane; **1**, ○, solvent, CCl_4); **2**, solvent, decalin; **3** (nitrate salt), solvent, 1,1,2,2-tetrachloroethane.

other data for DMA-d_3 under conditions in which it exists primarily as a self-association dimer (neat), associated with an aprotic dipolar solvent (DMSO-d_6), and hydrogen bonded at the carbonyl group (formamide and D_2O). The results clearly demonstrate that the association or hydrogen-bonding interactions substantially increase the rotational barrier (1 and 2 kcal/mol, respectively, in ΔF^*). The major effect of solvent is apparently on E_a, but log A (ΔS^*) also shows the expected change reflecting transition state desolvation.[9]

Rotational activation parameters were determined for the thioamide **2** using the solvents decalin and *n*-decane with thioamide concentrations of 0.016 mole fraction. The concentration dependence of $\delta\nu_\infty$ was not determined in either case. However, the low concentrations and large values of $\delta\nu_\infty$ observed strongly indicate, based on an earlier study of DMTA-d_3 in carbon tetrachloride,[7] that DMTA-d_3 is primarily monomeric under these conditions. Extensive kinetic data were accumulated using the solvent decalin and the results of the study are reported in Table I (see Figure 2) along with some other values for comparison. The very limited kinetic data in *n*-decane gave a value of ΔF^* identical with that found using decalin, but were insufficient to provide accurate values for E_a and log A.

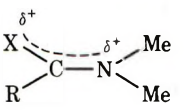
A comparison of the results using decalin and DMSO-d_6 shows that dipolar association with dimethyl sulfoxide substantially increases the rotational barrier. Once again the major part of the effect is in E_a but log A does show an increase in the associating medium. A result from another laboratory[10] for **2** in o-dichlorobenzene gives a ΔF^* value intermediate between those in DMSO-d_6 and decalin. The use of an approximate line shape analysis method makes the values of E_a and log A from that study suspect.[11] If the data in decalin correspond to the inherent C–N barrier, they indicate that the difference between an amide and thioamide is only about 3 kcal/mol rather than the 5 kcal/mol difference suggested by the data using the solvent DMSO-d_6. It appears that dipolar association with DMSO-d_6 has a much greater effect on the dipolar character of a thioamide than that of an amide.

It was possible to obtain rotational barrier data for the nitrate and chloride salts of *N,N*-dimethylacetamidinium ion (**3**) in 1,1,2,2-tetrachloroethane at very low concentrations (Table I and Figure 2). The behavior of the line widths of the individual NCH_3 signals with temperature indicated that ion pairing existed under these conditions for both salts, but greater effects were observed for the nitrate. Although there are differences between the two salts, there is remarkably little change in ΔF^* in going from the solvent DMSO-d_6 to tetrachloroethane (Table I). We had proposed that DMSO-d_6 was hydrogen bonded to both the rotational ground and transition states (**4a** and **4b**) but that this bonding might be a bit tighter in the latter.[3] The relatively low values for log A (ΔS^*) in DMSO-d_6 were offered as evidence for this. The absence of a solvent effect on ΔF^* for **3** now seems to support the similarity in solvent interactions with **4a** and **4b**. However, the detailed interaction of the anion with the rotational ground and transition states is not known.[12]



4a **4b**

Several years ago, we proposed a correlation between J (^{13}CH) for the NCH_3 groups on **1**–**3** and their C–N rotational barriers.[13] Haake had proposed that values of J (^{13}CH) for methyl groups bonded to nitrogen reflected the amount of positive charge on nitrogen.[14] Since the charge on the NCH_3 nitrogen of amides and related derivatives **5**



5

Table II
Comparison of ΔF^* for C–N Rotation in $CD_3C(X)N(CH_3)_2$ with ^{13}CH Coupling Constants for the NCH_3 Protons[a]

Registry no.	X	ΔF^* (25°), kcal/mol	$J(^{13}CH)$, Hz[b]
44364-33-2	NH	(<17)	135
20255-66-7	O	17.3	138
34302-08-4	S	20.3	140
50600-26-5	NH_2^+	22	141

[a] Values of ΔF^* from Table I except for X = NH, which comes from ref 3. [b] The ^{13}CH coupling constants for NCH_3 protons; see ref 3 and 13.

should depend on the extent of C–N double-bond character and since in turn the rotational barrier should also depend on this, we were disappointed that an inconsistency appeared based on our kinetic data using DMSO-d_6.[3] We are now gratified to be able to report that the rotational barriers determined in the nonpolar solvents at low concentration do correlate with the ^{13}CH coupling constants for the NCH_3 protons (Table II).

Experimental Section

Compounds. Syntheses and properties of all of the compounds have been previously described.[3]

Solvents. Isooctane (spectroquality, Matheson Coleman and Bell), carbon tetrachloride (spectrophotometric grade, Mallinckrodt), decalin (spectrophotometric grade, Aldrich), *n*-decane (99%, gold label grade, Aldrich), and 1,1,2,2-tetrachloroethane (Matheson Coleman and Bell) were used as received in sealed bottles.

Variable-Temperature Spectra, Temperatures, and Line Shape Analyses. The procedures followed were essentially those which we have previously used and described.[1,3] Kinetic data were obtained in all cases by total line shape analysis.[1,3]

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Synthesis and Fourier Transform Carbon-13 Nuclear Magnetic Resonance Spectroscopy of New Toxic Polyhalodibenzo-*p*-dioxins

Andrew S. Kende,* James J. Wade, David Ridge, and Alan Poland

Department of Chemistry, The University of Rochester, Rochester, New York 14627

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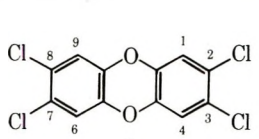
The extraordinary toxicity and potential environmental significance of certain polyhalodibenzo-*p*-dioxins has led us to carry out regiospecific syntheses of these compounds by condensation of catechol derivatives with various polyhalobenzenes. Electrophilic halogenation of 2,3-dihalodibenzo-*p*-dioxins, available by the above route, leads mainly to 2,3,7,8-tetrahalo derivatives, but these are more cleanly obtained by direct condensation of 4,5-dichlorocatechol with 1,2,4,5-tetrahalobenzenes. Fourier transform ^{13}C spectroscopy is shown to be a useful structural probe in this series. Some structure–activity relations for enzyme induction by polyhalodibenzo-*p*-dioxins are outlined.

The surprisingly high toxicity of certain halogenated dibenzo-*p*-dioxins has been demonstrated in a number of recent investigations.[1] The most thoroughly studied member of this group is 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (**1**, TCDD), which has been shown to be the cause of several outbreaks of chloracne among workers in factories which manufacture the herbicide 2,4,5-T (2,4,5-trichlorophenoxyacetic acid).[2] It is now recognized that structure **1** represents perhaps the most lethal small molecule known.[1d] Although present in only trace amounts during the manufacture of 2,4,5-T, the toxicity of this xenobiotic is so extraordinarily high that even these minute quantities constitute a potentially serious health hazard.



1 **2**

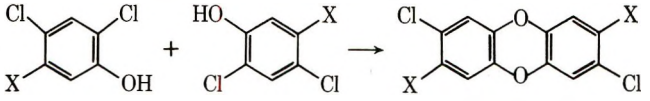
The identification of a toxic contaminant in poultry feed, 1,2,3,7,8,9-hexachlorodibenzo-*p*-dioxin (**2**), as a probable cause of the "chick edema" which has caused widespread loss of chickens in the United States since 1957[3] also demonstrates the environmental significance of certain polyhalogenated dibenzo-*p*-dioxins, apparently formed as by-products in the commercial synthesis of a number of chlorinated phenols. Thus the tetrachloro derivative **1** formed during the manufacture of 2,4,5-trichlorophenol is responsible for the contamination of 2,4,5-T, since the phenol is an intermediate in the manufacture of the herbicide. Because of the widespread use of chlorinated phenols, the extreme potency and environmental persistence of the chlorinated dibenzo-*p*-dioxins which may be present as impurities, and the teratogenic[4] and possible mutagenic effects of these contaminants at sublethal concentrations, further chemical and toxicological characterization of these compounds is urgently needed.

Until recently little was known about the biochemical mechanisms of toxicity for these compounds, and no systematic studies had attempted to relate molecular structure to toxicity or other biological properties in the dibenzo-*p*-dioxin series. In 1973, however, Poland and Glov-

er established that 1 (and certain congeners) are powerful inducers of the enzymes δ-aminolevulinic acid synthetase and aryl hydrocarbon hydroxylase in the chick embryo.[5] Enzymatic assays based on these properties now provide a means of detecting highly toxic dioxins at the nanogram level and, moreover, appear to demonstrate a parallel between enzyme-inducing activities and toxicities of various dioxins toward test animals. With the availability of such assays it became both feasible and imperative to try to define the structural parameters responsible for the extraordinary biological activities shown by some members of this series.

The present investigation has four main objectives: (1) to develop practical and regiospecific syntheses of certain polyhalodibenzo-*p*-dioxins, (2) to discover spectroscopic correlations among such compounds which may aid in identifying new members of the series, (3) to prepare radioactively labeled compounds of high purity for localization and metabolic studies and (4) to elucidate structural requirements for toxicity within this series.

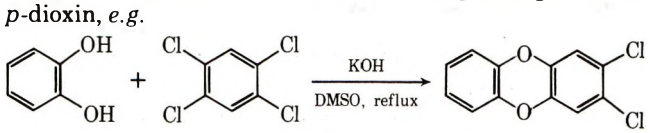
Chemical Background. The classical preparations of polyhalodibenzo-*p*-dioxins are limited to two types of processes: (1) self-condensation of a polyhalophenol and (2) direct halogenation of the parent dibenzo-*p*-dioxin or a monohalo derivative. The former method, exemplified by the reaction through which 1 arises as a commercial impurity, normally proceeds in moderate yield and is practical only when a single condensation product can be formed. Yields of 10–20% have been reported for the Ullman-type self-condensation of 2,4-dichlorophenol to 2,7-dichlorodibenzo-*p*-dioxin,[6] while Aniline[7] has obtained 1 in over 30% yield by a modified Ullman reaction from 2,4,5-trichlorophenol.



X = H or Cl

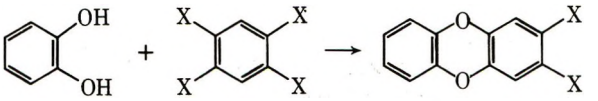
The second method, involving direct halogenation, is of limited scope and has been shown to give mixtures of products. Direct bromination of dibenzo-*p*-dioxin gives both 2,8- and 2,7-dibromodibenzo-*p*-dioxin, while under forcing conditions the 2,3,7,8-tetrabromo derivative is formed.[8] Direct chlorination of dibenzo-*p*-dioxin proceeds in poor yield to give first the 2-chloro and then the 2,7-dichloro derivative.[8] Further chlorination using catalysis by iodine and ferric chloride does produce 1 in moderate yield, but the product is mixed with tri- and pentachlorodibenzo-*p*-dioxins and isolation of pure 1 is extraordinarily difficult.[9]

Catechols in Dibenzo-*p*-dioxin Syntheses. Most of the drawbacks of the conventional syntheses outlined above can be avoided by carrying out the condensation between a catechol dianion and a polyhalobenzene in boiling dimethyl sulfoxide. Using this method, Pohland and Yang[6a] found that the dipotassium salt of catechol in refluxing DMSO reacts smoothly with certain tri- and tetrachlorobenzenes to give good yields of the corresponding dibenzo-*p*-dioxin, *e.g.*



3

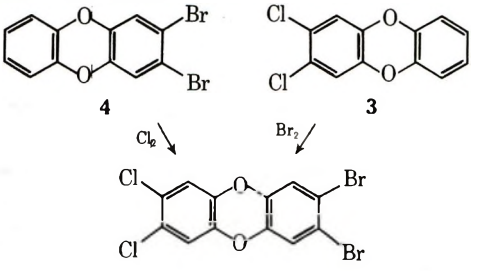
Our own work has systematically extended the scope of this condensation to more highly substituted catechols and to a broad range of polyhalobenzene acceptors. For example, the use of 1,2,4,5-tetrabromobenzene as acceptor gave 2,3-dibromodibenzo-*p*-dioxin (4), and 1,2,4,5-tetrafluorobenzene yielded the 2,3-difluoro derivative (5).



3, X = Cl
4, X = Br
5, X = F

The catechol dianion also reacts with other chlorinated benzenes under the above conditions. Reaction with 1,2,3,5-tetrachlorobenzene gives 1,3-dichlorodibenzo-*p*-dioxin (6), while hexachlorobenzene as acceptor produced 1,2,3,4-tetrachlorodibenzo-*p*-dioxin in good yield. The condensations of catechol with 1,2,3,4-tetrachlorobenzene or with pentachlorobenzene likewise occur readily, but each yields as expected two isomeric products which have not been individually characterized to date.

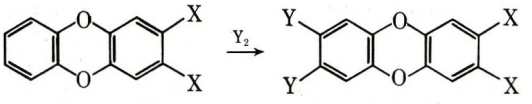
Electrophilic Substitution of 2,3-Dihalodibenzo-*p*-dioxins. The apparent generality of the reaction of catechol dianions with various polyhalobenzenes led us to examine the further halogenation of the primary condensation products. Chlorination of 2,3-dichlorodibenzo-*p*-dioxin (3) in the presence of iodine and ferric chloride gave a crystalline material which was predominantly 1, but contained varying amounts of tri- and pentachlorodibenzo-*p*-dioxins. Although extensive purification produced 1 of above 98% purity, the overall yield of pure 1 by this route was unsatisfactory, owing in part to variable yields in the initial condensation with catechol and also to the extensive purification necessary to obtain 1 pure enough for biological study. Chlorination of the dibromo compound 4 gave 2,3-dibromo-7,8-dichlorodibenzo-*p*-dioxin (7), identical with the product prepared by bromination of the dichloro compound 3. The dibromo compound 4 was also brominated to give 2,3,7,8-tetrabromodibenzo-*p*-dioxin (8). Finally, the difluoro derivative 5 was converted in a



4 3

7

similar manner to the 2,3-dichloro-7,8-difluoro- and 2,3-dibromo-7,8-difluorodibenzo-*p*-dioxins (9 and 10, respectively).



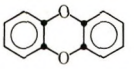
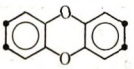
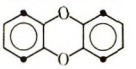
3, X = Cl
4, X = Br
5, X = F

1, X = Y = Cl
7, X = Br; Y = Cl
8, X = Y = Br
9, X = F; Y = Cl
10, X = F; Y = Br

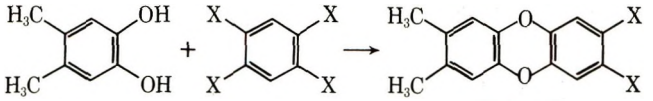
The dichlorodibenzo-*p*-dioxin 3 could also be nitrated using nitronium tetrafluoroborate. The product appeared to consist of two isomeric dichlorodinitrodibenzo-*p*-dioxins, however, and was not characterized further.

Substituted Catechols as Nucleophilic Components. The catechol condensation reaction was slightly modified in order to prepare an isostere of 1. This was conveniently achieved by reaction of 4,5-dimethylcatechol[10] dianion with 1,2,4,5-tetrachlorobenzene to yield 2,3-dichloro-7,8-dimethyldibenzo-*p*-dioxin (11). The 2,3-dibromo counterpart (12) is similarly available from 1,2,4,5-tetrabromobenzene.

Table I
Fourier Transform ^{13}C Nmr Data for Some Chlorinated Dibenzo-*p*-dioxins[a]

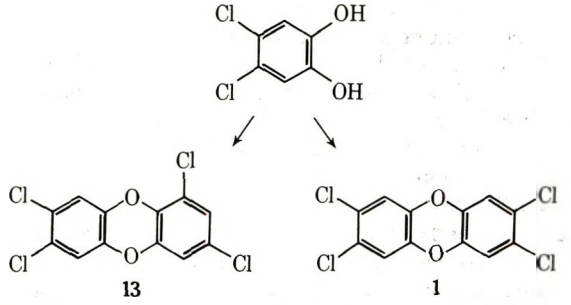
Cl substitution pattern			
None	142.2 (33%)	123.6 (100%)	116.2 (90%)
2,3	141.1 (46%)	126.3 (28%) 124.2 (100%)	117.5 (85%) 116.3 (84%)
1,2,3,4	140.4 (39%) 138.9 (12%)	126.9 (11%) 125.0 (100%)	119.9 (14%) 116.6 (91%)
1,3[b]	143.3 (8%) 141.2 (8%) 141.1 (11%)	124.5 (100%) 124.3 (70%)	116.7 (51%) 116.3 (52%) 115.2 (48%)
1[b]	143.1 (16%) 141.6 (8%)	124.6 (87%) 124.3 (100%) 124.0 (89%) 123.2 (81%)	116.6 (50%) 116.2 (62%) 114.7 (62%)
1,2,4[b]	140.7 (24%)	127.2 (10%) 124.9 (100%) 124.8 (100%) 124.1 (57%)	119.6 (8%) 116.9 (97%)
2,7[b]		123.9 (100%)	116.6 (81%) 117.0 (79%)
Average	141.4 ± 2.5 ppm	124.8 ± 2.5 ppm	116.8 ± 3.0 ppm

[a] Chemical shifts are given in parts per million downfield from TMS. The relative peak heights are given in parentheses. [b] Weak peaks missing or unresolved.



11, X = Cl
12, X = Br

Although Pohland and Yang[6a] report that tetrachlorocatechol does not condense with 1,2,4,5-tetrachlorobenzene, we have found that both 4-chlorocatechol[11] and 4,5-dichlorocatechol[11] dianions are useful nucleophilic partners toward tetrachlorobenzenes. The former reacts smoothly with 1,2,4,5-tetrachlorobenzene to give 2,3,7-trichlorodibenzo-*p*-dioxin. Reaction of 4,5-dichlorocatechol dianion with 1,2,3,5- and 1,2,4,5-tetrachlorobenzene yields the new 1,3,7,8-tetrachlorodibenzo-*p*-dioxin (13) and 1, respectively.



13 1

The synthesis of 1 from 4,5-dichlorocatechol provides a one-step route, giving material of very high purity. Despite the low yield, this is the preferred synthesis of pure, uniformly labeled [^{14}C]-TCDD, and we have prepared the latter by this route to give material having a specific activity of 147.5 mCi/mmol.

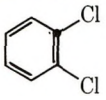
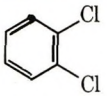
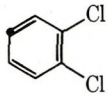
Cmr Spectroscopy of Halogenated Dibenzo-*p*-dioxins. A major problem for any complete and systematic study of the halogenated dibenzo-*p*-dioxins is the reliable identification of the structures of compounds in the series. The evidence for the structures of compounds we have synthesized is based primarily on the method of synthesis and, where possible, upon comparison with a sample of known structure (*e.g.*, by X-ray crystallography for 1 itself).[9] A combination of gas chromatography and mass spectroscopy is of utmost importance in assessing the homogeneity and degree of halogenation of the compounds, and both techniques were used extensively in the present study. These techniques, however, do not reliably define the positions of halogenation in this series. Pohland and Yang have described the possible use of infrared and phosphorescence spectra in regard to this problem and have tabulated spectroscopic data using these methods.[6a] These investigators have also examined the esr spectra of radical cations derived from chlorinated dibenzo-*p*-dioxins.[12]

It is clear from the spectroscopic studies cited that a need remains for rapid identification of the substitution pattern of an unknown polyhalodibenzo-*p*-dioxin. Proton magnetic resonance spectroscopy appears to be remarkably useless in this context because the aromatic resonances for these compounds occur at virtually identical chemical shifts, making assignment of peaks difficult and integration unsatisfactory. For example, the 100-MHz pmr spectrum of 1,2,3,4-tetrachlorodibenzo-*p*-dioxin in tetrachloroethylene solvent appears as a sharp singlet at δ 7.10, that of the 2,3-dichloro compound as singlets at δ 6.97 and 7.07, and the spectrum of 1 as a singlet at δ 7.00.

It seemed possible that natural abundance ^{13}C Fourier transform magnetic resonance spectroscopy (cmr) might be useful for structural assignments in this series. A brief study of several dibenzo-*p*-dioxins suggests that this technique may be of special value for such structural studies. As summarized in Table I, our data reveal chemical shift parameters and relative peak heights which carry substantial information bearing on the substitution pattern of the dibenzo-*p*-dioxin system.

Two main features of the cmr data should be noted. First of all, the resonances due to the lateral carbons (2, 3, 7, and 8), the "peri" carbons (1, 4, 6, and 9), and the junction carbons (11, 12, 13, and 14) each appear in one of three separate and characteristic regions of the spectrum. Although chlorine substitution anywhere may effect slight changes in the chemical shifts of all the carbons, any given shift is relatively small, and each carbon resonance remains in its characteristic region. This observation regarding the minute effect of chlorine on ^{13}C chemical shifts is in accord with published data (Table II).[13]

Table II
^{13}C Chemical Shifts for Symmetrical *o*-Dichlorobenzenes[a,b]

		
3.7	2.0	−0.5

[a] Reference 13. [b] Shifts are given in parts per million relative to benzene.

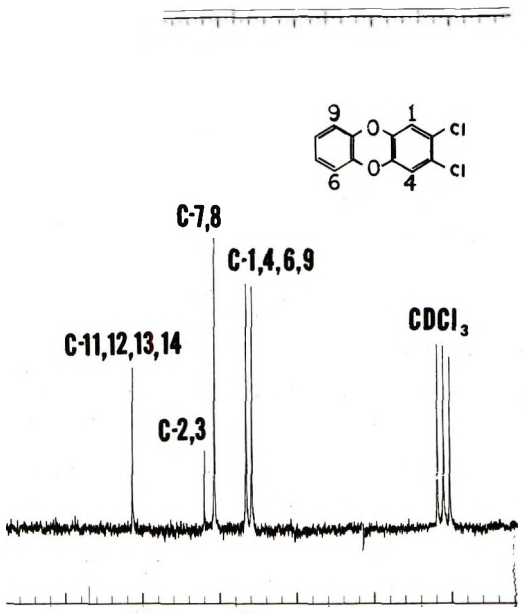


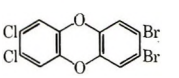
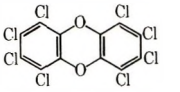
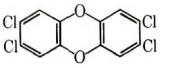
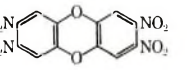
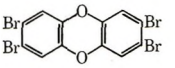
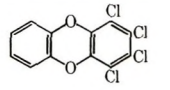
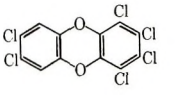
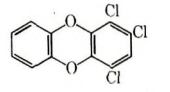
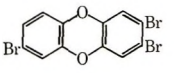
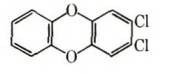
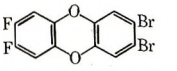
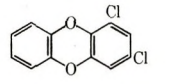
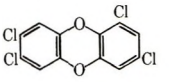
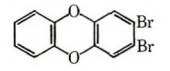
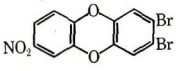
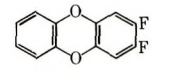
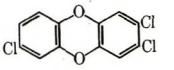
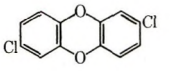
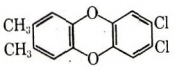
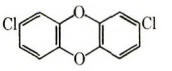
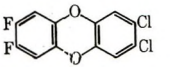
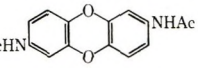
Figure 1. Fourier transform ^{13}C nmr spectrum of 2,3-dichlorodibenzo-*p*-dioxin, 3.6% in $CHCl_3$, with $CDCl_3$ internal reference. Chemical shifts are in Table I.

The second important feature is that the peaks due to carbon atoms bearing a hydrogen are significantly enhanced in intensity relative to those lacking a hydrogen substituent. Such enhancement (heteronuclear Overhauser effect) is anticipated and derives from the relatively short spin lattice relaxation times of carbons comprising a CH unit. Other things being equal, then, one can assume that an intense singlet probably denotes CH, and a weak singlet defines either CO or CCl, assuming no degeneracy for the spectrum. Figure 1 illustrates these intensity differences for the cmr spectrum of 2,3-dichlorodibenzo-*p*-dioxin. In some samples the weak signals could not always be distinguished from the noise level.

Considering these characteristics of the cmr spectrum it should often be possible, in conjunction with mass spectral data, to employ cmr in defining the substitution pattern of an unknown dibenzo-*p*-dioxin. Although the assignment of each individual peak to a specific position is not always unambiguous, especially for an unsymmetrical system such as the 1,3-dichloro compound **6**, the overall pattern of the spectrum will generally be indicative of a particular structure in view of the substantial chemical shift differences distinguishing the three sets of carbon atoms already defined.

Certain structures, however, are still ambiguous using the cmr technique. Thus we probably could not distinguish *a priori* between the 1,3-dichloro compound and the 1,7- or 1,8-dichloro isomer, nor between the 1,2,3,7,8,9-hexachloro compound and its 1,2,3,6,7,8-hexachloro isomer. A further drawback is the very low solubility of some of the highly chlorinated dioxins, necessitating prolonged scanning of the spectrum. Nevertheless, Fourier transform cmr spectroscopy appears to be a useful adjunct to other techniques for structure elucidation in this series.

Table III
Structure–Activity Relations for AHH Induction in Chick Embryo Liver, Expressed Relative to TCDD Activity = 1.0

	1.1		0
	1.0		0
	1.0		0
	0.8		0
	0.6		0
	0.2		0
	0.2		0
	0.01		0
	0.02		0
	0.01		0
	0.01		0

Enzyme Induction by Halogenated Dibenzo-*p*-dioxins. The dibenzo-*p*-dioxins prepared in this study were assayed for their ability to induce aryl hydrocarbon hydroxylase (AHH) in the chick embryo according to the published procedure.[5] A summary of relative activities (1 = 1.00) for all compounds available to us in this series is shown in Table III.

Several trends can be noted from the collected data. The halogen-free compounds are inert, as is the 1,2,3,4-tetrachloro derivative. When three of the four lateral positions of the dibenzo-*p*-dioxin system are halogenated, the compound becomes active, but is not as active as when all four lateral positions are halogenated. Replacement of halogen by nitro at all four lateral positions destroys activity. The 2,3-dichloro-7,8-dimethyl compound, roughly isosteric with TCDD, is inactive. The fluorinated compounds are less active than their tetrachloro or tetrabromo counterparts. Furthermore, the 2,3,7-tribromo compound is significantly more active than the corresponding trichloro compound.

Our data lead to the following rules, based on the AHH-inducing activities of some two dozen compounds: (1) positions 2, 3, 7, and 8 must contain at least three halogen substituents; (2) substituents at these lateral positions have the order of activity Br > Cl > F > NO_2; (3) at least

one hydrogen atom must remain on the dibenzo-*p*-dioxin nucleus.

Further Investigations. Further chemical and biological studies on halogenated tricyclic aromatic systems are clearly warranted because of the potential health hazard which they represent and because of the extraordinary potency of certain members of this class as inducers of selected enzyme systems. Investigations continue in these laboratories using ^{14}C-labeled materials to study metabolism, distribution, and storage of such xenobiotics in animals. Chemical studies to extend our synthetic methodology to related aromatic systems are also in progress.

Experimental Section

General Comments. Melting points were determined on a Mel-Temp apparatus and are uncorrected. Ultraviolet (uv) spectra were obtained on a Cary 118 spectrophotometer. Proton magnetic resonance (pmr) spectra were determined with a Jeolco C60HL or JNM HL100 spectrometer and are given in parts per million (δ) downfield from tetramethylsilane as an internal standard. Mass spectra were obtained using a direct (solid) inlet at 70 eV on a Hitachi Perkin-Elmer RMU-6E instrument. The glpc data were obtained on a Perkin-Elmer 900 or a Hewlett-Packard 700 instrument with a hydrogen flame ionization detector, using a 6 ft × 0.125 in. 10% SE-30 cloumn at a nitrogen flow rate of 30 ml/min. Glc-mass spectra were obtained by Varian Associates on a MAT-111 instrument and by the Du Pont Co. on a 490-B mass spectrometer. The Fourier-transform ^{13}C nmr spectra were determined with a Jeolco JNM-PS-100 spectrometer.

Preparative thin layer chromatography (tlc) was carried out on commercially prepared 20 × 20 cm silica gel plates (E. Merck) having the thickness indicated. Dimethyl sulfoxide solvent was dried by distillation at reduced pressure from calcium hydride. Microanalyses were performed by Chemalytics, Inc., Tempe, Ariz. The purity of all halogenated dibenzo-*p*-dioxins was shown by glc as at least 98% unless otherwise indicated in the text.

Caution: Many of the compounds described here are highly toxic. All of the halogenated dibenzo-p-dioxins should be handled with extreme care, using precautions which parallel work with radioactive compounds. Arrangements should be made for prompt and safe disposal of wastes, all glassware should be rigorously cleaned with chromic–sulfuric acid mixture after use, and disposable gloves, aprons, and absorbent bench-top and hood lining should be used. Contact or absorption of toxic dioxins may lead to acne, porphyria, and irreversible liver damage.

2,3-Dichlorodibenzo-*p*-dioxin (3). This compound was prepared according to the procedure of Pohland and Yang[6a] in 81% yield after recrystallization from methanol. Three successive recrystallizations from isooctane yielded a colorless solid, mp 159–160° (lit. mp 163–164°), glc retention time (220°) 5.2 min.

Anal. Calcd for $C_{12}H_6O_2Cl_2$: C, 56.95; H, 2.39; Cl, 28.02. Found: C, 57.02; H, 2.41; Cl, 28.25.

2,3-Dibromodibenzo-p-dioxin (4). The dipotassium salt of catechol was prepared by dissolving 110 mg (1.00 mmol) of catechol in 2.0 ml (2.00 mmol) of 1.00 *N* KOH solution. The solution was evaporated to dryness *in vacuo*, 400 mg (1.01 mmol) of tetrabromobenzene was added, and the mixture was refluxed in 2 ml of dry dimethyl sulfoxide under nitrogen for 4 hr. The cooled reaction mixture was poured into 40 ml of cold water and extracted with three 30-ml portions of chloroform. The combined extracts were washed successively with two 30-ml portions of 2% NaOH solution, 30 ml of water, and 30 ml of brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by tlc (2 mm, elution with hexane, R_f 0.5) to yield 87 mg (25%) of the dibromo compound. Three recrystallizations from isooctane gave a colorless solid: mp 157.5–158°; nmr ($CDCl_3$) δ 6.88 (s, 4), 7.03 (s, 2); uv max ($CHCl_3$) 308 nm (ϵ 3890); mass spectrum (70 eV) *m/e* (rel intensity) 344 (48), 342 (100), 340 (53), 263 (4), 261 (4), 182 (36); glc retention time (200°) 18.3 min.

Anal. Calcd for $C_{12}H_6O_2Br_2$: C, 42.14; H, 1.77; Br, 46.73. Found: C, 42.44; H, 1.72; Br, 46.53.

2,3-Difluorodibenzo-*p*-dioxin (5). This dioxin, prepared from 1,2,4,5-tetrafluorobenzene by the above procedure, was obtained in 41% yield as a colorless solid: mp 174–176°; nmr ($CDCl_3$) δ 6.88 (s), 6.60 (d, J = 8 Hz); uv max ($CHCl_3$) 296 nm (ϵ 4140); mass spectrum (70 eV) *m/e* (rel intensity) 220 (100), 191 (6), 173 (16), 164 (16); glc retention time (200°) 5.1 min.

Anal. Calcd for $C_{12}H_6O_2F_2$: C, 65.46; H, 2.74. Found: C, 65.50; H, 2.54.

1,3-Dichlorodibenzo-*p*-dioxin (6). The dipotassium salt of catechol was prepared by dissolving 156 mg (1.42 mmol) of catechol in 2.38 ml (2.88 mmol) of 1.21 *N* KOH solution. This solution was evaporated to dryness at 50° *in vacuo*, 281 mg (1.30 mmol) of 1,2,3,5-tetrachlorobenzene was added, and the mixture was refluxed under nitrogen in 3 ml of dry dimethyl sulfoxide for 19 hr. The cooled reaction mixture was then poured into 15 ml of cold water and extracted with four 10-ml portions of chloroform. The combined extracts were washed successively with three 10-ml portions of 2% NaOH solution, two 10-ml portions of water, and 10 ml of brine, dried ($MgSO_4$), and concentrated *in vacuo*. The concentrate was purified by tlc (0.5 mm, elution with hexane, R_f 0.3) to yield 100 mg (31%) of colorless solid: mp 113.5–114.5°; uv max ($CHCl_3$) 296 nm (ϵ 3100); mass spectrum (70 eV) *m/e* (rel intensity) 254 (68), 252 (100), 217 (5), 189 (24), 161 (6), 126 (20); glc retention time (220°) 4.1 min.

Anal. Calcd for $C_{12}H_6O_2Cl_2$: C, 56.95; H, 2.39; Cl, 28.02. Found: C, 56.95; H, 2.36; Cl, 28.07.

1,2,3,4-Tetrachlorodibenzo-*p*-dioxin. This substance was formed in 41% yield from hexachlorobenzene, employing the above procedure, as a colorless, crystalline solid: mp 188–190° (lit.[5a] mp 189°); uv max ($CHCl_3$) 315 nm (ϵ 2720); mass spectrum (70 eV) *m/e* (rel intensity) 324 (52), 322 (100), 320 (81), 259 (13), 257 (13, 194 (10); glc retention time (220°) 8.8 min.

Anal. Calcd for $C_{12}H_4Cl_4O_2$: C, 44.76; H, 1.25. Found: C, 45.02; H, 1.17.

Condensation of Catechol with 1,2,3,4-Tetrachlorobenzene. The dipotassium salt of catechol was prepared by dissolving 115 mg (1.05 mmol) of catechol in 1.73 ml (2.09 mmol) of 1.2 *N* KOH solution. This solution was evaporated to dryness *in vacuo*, 217 mg (1.01 mmol) of 1,2,3,4-tetrachlorobenzene was added, and the mixture was refluxed in 0.75 ml of dimethyl sulfoxide under nitrogen for 18 hr. The cooled reaction mixture was poured into 10 ml of cold water and extracted with four 10-ml portions of chloroform. The combined extracts were washed successively with two 10-ml portions of 1% NaOH solution, 10 ml of water, and 10 ml of brine, dried ($MgSO_4$), and concentrated *in vacuo*. The concentrate was purified by tlc (0.5 mm, elution with CCl_4, R_f 0.4) to yield 102 mg (40%) of colorless solid, a mixture of two compounds by glc analysis: mp 80–115°, uv max ($CHCl_3$) 293 nm (ϵ 2440); glc–mass spectral data—retention time (200°) 6.9 min [64%, mass spectrum (70 eV) *m/e* (rel intensity) 256 (10), 254 (64), 252 (100), 217 (8), 191 (9), 189 (27), 161 (10), 127 (12), 126 (28)], 7.7 min [36%, mass spectrum (70 eV) *m/e* (rel intensity) 256 (10), 254 (62), 252 (100), 217 (10), 191 (13), 189 (33), 161 (12), 127 (15), 126 (30)].

Condensation of Catechol with Pentachlorobenzene. This reaction was carried out as described above for the 1,2,3,4-tetrachlorobenzene case, using 117 mg (1.06 mmol) of catechol, 1.76 ml (2.12 mmol) of 1.21 *N* KOH solution, and 256 mg (1.02 mmol) of pentachlorobenzene. Purification of the product by tlc (0.5 mm, elution in CCl_4, R_f 0.4) yielded 103 mg (35%) of a colorless solid, a mixture of two compounds by glc analysis: mp 93–104°; uv max ($CHCl_3$) 296 nm (ϵ 2200); glc–mass spectral data—retention time (200°) 12.2 min [66%, mass spectral data (70 eV) *m/e* (rel intensity) 290 (30), 288 (100), 286 (100), 253 (8), 251 (11), 225 (20), 223 (29), 197 (7), 195 (11), 162 (7), 160 (171)], 13.6 min [34%, mass spectrum (70 eV) *m/e* (rel intensity) 290 (35), 288 (99), 286 (100), 253 (8), 255 (12), 225 (27), 223 (38), 197 (8), 195 (9), 162 (9), 160 (23)].

2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (1). To a solution of 16 mg (0.063 mmol) of 2,3-dichlorodibenzo-*p*-dioxin in 2 ml of chloroform in a 12-ml conical test tube were added a small crystal of ferric chloride and a small crystal of iodine. Chlorine gas was slowly bubbled through the solution for 21 hr at room temperature. The mixture was then concentrated to 0.8 ml by evaporation under a stream of nitrogen. The chloroform-soluble material was separated by centrifugation; the precipitate was shaken with another 0.75 ml of chloroform and separated by centrifugation. The precipitate was then shaken with 1.5 ml of chloroform and 0.5 ml of water, the mixture was centrifuged, the aqueous phase was drawn off by pipet, and the chloroform was evaporated to dryness under a stream of nitrogen. The residue was recrystallized from anisole to yield 8.4 mg (41%) of colorless needles. Glc analysis (230°) indicates that the material consists of 85% 2,3,7,8-tetrachlorodibenzo-p-dioxin [retention time 8.3 min; mass spectrum (70 eV) *m/e* 322] and that the remainder is 2,3,7-trichlorodibenzo-*p*-dioxin [retention time 5.1 min; mass spectrum (70 eV) *m/e* 286] and, presumably, 1,2,3,7,8-pentachlorodibenzo-*p*-dioxin (retention time 13.2 min). Three successive recrystallizations gave material of >98% purity by glc analysis: mp 305–307° (lit.[6a] mp 305°); uv

max ($CHCl_3$) 306 nm (ε 6030); mass spectrum (70 eV) *m/e* (rel intensity) 324 (48), 322 (100), 320 (74), 259 (23), 257 (50), 194 (23).

2,3-Dibromo-7,8-dichlorodibenzo-*p*-dioxin (7). To a solution of 25 mg (0.099 mmol) of 2,3-dichlorodibenzo-*p*-dioxin in 1 ml of chloroform in a 12-ml conical test tube were added a small crystal of iodine, a small crystal of ferric chloride, and 10 drops of bromine. The mixture was allowed to stand for 3 days, during which time several drops of bromine were occasionally added. The chloroform-soluble material was then separated by centrifugation; the precipitate was shaken with another 0.75 ml of chloroform and separated by centrifugation. The precipitate was then shaken with 1.5 ml of chloroform and 0.5 ml of 5% sodium thiosulfate solution, the mixture was centrifuged, the aqueous phase was drawn off by pipet, and the chloroform was evaporated to dryness under a stream of nitrogen. The residue was recrystallized from anisole to yield 31.2 mg (76%) of colorless needles. Glc analysis (230°) indicates that the material is 92% dibromodichloro compound [retention time 17.8 min; mass spectrum (70 eV) *m/e* 408] and 8% bromodichloro compound [retention time 7.7 min; mass spectrum (70 eV) *m/e* 330]. Three successive recrystallizations from anisole gave material of >98% purity by glc analysis. This material had the same retention time as a sample of material prepared by chlorination of 2,3-dibromodibenzo-*p*-dioxin: mp 316–317.5°; uv max ($CHCl_3$) 307 nm (ε 4600); mass spectrum (70 eV) *m/e* (rel intensity) 414 (32), 412 (85), 410 (100), 408 (38), 349 (4), 347 (5), 345 (4), 305 (3), 303 (6), 301 (3).

2,3,7,8-Tetrabromodibenzo-*p*-dioxin (8). This compound was prepared as described above for 2,3-dibromo-7,8-dichlorodibenzo-*p*-dioxin (7), using 25.5 mg (0.0745 mmol) of 2,3-dibromodibenzo-*p*-dioxin to yield 24.9 mg (67%) of white crystals. Glc analysis indicates that the material consists of 95% tetrabromo compound [retention time 31.8 min; mass spectrum (70 eV) *m/e* 496] and presumably 5% tribromo compound (retention time 13.5 min). Two successive recrystallizations from anisole gave material of >98% purity by glc analysis: mp 334–336° (lit.[8] mp 334°); uv max ($CHCl_3$) 308 nm; mass spectrum (70 eV) *m/e* (rel intensity) 504 (19), 502 (69), 500 (100), 498 (69), 496 (19), 423 (9), 421 (23), 417 (9), 342 (9), 340 (18), 338 (9).

***2,3-Dichloro-7,8-difluorodibenzo-p-dioxin* (9).** To a solution of 26 mg (0.118 mmol) of 2,3-difluorodibenzo-*p*-dioxin (5) in 1 ml of chloroform in a 12-ml conical test tube were added a small crystal of iodine and a small crystal of ferric chloride. Chlorine gas was bubbled slowly through the solution for 22 hr. The solution was shaken with 0.5 ml of water and centrifuged, the aqueous layer was drawn off using a pipet, and the chloroform was evaporated to dryness under a stream of nitrogen. The residue was recrystallized from a small amount of anisole to yield 8.2 mg (24%) of fluffy white crystals: mp 223–225°; uv max ($CHCl_3$) 300 nm (ε 3900); mass spectrum (70 eV) *m/e* (rel intensity) 290 (66), 288 (100), 227 (6), 225 (18), 162 (100); glc retention time (200°) 6.5 min.

2,3-Dibromo-7,8-difluorodibenzo-*p*-dioxin (10). Bromination of 2,3-difluorodibenzo-*p*-dioxin (5) by the procedure described above for compound 7 gave the dibromo derivative **10**: mp 210–212°; uv max ($CHCl_3$) 301 nm (ε 4600); mass spectrum (70 eV) *m/e* (rel intensity) 380 (50), 378 (100), 376 (52), 299 (3), 297 (3), 271 (7), 269 (7), 218 (32), 188 (5); glc retention time (200°) 11.4 min (97%).

4,5-Dimethylcatechol. This compound was prepared in 33% yield by the method of Teuber and Staiger,[10] mp 83–85° (lit. mp 87–88°).

2,3-Dichloro-7,8-dimethyldibenzo-*p*-dioxin (11). The dipotassium salt of 4,5-dimethylcatechol was prepared by dissolving 24.6 mg (0.178 mmol) of the catechol in 0.30 ml (0.363 mmol) of 1.21 *N* KOH solution. The solution was evaporated to dryness *in vacuo*, 36 mg (0.167 mmol) of 1,2,4,5-tetrachlorobenzene was added, and the mixture was refluxed in 2 ml of dry dimethyl sulfoxide under nitrogen for 18 hr. The cooled reaction mixture was poured into 6 ml of cold water and extracted with four 10-ml portions of chloroform. The combined extracts were washed successively with 10 ml of 1% NaOH solution, 10 ml of water, and 10 ml of brine, dried ($MgSO_4$), and concentrated *in vacuo* to 47 mg of solid. Recrystallization from anisole yielded 22.9 mg (49%) of colorless solid: mp 231–231.5°; nmr ($CDCl_3$) δ 2.15 (s, 6), 6.60 (s, 2), 6.95 (s, 2); uv max ($CHCl_3$) 301 nm (ε 4200); mass spectrum (70 eV) *m/e* (rel intensity) 282 (65), 280 (100), 267 (13), 265 (22); glc retention time (220°) 11.5 min.

Anal. Calcd for $C_{14}H_{10}O_2Cl_2$: C, 59.81; H, 3.59; Cl, 25.22. Found: C, 60.05; H, 3.50; Cl, 24.94.

2,3-Dibromo-7,8-dimethyldibenzo-*p*-dioxin (12). This dioxin was formed by condensation of 4,5-dimethylcatechol and 1,2,4,5-tetrabromobenzene according to the procedure reported for the dichloro analog **11**: mp 229–230°; uv max ($CHCl_3$) 302 nm (ε 4800); mass spectrum (70 eV) *m/e* (rel intensity) 372 (48), 370 (100), 368 (52), 357 (7), 355 (14), 353 (7), 210 (16); glc retention time (230°) 11.6 min.

4-Chlorocatechol. This intermediate was prepared in 44% yield by the method of Willstätter and Müller,[11] mp 86–87.5° (lit. mp 90–91°).

4,5-Dichlorocatechol. This substance was prepared in 24% yield by the method of Willstätter and Müller,[11] mp 115.5–117.5° (lit. mp 116–117°).

2,3,7-Trichlorodibenzo-*p*-dioxin. The dipotassium salt of 4-chlorocatechol was prepared by dissolving 20.0 mg (0.138 mmol) of the catechol in 0.24 ml (0.29 mmol) of 1.21 *N* KOH solution. The solution was evaporated to dryness *in vacuo*, 26.5 mg (0.123 mmol) of 1,2,4,5-tetrachlorobenzene was added, and the mixture was refluxed under nitrogen in 0.5 ml of dry dimethyl sulfoxide for 22 hr. The cooled reaction mixture was poured into 7 ml of cold water and extracted with three 10-ml portions of chloroform. The combined extracts were washed successively with two 10-ml portions of 2% NaOH solution, 10 ml of water, and 10 ml of brine, dried ($MgSO_4$), and concentrated by evaporation of the chloroform under a stream of nitrogen to leave 26.8 mg of brown solid. This material was sublimed (120°, 1 mm) to yield 16.0 mg (50%) of a colorless solid. A second sublimation yielded 14.8 mg of solid. Glc analysis (230°) indicated that the material consists of 86% of the desired trichloro compound (retention time 3.9 min) and 14% 2,3-dichlorodibenzo-*p*-dioxin (retention time 2.3 min): mp 153–158°; uv max ($CHCl_3$) 304 nm (ε 3460); mass spectrum (70 eV) *m/e* (rel intensity) 290 (34), 288 (100), 286 (100), 253 (10), 251 (10), 225 (28), 223 (46). Further crystallizations or sublimations gave no improvement in homogeneity of this sample.

2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (1). The dipotassium salt of 4,5-dichlorocatechol was prepared by dissolving 29.0 mg (0.162 mmol) of the catechol in 0.29 ml (0.29 mmol) of 1.00 *N* KOH solution. The solution was evaporated to dryness *in vacuo*, the last traces of water were removed by azeotroping with mixtures of benzene and ethanol, 27.1 mg (0.126 mmol) of 1,2,4,5-tetrachlorobenzene was added, and the mixture was refluxed under nitrogen in 1.5 ml of dry dimethyl sulfoxide for 17 hr. The cooled reaction mixture was poured into 10 ml of cold water and extracted with ten 10-ml portions of chloroform. The combined extracts were washed successively with two 20-ml portions of 2% NaOH solution, 20 ml of water, and 20 ml of brine, dried (Na_2SO_4), filtered, and evaporated to dryness under a stream of nitrogen. The residue was washed with two 0.5-ml portions of chloroform, using a centrifuge to concentrate the solid and pipeting off the solvent. The solid was sublimed (240–250°) to give 7.6 mg (19%) of colorless needles. Glc analysis (230°) indicated that this material is 99% pure: mp 306–307° (lit.[6a] mp 305°); uv max ($CHCl_3$) 306 nm (ε 6000); mass spectrum (70 eV) *m/e* (rel intensity) 324 (48), 322 (100), 320 (74), 259 (23), 257 (50), 194 (23); glc retention time (230°) 8.3 min.

1,3,7,8-Tetrachlorodibenzo-*p*-dioxin (13). Condensation of 4,5-dichlorocatechol with 1,2,3,5-tetrachlorobenzene by the above procedure gave 40% of colorless dioxin **13**: mp 193.5–195°; uv max ($CHCl_3$) 304 nm (ε 4160); mass spectrum (70 eV) *m/e* (rel intensity) 324 (54), 322 (100), 320 (84), 287 (5), 285 (5), 259 (19), 257 (19), 194 (11); glc retention time (220°) 10.8 min.

Anal. Calcd for $C_{12}H_4O_2Cl_4$: C, 44.76; H, 1.25. Found: C, 45.13; H, 1.51.

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Registry No.—**1**, 1746-01-6; **3**, 29446-15-9; **4**, 50585-37-0; **5**, 50585-38-1; **6**, 50585-39-2; **7**, 50585-40-5; **8**, 50585-41-6; **9**, 50585-

42-7; **10**, 50585-43-8; **11**, 50585-44-9; **12**, 50585-45-0; **13**, 50585-46-1; catechol dipotassium salt, 50585-47-2; 1,2,4,5-tetrafluorobenzene, 327-54-8; 1,2,3,4-tetrachlorodibenzo-*p*-dioxin, 30746-58-8; hexachlorobenzene, 118-74-1; 1,2,3,4-tetrachlorobenzene, 634-66-2; pentachlorobenzene, 608-93-5; 4,5-dimethylcatechol dipotassium salt, 50585-48-3; 2,3,7-trichlorodibenzo-*p*-dioxin, 33857-28-2; 4-chlorocatechol dipotassium salt, 50585-49-4; 4,5-dichlorocatechol dipotassium salt, 50585-50-7.

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Synthesis of Some Tricyclic Nucleosides Related to the "Y" Base of tRNA[1a,b]

Gary L. Anderson,[1c] Boshra H. Rizkalla, and Arthur D. Broom*

Department of Biopharmaceutical Sciences, College of Pharmacy, University of Utah, Salt Lake City, Utah 84112

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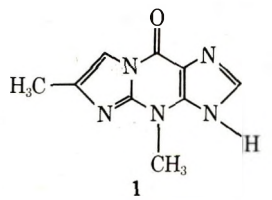
The synthesis of three tricyclic nucleosides, 5*H*(7*H*)-9-oxo-3-β-D-ribofuranosyl-1,2,4-triazolo[2,3-*a*]purine (**3**), 6,7-dimethyl-10-oxo-3-β-D-ribofuranosyl-1,2,4-triazino[2,3-*a*]purine (**4**), and 10-oxo-3-β-D-ribofuranosyl-1,2,4-triazino[2,3-*a*]purine (**5**), is reported. These are structural analogs of the "Y" base of tRNA. The use of the nuclear Overhauser effect in proton assignment of **3** is described, as well as the fluorescence of **3** and **4**. Covalent hydration of **5** is discussed.

Transfer ribonucleic acids specific for phenylalanine ($tRNA^{Phe}$) from a variety of sources have recently been shown to contain certain highly fluorescent heterocyclic bases, the simplest of which is the tricyclic derivative **1**.[2] Other tricyclic fluorescent derivatives of naturally occurring purines, exemplified by 1,N^6-ethenoadenosine (ε-adenosine), have recently been synthesized[3] and shown to enter into a number of biochemical pathways.[4] The availability of 1-aminoguanosine (**2**) in our laboratories[5] led us to undertake the synthesis of certain tricyclic nucleosides derived from guanosine and structurally related to the "Y" base (**1**).



1

Results and Discussion

Synthetic Aspects. The cyclization procedures used to obtain the tricyclic nucleosides are shown in Scheme I. Attempts to prepare the triazolopurine ribonucleoside **3** using diethoxymethyl acetate[6] gave complex mixtures from which **3** could be isolated only with great difficulty. The procedure of Clark and Lister[7] using DMF–$POCl_3$ has been widely used for cyclization of weakly basic 1,2-diamino compounds. Application of this procedure to 1-aminoguanosine (**2**) gave the desired **3** in good yield. The structure of **3** was confirmed by elemental analysis and uv and pmr spectra. The uv spectra (Table I) reveal substantial bathochromic shifts relative to starting material **2** and are very similar to those reported for the imidazo[1,2-*a*]purine ribonucleoside obtained by the reaction of guanosine with glycidaldehyde.[8]

The condensation of 1,2-diaminopyrimidines with 1,2-dicarbonyl compounds (the Isay synthesis) has found extensive use in the synthesis of pteridines.[9] Application of this reaction with **2** using biacetyl and glyoxal gave 6,7-dimethyl-10-oxo-3-β-D-ribofuranosyl-1,2,4-triazino[2,3-*a*]purine (**4**) and its unmethylated derivative **5**, respectively. Nucleoside **4** was found to have elemental analysis and uv and pmr spectra consistent with the assigned structure (Scheme I). The uv spectra of **5**, however, were grossly different from those of its dimethyl counterpart **4** (Table I), the pmr spectra were incompatible with structure **5** (Table II), and elemental analysis revealed the presence of 2.5 equiv of water/mol of **5**. The data were consistent with the existence in solution of **5** as a covalent hydrate and **4** as the anhydrous molecule. The interpretation receives support from the observation by Clark[10] that ethyl pteridine-4-carboxylate readily forms a covalent hydrate in solution whereas its 6,7-dimethyl derivative is only slightly hydrated at equilibrium, and is confirmed by the pmr data discussed below.

Pmr Considerations. Examination of the aromatic region of the pmr spectrum of the triazolo[2,3-*a*]purine nucleoside **3** revealed two one-proton singlets downfield 0.30 and 0.80 ppm from the H-8 signal of 1-aminoguanosine (**2**)

Table I
Uv Absorption Maxima (nm)

Compd	pH 1 λmax	pH 1 Log εmax	pH 7 λmax	pH 7 Log εmax	pH 11 λmax	pH 11 Log εmax
2	257	4.064	255	4.167	257	4.155
3	276	4.068	285	4.163	285	4.153
4	248	4.290	254	4.291	254	4.279
	292	3.634	297	3.606	297	3.629
	358	3.480	362	3.521	362	3.510
5	257	4.029	247	4.145	257	4.093
	295	3.687	255	4.093	306	3.587
			303	3.598		

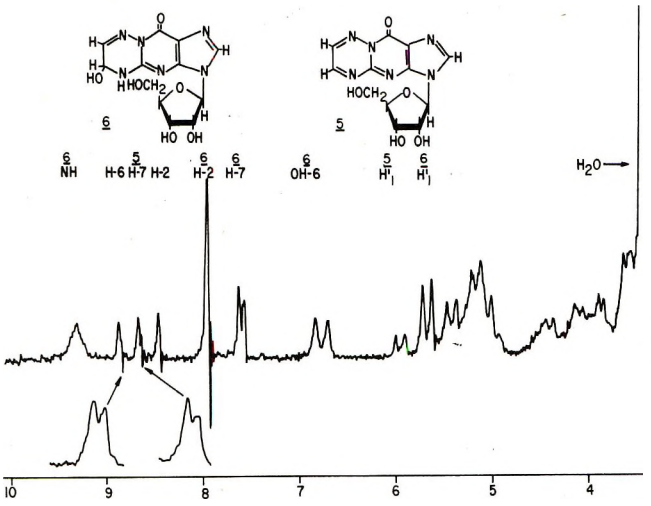


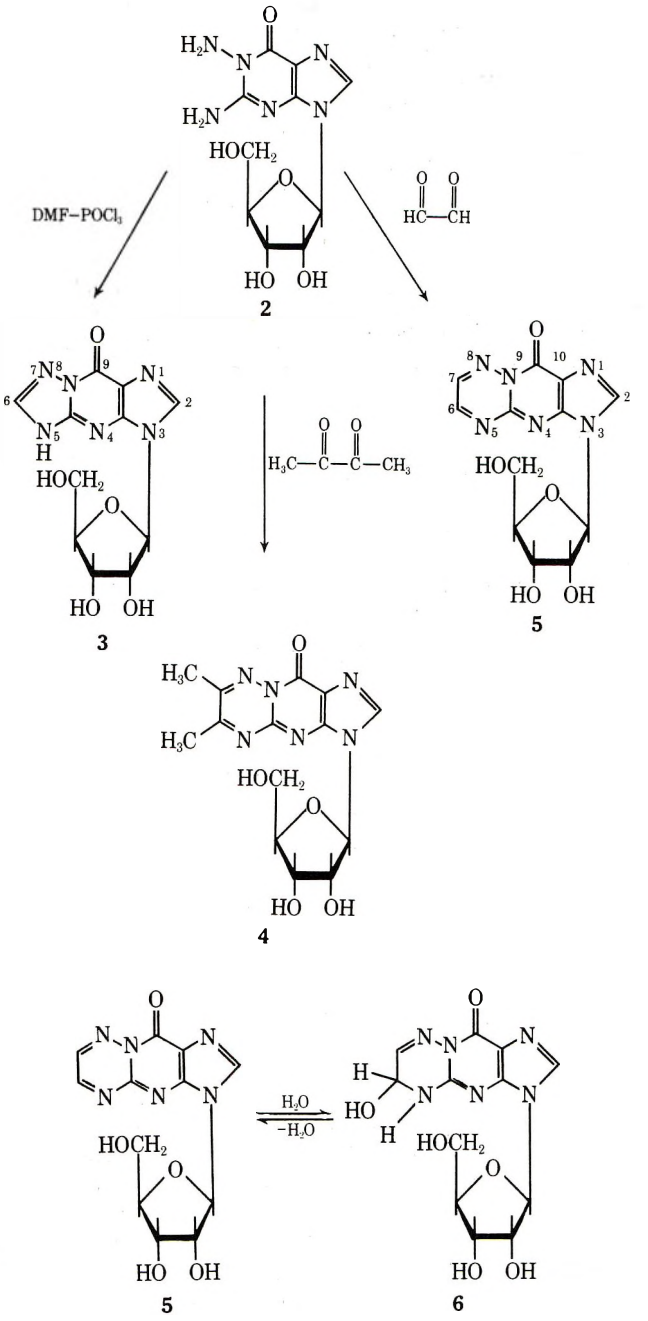
Figure 1. Pmr spectrum in $(CD_3)_2SO$ of 10-oxo-3-β-D-ribofuranosyl-1,2,4-triazino[2,3-a]purine (**5**) and its covalent hydrate (**6**). For details of interpretation see text.

(Table II). The H-8 proton of a purine nucleoside is known to undergo facile exchange upon heating in D_2O.[11] Attempts to assign the base protons of **3** using this method failed because the two carbon-bound protons showed similar rates of exchange. Nuclear Overhauser enhancement of pmr signals of specific protons arising from saturation of the spin of a proton in close physical proximity has been used in studies of conformation of purine and pyrimidine nucleosides.[12] Application of this technique permitted a facile assignment of the H-2 and H-6 signals of **3**. Irradiation of the H-1′ signal led to a 14% enhancement of the signal at δ 8.10, whereas the signal at δ 8.60 showed an enhancement of only 5%. Examination of molecular models reveals that, regardless of conformation, H-1′ must be in closer proximity to H-2 than H-6. This permits the assignment of the enhanced signal at δ 8.10 to H-2 and that of the nearly unchanged signal at δ 8.60 to H-6.

The pmr data for **4** (Table II) are also in complete accord with the proposed structure. The H-2 proton of **4** in $(CD_3)_2SO$ solution appears as a sharp singlet at δ 8.36. The remarkable consistency of successive downfield shifts of the imidazole proton and the sugar H-1′ in the series **4** ≅ **5** > **3** > **2** is worthy of note (Table II). The marked deshielding effect on protons distant from the actual site of ring closure may be attributed to an increase in the ring current of the molecule and suggests further that fusion of a six-membered ring (compounds **4** and **5**) to a purine enhances the imidazole ring current to a greater extent than fusion of a five-membered ring (compound **3**).

The pmr spectrum of **5** in $(CD_3)_2SO$ was quite complex and suggestive of the presence of two compounds in solution. In D_2O solution, however, a greatly simplified spectrum satisfying the requirements for a single covalent monohydrate of **5** (compound **6**) was obtained. The salient

Scheme I



features of the pmr spectrum of **6** (Table II) include a sharp singlet for H-2 (δ 7.91), a pair of doublets at δ 7.64 (H-7, "sp^2" type proton) and 5.41 (H-6, methine proton), and a doublet at δ 5.79 corresponding to H-1′. The spectrum in $(CD_3)_2SO$ (Figure 1), in addition to signals corresponding to those described above, contains an additional signal and coupling from the 6-OH proton and a broad signal from the 5-NH. A new set of signals corresponding to the anhydrous compound **5** is observed, including a singlet at δ 8.46 (H-2), a doublet at δ 5.96 (H-1′), and a pair of doublets ($J_{6,7}$ = 1.4 Hz) at δ 8.67 and 8.85 corresponding to the two triazine protons. Unequivocal assignment of the proton signals to the respective molecules was made possible by comparison of the integral values; typically, the ratio of **6** to **5** in $(CD_3)_2SO$ solution was 7:2. The position of hydration was shown by the pmr data cited above to occur across a C=N bond in the triazine ring; the assignment of the 5,6 double bond was made by analogy with recent work in which the 1,2,4-triazine system was shown to undergo covalent hydration at the analogous 4,5 double bond.[13]

Table II
Pmr Frequencies, δ, in $(CD_3)_2SO$ (DSS)

Compd	H_2[a]	H_1'	H_8	H_7	Others
2	7.80 (s)	5.62 (d) $J_{1',2'}$ = 5.7 Hz			6.79 (b) NH_2
3	8.10 (s)	5.77 (d) $J_{1',2'}$ = 5.4 Hz	8.60 (s)		
4	8.36 (s)	5.90 (d) $J_{1',2'}$ = 5.3 Hz			2.59 CH_3 (s) 2.65 CH_3 (s)
4[b]	8.19 (s)	5.90 (d) $J_{1',2'}$ = 5.1 Hz			2.66 CH_3(s) 2.71 CH_3 (s)
5	8.46 (s)	5.96 (d) $J_{1',2'}$ = 5.6 Hz	8.67 (d) $J_{6,7}$ = 1.4 Hz	8.85 (d)	
6	7.94 (s)	5.69 (d) $J_{1',2'}$ = 5.6 Hz	~5.4 (m)[c]	7.59 (d) $J_{6,7}$ = 2.7 Hz	6.77 (d) 6-OH $J_{6H,6OH}$ = 8 Hz 9.22 (b) 5-NH
6[d]	7.91 (s)	5.79 (d) $J_{1',2'}$ = 5.6 Hz	5.41 (d) $J_{6,7}$ = 3.0 Hz	7.64 (d)	

[a] H_8 of purine listed under H_2 for comparison. [b] Solvent D_2O. [c] Obscured by sugar OH protons. [d] Solvent D_2O–$(CD_3)_2SO$ (4:1 v/v).

Fluorescence Studies. A detailed examination of the fluorescence properties of these molecules was not undertaken. Examination of the emission maxima of aqueous solutions of **2**, **3**, and **4**, however, revealed that concentrations of 3×10^{-5} *M* gave measurable emissions at 450 nm with an exciting wavelength of 285 nm for **3** and 540 nm (exciting wavelength 360 nm) for **4** compared with an emission at 370 nm (excitation 285 nm) for **2**. The emission maxima observed for **3** and **4** are far from those observed for purines in general,[14] and are reminiscent of those of the "Y" base.[15]

Experimental Section

Elemental analyses were performed by Heterocyclic Chemical Corp., Harrisonville, Mo. Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. Uv spectra were obtained using a Cary Model 15 spectrometer. Uncorrected fluorescent spectra were obtained using an Aminco-Bowman spectrofluorometer. Pmr spectra were obtained with Jeolco C6OH spectrometer at ambient temperature. NOE experiments were run in frequency sweep mode. H-6 and H-2 peak areas were measured using the integrator when H_1' was decoupled and undecoupled. Each reported area was the average of ten measurements.

5*H*(7*H*)-9-Oxo-3-β-D-ribofuranosyl-1,2,4-triazolo[2,3-*a*]purine (3). 1-Aminoguanosine[5] (**2**, 500 mg, 1.68 mmol), 10 ml of DMF, and 0.5 ml of $POCl_3$ were stirred at room temperature for 3 hr. The white precipitate was filtered, then dissolved in 20 ml of hot EtOH–H_2O (9:1), filtered, and cooled at 5° overnight to give 345 mg (67%) of white crystals. Recrystallization twice from hot water gave an analytical sample, mp 300°.

Anal. Calcd for $C_{11}H_{12}N_6O_5 \cdot 0.5H_2O$: C, 41.6; H, 4.12; N, 26.5. Found: C, 41.5 H, 3.91; N, 26.4.

6,7-Dimethyl-10-oxo-3-β-D-ribofuranosyl-1,2,4-triazino[2,3-*a*]purine (4). To a suspension of **2** (750 mg, 2.5 mmol) in 300 ml of 70% aqueous ethanol was added 2,3-butanedione (1.5 ml, 15 mmol) and 3.75 ml of 0.1 *N* HCl. The suspension was stirred for 10 days at room temperature (a yellow solution resulted after 1 day). The solution was evaporated *in vacuo* and coevaporated with three 100-ml portions of ethanol. The yellow crystals were recrystallized from ethanol to give 537 mg (60%), mp 169–171° dec.

Anal. Calcd for $C_{14}H_{16}N_6O_5 \cdot 0.5H_2O$: C, 47.1; H, 4.79; N, 23.5. Found: C, 47.1; H, 5.00; N, 23.5.

5,6-Dihydro-6-hydroxy-10-oxo-3-β-D-ribofuranosyl-1,2,4-triazino[2,3-*a*]purine (6). To a solution of glyoxal, prepared by refluxing glyoxal trimer (500 mg, 2.9 mmol) in 100 ml of H_2O for 30 min, was slowly added **2** (500 mg, 1.68 mmol) in 100 ml of hot H_2O. The solution was stirred at 50° for 1 hr, then placed on a column of Dowex IR-120 (H^+ form, 100 ml). The column was washed with 2 l. of water. The resin was placed in a beaker and adjusted to pH 6 with NH_4HCO_3 solution, filtered, and washed twice with H_2O and the yellow filtrate was evaporated *in vacuo* to dryness (bath at 30°). The yellow residue was dissolved in 200 ml of H_2O and lyophilized to give 370 mg (60%), mp 180° dec, softens at 110°.

Anal. Calcd for $C_{12}H_{14}N_6O_6 \cdot 1.5H_2O$: C, 39.5; H, 4.69; H, 23.0. Found: C, 39.5; H, 4.75; N, 22.7.

Registry No.—**2**, 19039-33-9; **3**, 50585-21-2; **4**, 50585-22-3; **5**, 50585-23-4; **6**, 50585-24-5.

References and Notes

(1) (a) Supported in part by Training Grant CA 5209 from the National Cancer Institute, NIH. (b) Presented in part at the Fourth International Congress of Heterocyclic Chemistry, Salt Lake City, Utah, July 1973. (c) Fellow of the American Foundation for Pharmaceutical Education.
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Synthesis and Photochemical Decomposition of Some Substituted 1,2-, 1,2,3-, and 1,2,4-Azafulvenes

Edward M. Burgess* and Joseph P. Sanchez

School of Chemistry, Georgia Institute of Technology, Atlanta, Georgia 30322

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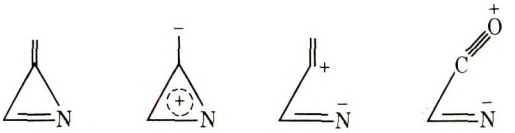
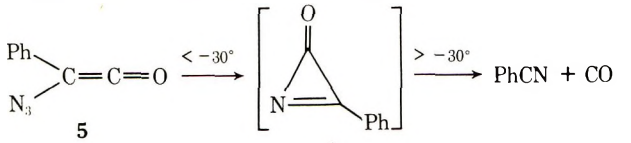
A series of phenylpyrazole and -triazole diphenylcarbinols have been converted to the hydrochloride salts of the carbinyl chlorides and thence to the corresponding azafulvenes by dehydrohalogenation with triethylamine at −78°. Irradiation of the triazafulvenes at this temperature gave a mixture of isolable products which implicate azatriafulvene and azete as possible unstable precursors. The latter intermediate may also be involved in the photochemical decomposition of triphenyltriazine, which was also examined. The diazafulvenes prepared proved isolable but photochemically inert.

Continuation of our studies on the potential synthesis of small-ring heterocycles by photochemical expulsion of a stable fragment such as nitrogen from a suitable larger-membered ring precursor has led us to examine the photochemistry of some substituted di- and triazafulvenes.[1] From initial mechanistic speculation one could envision the fragmentation of heterofulvenes with a contiguous triaza function as an entry into the class of theoretically interesting azatrifulvenes, **1**. Such systems would suffer a destabilizing electrostatic effect from the heterosubstitution in the charge-separated resonance contributor, **2**, but be more stable toward thermal fragmentation if the required (orbital symmetry) intermediate, **3**, is considered relative to an azirinone-derived model (**4**).



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

In fact, a synthetic effort directed toward the synthesis of **6** *via* the azidoketene **5** gave only benzonitrile and carbon monoxide.[2] Presently, we wish to describe the details



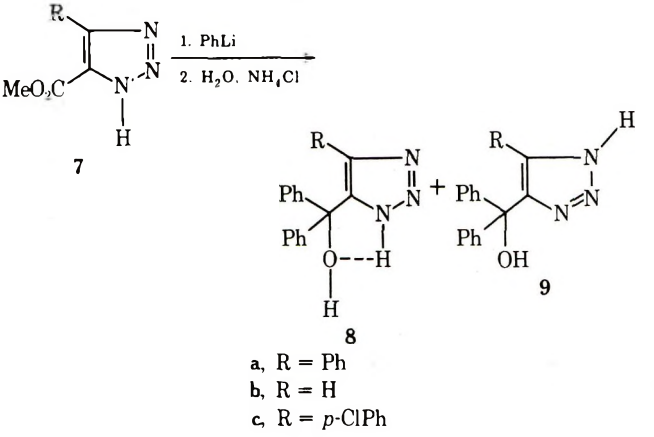
5 **6**

of the synthesis and photochemical reactions of some 1,2-, 1,2,3-, and 1,2,4-azafulvenes.

Results and Discussion

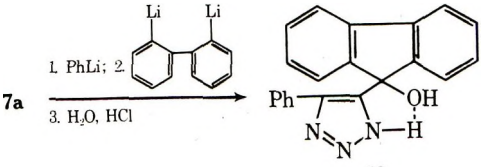
Recent synthetic efforts in the area of heterofulvenes have been successful in the construction of 1,4-diazafulvenes *via* dehydrohalogenation[3] of substituted 2-chloromethylimidazolium chlorides or oxidation[4] of *p*-4,5-diphenyl-2-imidazolylphenol and azafulvenes by analogous reactions with suitable pyrrole precursors.[5] The azafulvenes prepared in this study were derived from the appropriate chlorodiphenylmethylazole hydrochloride salts by deprotonation and dehydrohalogenation with triethylamine.

Synthesis of 1,2,3- and 1,2,4-Triazafulvenes. The addition of phenyllithium to methyl 4-phenyl-1,2,3-triazole-5-carboxylate[6] (**7a**), ethyl 1,2,3-triazole-5-carboxylate[7] (**7b**), or methyl 4-(*p*-chlorophenyl)-1,2,3-triazole-5-carboxylate (**7c**) followed by hydrolysis gave the carbinols **8a–c** and **9a**. The precursor **7a** was prepared by the addition of sodium azide to methyl *p*-chlorophenylpropiolate[8] in DMF at 30°. The fluorenol derivative **10** resulted from the action of *o,o'*-dilithiobiphenyl[9] on the lithium salt of **7a** in



7 **8** **9**

a, R = Ph
b, R = H
c, R = *p*-ClPh



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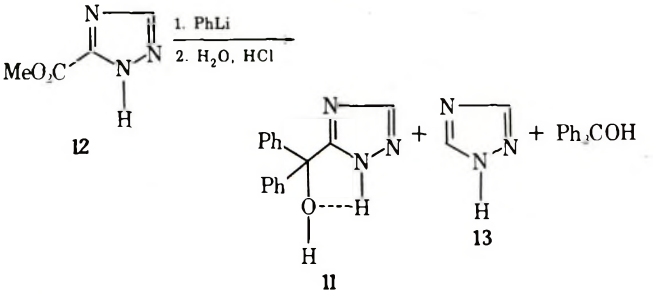
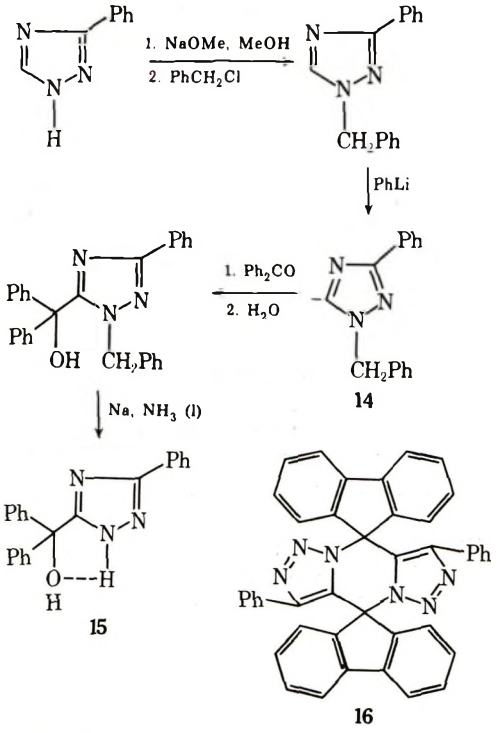
ether solution. In the 1,2,4-triazole system, the synthesis of carbinol **11** *via* addition of phenyllithium to methyl 1,2,4-triazole-3-carboxylate[10] (**12**) was complicated by a



12 **11** **13**

competing retro-aldol reaction which gave **13** and triphenylcarbinol. The corresponding 3-phenyl derivative, **15**, resulted from the addition of the 1-benzyl-3-phenyl-1,2,4-triazolyl anion,[11] **14**, to benzophenone followed by reductive debenzylation. The requisite chlorodiphenylmethylazole hydrochloride salts were obtained in high yield from treatment of carbinols **8a**, **8b**, **8c**, **11**, and **15** with thionyl chloride in benzene at 30°. On the other hand, the reaction of **10** with this reagent gave a dimer ($C_{42}H_{26}N_6$) whose spectral display and observed facile acid-catalyzed hydrolysis to **10** suggests a structural assignment of **16**. It is not known if such a transformation involves an antiaromatic azafulvalene intermediate, although a similar dehydration-dimerization reaction product has been reported in the case of α,α-diphenyltetrazole-5-methanol.[12]

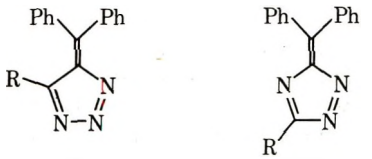


14

15

16

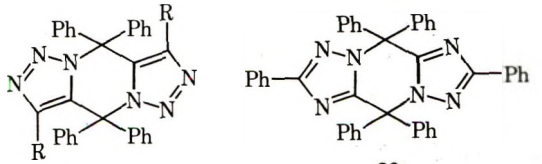
All of the above salts smoothly underwent dehydrohalogenation in the presence of triethylamine in THF–benzene (1:1) at −78° to afford solutions of the fulvenes **17** and **18**. However, the color of solutions of **17a** and **18a** at this temperature began to fade rapidly and further exploration of the chemistry of these fulvenes was thus abandoned.



17 18

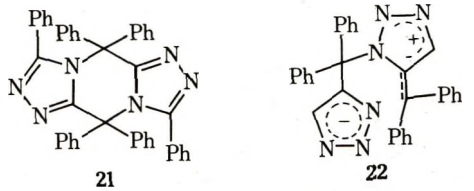
a, R = H
b, R = Ph
c, R = *p*-ClPh

17b, **17c**, and **18b** were stable in this solvent combination for >8 hr at −78° and exhibited λ_{max} at 463, 454, and 442 nm, respectively. Fulvenes **17b** and **18b** at −78° reacted slowly with methanol to give the subsequently characterized (methoxydiphenylmethyl)phenylazoles while **17b** rapidly provided the corresponding tertiary amine with piperidine at this temperature. If allowed to warm to 30° in solution, these fulvenes dimerized to give the photochemically inert 4*H*,10*H*-ditriazolo[1,2-*a*:1′,2′-*d*]pyrazines **19** and **20** or **21**, a decision between the latter two structures not being possible with the available spectral information.[13] A strong dependence of the rate of dimerization



19a, R = Ph
b, R = *p*-ClPh

20



21 22

Table I
Approximate Fulvene Lifetimes in Various Solvents (0.01 *M*) at −78° As Determined by Uv Absorption (Except for 17a)

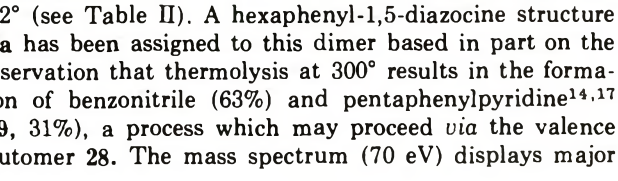
Fulvene	$\sim t_{1/2}$, min	Solvent
17a	<1	THF
17b	20	THF–MeCN (2:1)
	250	THF
	>500	THF–PhH (1:1)
18a	15	THF
18b	>500	THF–PhH (1:1)

Table II
Photoproduct Distribution

	Conversion, %					
Fulvene	23 and 24	25	26	27	30	Total
17b	50	7	11	26		94
18b	48	11	17	12	8	96
17c	67	14	7	5		93

on the solvent polarity was exhibited by both **17** and **18** and the 1,2,4-azafulvene system appeared to have a greater lifetime than its 1,2,3 congener in this respect (Table I). Since thermal [6 + 6] concerted cycloadditions occur in an unfavorable antarafacial manner, it may be assumed that this solvent effect is a result of stabilization of a transition state leading to a dipolar intermediate such as **22** in a nonconcerted dimerization. With regard to the observed stability differential between **17** and **18** with similar substitution, HMO theory reveals a greater π-charge density at position 1,4 relative to 2,3 in the highest occupied molecular orbital of the reference nonalternant hydrocarbon, fulvene, and one would therefore expect heteroatom replacement at 1,4 to be more effective than at 2,3 in increasing resonance energy.

Photolysis of 1,2,3- and 1,2,4-Triazafulvenes. Irradiation (Pyrex) of 0.025 *M* THF–benzene (1:1) solutions of either **17b** or **18b** at −78° resulted in the slow (4–5 hr) evolution of nitrogen and formation of a chromatographically separable mixture of benzonitrile (**23a**),[14] diphenylacetylene (**24**)[14] triphenylacrylonitrile (**25a**),[14,15] and 2,3-diphenylquinoline (**26a**)[14,16] in addition to a yellow, crystalline dimer (**27a**) of constitution $(C_{21}H_{15}N)_2$, mp 230–232° (see Table II). A hexaphenyl-1,5-diazocine structure **27a** has been assigned to this dimer based in part on the observation that thermolysis at 300° results in the formation of benzonitrile (63%) and pentaphenylpyridine[14,17] (**29**, 31%), a process which may proceed *via* the valence tautomer **28**. The mass spectrum (70 eV) displays major



27a, R = Ph
b, R = *p*-ClPh

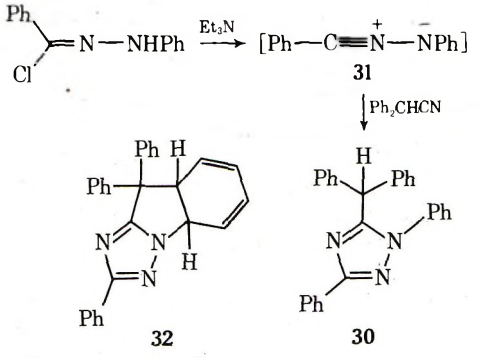
28 29

ions of *m*/e (rel intensity) 562 (100); M^+, 485 (10); M^+ − Ph, 459 (26); M^+ − PhCN, 383 (27); M^+ − PhCN − Ph, 281 (10); $M^+/2$ with a prominent doubly charged ion at 281.5 corresponding to MH^{2+}. This fragmentation parallels that reported for azocine[18] and 1,2-diazocine,[19] where mass spectral loss of HCN is a highly probable event (93 and 100%, respectively). The λ_{max} in EtOH occurred at 258 nm (ϵ 42,150) and showed a bathochromic shift to 263 nm (ϵ 37,000) in dilute ethanolic HCl and the reversible formation of a stable cation in 98% H_2SO_4 with λ_{max} 618

nm, the latter having possibly a diazabicyclo[5.1.0]octadienyl structure.[20]

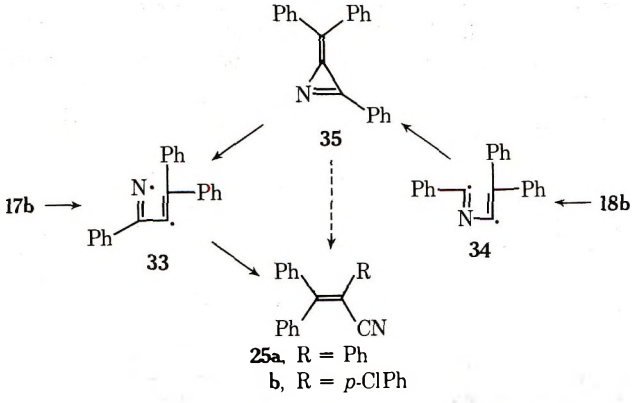
The photolysis of the *p*-chlorophenylfulvene **17c** under identical conditions afforded a mixture of *p*-chlorobenzonitrile (**23ab**), diphenylacetylene (**24**), 1-(*p*-chlorophenyl)-2,2-diphenylacrylonitrile[14,21] (**25b**), 2-(*p*-chlorophenyl)-3-phenylquinoline[14,22] (**26b**), and an analogous diazocine (**27b**), mp 243–244°. The latter compound had a mass spectrum (70 eV) of major ions at *m/e* (rel intensity) 634 (21); M^+ ($^{37}Cl_2$), 633 (38), 632 (82); M^+ ($^{37}Cl,^{35}Cl$), 631 (60), 630 (100); M^+ ($^{35}Cl_2$), 527 (12); M^+ − PhCN, 493 (16); M^+ − ClPhCN, 452 (13); M^+ − PhC_2Ph, 417 (46), M^+ − $ClPhC_2Ph$ in which the small but competitive loss of a nitrile *vs.* acetylene fragment is in contrast with that observed for **27a**. A hypsochromic effect of the chloro substituents on the various ultraviolet absorption maxima when compared to **27a** is apparent from the observation λ_{max} (EtOH) 247 nm (ϵ 36,750), λ_{max} (HCl–EtOH) 263 nm (ϵ 19,160), and λ_{max} (H_2SO_4) 525 nm.

Finally, 1,3-diphenyl-5-diphenylmethyl-1,2,4-triazole (**30**) was isolated from the photolysis of **18b** and identified by comparison with the product resulting from the addition of nitrile ylide[23] **31** to diphenylacetonitrile. A possible excited-state [$_\pi6_s$ + $_\pi6_s$] combination of **18b** with benzene to give **32** followed by an appropriate 1,3 shift and tautomerization may offer a suitable mechanistic rationalization for this product.



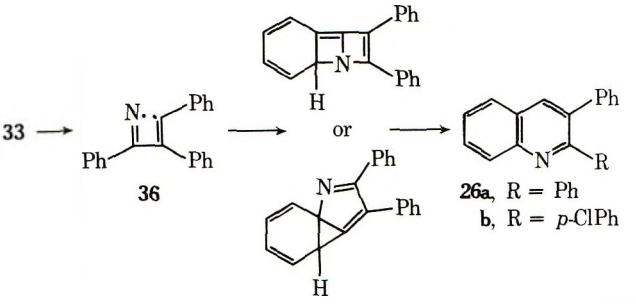
32 30

Mechanistic Considerations. The genesis of benzonitrile (or the *p*-chloro analog) and diphenylacetylene from initial fragmentation of the diradicals **33** and **34**, derived by photochemical loss of nitrogen from the respective fulvenes, and the rearrangement of **33** by a 1,2-phenyl shift[24] to a triphenylacrylonitrile are easily visualized. However,



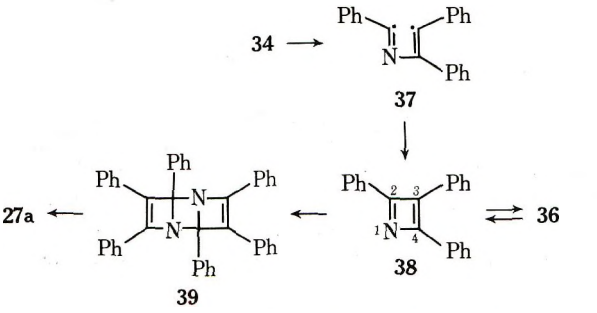
25a, R = Ph
b, R = *p*-ClPh

the conversion of **34** to **25** represents a substantial degree of bond reorganization and the most *direct* mechanistic pathway possible would seem to require the azatrifulvene **35** as an intermediate. The C–N bond cleavage necessary for the transformation of **35** to **25** *via* **33** has precedence derived from observations[24] on azirine thermal decomposition products.[25] The appearance of **26** as a common photoproduct seems to be the result of a 1,2-phenyl shift in **33** to give **36** followed by an appropriate cyclization and aromatization. However, the transformation of **34** to **36** may



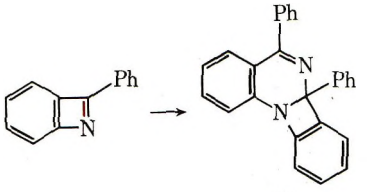
36 26a, R = Ph
b, R = *p*-ClPh

not involve **35** but rather proceed *via* **37** to an intermediate triphenylazete (**38**) which then rearranges to **26a**, an argument which demands that the azete once formed always undergoes 1,2-bond cleavage (as opposed to the 3,4 alternative) in such a rearrangement. Such a proposal has the additional attractive feature that the origin of the diazocine **27a** may be viewed as a result of thermal electrocyclic ring opening[26] of a [$_\pi2_s$ + $_\pi4_s$] dimerization product **39** derived from **38**. Although the dimerization of **38** to give



37 38 39

ultimately a symmetrical diazocine could result from a 2,3-face combination, the proposed formation of a dimer with angular heteroatom sites is consistent with that recently observed for the dimerization of the benzoazete to **40**.[27] It is interesting to note that only one dimer results



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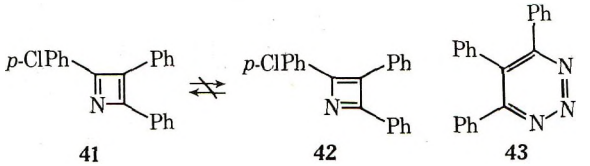
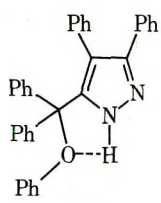
from the photolysis of **17c**, which may imply that the isomerization **41** ⇄ **42** is not occurring.

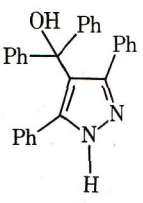


41 42 43

Support for the hypothesis that an intermediate such as **38** can lead to both **26** and **27** was received from our reexamination[28] of the photochemistry of triphenyl-*v*-triazine (**43**). Irradiation (Pyrex) of this latter triazine in benzene–THF (1:1) solution (0.025 *M*) at 30° for 5 hr gave, in addition to the previously reported benzonitrile and diphenylacetylene, both **27a** and **26a** (see Table II).

Synthesis of 1,2- and 2,3-Diazafulvenes. The addition of phenyllithium to methyl 3,4-diphenylpyrazole-5-carboxylate,[29] methyl 3,5-diphenylpyrazole-4-carboxylate,[30] and methyl 3,4-diphenylenepyrazole-5-carboxylate[31] followed by hydrolysis provided the requisite carbinols **44**, **45**, and **46**, whose conversions to the corresponding chlorodiphen-


44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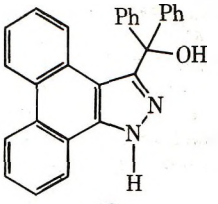
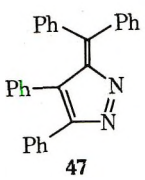
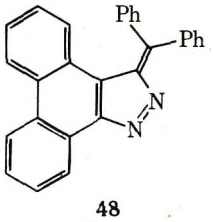
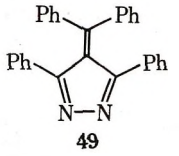

46

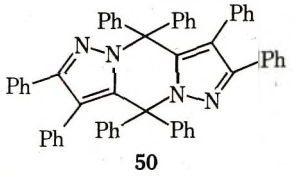
ylpyrazole hydrochlorides with thionyl chloride in benzene at 30° was unexceptional. Dehydrohalogenation of these salts with triethylamine in THF at −78° gave solutions of the corresponding fulvenes **47**, **48**, and **49** from which **47** and **49** could be isolated as stable, red, crystalline solids


47


48


49

at room temperature. Diazafulvenes **47** and **49** displayed a λ_{max} (THF) at 393 and 382 nm, respectively, and both had similar mass spectral ions at *m/e* 385 ($M^+ + 1$), 384 (M^+), and 307 ($M^+ - C_6H_5$). While **49** appeared to be stable at its melting temperature of 155–156°, **47** in the solid state at 120–130° underwent dimerization to give **50**, mp 179–181°. Similarily, a 0.003 *M* solution of **47** in THF–benzene (1:1) upon photolysis (quartz) at 5° for 20 min gave **50** in high yield, while **49** was inert under these


50

conditions. Irradiation (Pyrex) of a THF–benzene (1:1) solution of **48** at −78° led to disappearance of the fulvene in 20 min with no gas evolution, but attempts to isolate the dimer in this case failed and only **46** was obtained.

Experimental Section[32]

5(4),α,α-Triphenyl-1,2,3-triazole-4(5)-methanol (8a). A solution of phenyllithium (0.573 mol) was prepared by the addition of 90 g (0.573 mol) of bromobenzene in 100 ml of anhydrous ether to 7.9 g (1.40 mol) of lithium ribbon (containing 1% sodium metal) in 400 ml of anhydrous ether. The solution, under a positive nitrogen atmosphere, was chilled to −78° and 37.5 g (0.185 mol) of methyl 4-phenyl-1,2,3-triazole-5-carboxylate[6] was added portionwise as a solid. The mixture was allowed to warm to room temperature, then refluxed for 18 hr, cooled, and decomposed using 150 ml of 5% aqueous hydrochloric acid. A fluffy white precipitate formed, which was collected by filtration and dried *in vacuo* to yield 21 g (35%) of **8a**, mp 218–221° dec. A sample recrystallized from benzene–ethanol melted at 220–221° dec: ir (KBr) 3300 cm^{-1} (broad OH and NH); nmr (DMSO-d_6) δ 7.83–6.92 (m, 15 H); mass spectrum (70 eV) *m/e* (rel intensity) 327 (100), 281 (67).

Anal. Calcd for $C_{21}H_{17}N_3O$: C, 77.04; H, 5.23; N, 12.84. Found: C, 77.19; H, 5.33; N, 12.84.

4(5),α,α-Triphenyl-1,2,3-triazole-5(4)-methanol (9a). The organic layer of the above filtrate was separated, washed with water, and dried ($MgSO_4$), and the solvent was evaporated *in vacuo*. Upon diluting with pentane a fluffy white solid separated which was collected by filtration and dried to give 32 g (53%) of **9a**, mp 158–169° dec. Recrystallization from benzene twice afforded an analytical sample of **9a**: mp 159–160° dec; ir (KBr) 3320 (OH) and 3190 cm^{-1} (NH); nmr (DMSO-d_6) δ 7.70–6.82 (m, 15 H); mass spectrum (70 eV) *m/e* (rel intensity) 327 (100), 281 (23), and 250 (100).

Anal. Calcd for $C_{21}H_{17}N_3O$: C, 77.04; H, 5.23; N, 12.84. Found: C, 77.16; H, 5.36; N, 12.85.

Methyl 4-*p*-Chlorophenyl-1,2,3-triazole-5-carboxylate (7c). To a suspension of 13 g (0.2 mol) of sodium azide in 175 ml of dimethylformamide at room temperature was added dropwise a solution of 39 g (0.2 mol) of methyl *p*-chlorphenylpropiolate[33] in 50 ml of dimethylformamide. The addition was slightly exothermic (38°) and after it was complete (1 hr) the mixture was stirred for 18 hr at 30°. The solvent was removed *in vacuo*, and the residue was dissolved in 550 ml of water and washed with ether. The water layer was acidified with concentrated hydrochloric acid, extracted with ether, dried ($MgSO_4$), and filtered and the solvent was evaporated *in vacuo* to give 44 g (92%) of **7c**, mp 167–168°. Two recrystallizations from ethanol afforded an analytical sample: mp 170–171°; ir ($CHCl_3$) 3120 (NH), 1730 (C=O), 1140, 1098, 1015, and 838 cm^{-1}; nmr (DMSO-d_6) δ 8.08–7.42 (m, 4 H), 3.88 (s, 3 H); mass spectrum (70 eV) *m/e* (rel intensity) 239 (35), 237 (100), 208 (28), and 206 (79).

Anal. Calcd for $C_{10}H_8ClN_3O_2$: C, 50.54; H, 3.39; N, 17.58. Found: C, 50.71; H, 3.47; N, 17.57.

4(5)-*p*-Chlorophenyl-α,α-diphenyl-1,2,3-triazole-5(4)-methanol (8c). To a solution of phenyllithium (0.31 mol, prepared as above) in 300 ml of ether was added 23.8 g (0.1 mol) of the solid ester **7c** portionwise. After the initial exothermic reaction ceased, the mixture was refluxed for 18 hr and decomposed using 125 ml of 5% aqueous hydrochloric acid. After the layers were separated, the organic layer was washed with water, dried ($MgSO_4$), and filtered and the solvent was evaporated *in vacuo* to give 33.6 g (96%) of **8c**, mp 172–175°. An analytical sample was obtained upon recrystallization once from ethanol and once from benzene: mp 174–175°; ir ($CHCl_3$) 3420 (OH), 3170 (NH), 1492 (C=C), 1448 (C=C), 1095, 1010, 840, and 704 cm^{-1}; nmr (DMSO-d_6) δ 7.79–6.93 (m, 14 H); mass spectrum (70 eV) *m/e* (rel intensity) 363 (29), 361 (64), 317 (10), 315 (18), 286 (28), and 284 (100).

Anal. Calcd for $C_{21}H_{16}ClN_3O$: C, 69.71; H, 4.46; N, 11.61. Found: C, 69.59; H, 4.54; N, 11.63.

α,α-Diphenyl-1,2,3-triazole-4(5)-methanol (8b). A solution of phenyllithium (0.35 mol, prepared as above) in 400 ml of anhydrous ether was cooled to 5° and 13 g (0.093 mol) of solid ethyl 1,2,3-triazole-4(5)-carboxylate[7] was added portionwise. The mixture was refluxed for 18 hr and decomposed using 125 ml of saturated aqueous ammonium chloride solution. The ether layer was washed with water, dried ($MgSO_4$), and filtered and the solvent was evaporated *in vacuo* to give 20.5 g (88%) of 8b, mp 184–186°. One recrystallization from benzene afforded an analytical sample: mp 185–186°; ir (KBr) 3277 (OH), 3178 (NH), 1658 (C=N), 1450 (C=C), 1123, 856, and 701 cm^{-1}; nmr (DMSO-d_6) δ 7.61 (s, 1 H) and 7.52–7.04 (m, 10 H); mass spectrum (70 eV) *m/e* (rel intensity) 251 (50), 174 (100), 105 (57), and 96 (68).

Anal. Calcd for $C_{15}H_{13}N_3O$: C, 71.69; H, 5.21; N, 16.72. Found: C, 71.59; H, 5.27; N, 16.53.

5(4)-(9-Hydroxy-9-fluorene)-4(5)-phenyl-1,2,3-triazole (10). To a stirred solution of 0.034 mol of *o,o'*-dilithiobiphenyl[9] in 100 ml of anhydrous ether was added 0.034 mol of the lithium anion of methyl 4-phenyl-1,2,3-triazole-5-carboxylate[6] as an ether suspension. This was prepared by the addition of 20.4 ml (0.034 mol) of phenyllithium (1.66 *M*) to a solution of 6.9 g (0.034 mol) of the ester in 50 ml of anhydrous ether. After this suspension had been added, the mixture was refluxed for 18 hr and then decomposed using 5% aqueous hydrochloric acid (125 ml). The organic layer was washed with water (2 × 50 ml), dried ($MgSO_4$), and filtered and the solvent was evaporated *in vacuo*, yielding 6.2 g (56%) of **10**, mp 216–219°. Two recrystallizations from ether–pentane afforded an analytical sample: mp 219–220°; ir (KBr) 3210 cm^{-1} (NH and OH, broad); nmr (DMSO-d_6) δ 7.87–6.48 (m, 13 H); mass spectrum (70 eV) *m/e* (rel intensity) 325 (40), 181 (54), and 152 (100).

Anal. Calcd for $C_{21}H_{15}N_3O$: C, 77.52; H, 4.65; N, 12.92. Found: C, 77.35; H, 4.75; N, 12.83.

α,α-Diphenyl-1,2,4-triazole-3(5)-methanol (11). A solution of phenyllithium (1.0 mol, prepared as above) in 1 l. of ether was chilled in an ice bath to 5° and 38.1 g (0.3 mol) of solid methyl 1,2,4-triazole-3-carboxylate (**10**) was added portionwise under a positive nitrogen atmosphere. The mixture was allowed to come to 30° and then refluxed for 18 hr. The reaction mixture was then decomposed by the addition of 250 ml of saturated aqueous ammonium chloride solution to yield a heavy precipitate, which was removed by filtration and dried *in vacuo* to give 32 g (42%) of **11**, mp 215–218°. From the filtrate, the organic layer was washed with water, dried ($MgSO_4$), and filtered and the solvent was evaporated *in vacuo* to give 11 g of triphenylcarbinol, mp 154–156°.[14] The water layers were combined and neutralized with aqueous hydrochloric acid to pH 7, after which the crystals formed were

removed by filtration to give an additional 18 g (24%) of **11**, mp 218–220°. These two crops were combined and recrystallized from benzene to give a total of 47 g (62%) of **11**, mp 221–223°. An analytical sample was obtained by recrystallization from benzene: mp 222–223°; ir (KBr) 3380 (NH) and 3150 cm^{-1} (OH); nmr (DMSO-d_6) δ 8.28 (s, 1 H) and 7.82–7.03 (m, 10 H); mass spectrum (70 eV) *m/e* (rel intensity) 251 (100), 233 (44), 174 (80), 105 (51), and 96 (38).

Anal. Calcd for $C_{15}H_{13}N_3O$: C, 71.69; H, 5.21; N, 16.72. Found: C, 71.79; H, 5.26; N, 16.63.

1-Benzyl-3-phenyl-1,2,4-triazole (14). To a magnetically stirred solution of 26.5 g (0.39 mol) of sodium ethoxide in 100 ml of ethanol was added portionwise 50.8 g (0.35 mol) of 3-phenyl-1,2,4-triazole.[11] The mixture was stirred for 5 min and 66.7 g (0.525 mol) of freshly distilled benzyl chloride was added. The reaction mixture was refluxed for 1 hr and then stirred at 30° for an additional 18 hr. The sodium chloride formed was removed by filtration and the filtrate was concentrated *in vacuo*, yielding an oily suspension of crystals. The oil was decanted and the solid was crystallized from toluene–pentane to give 41 g (50%) of **14**, mp 100–102°. A second crop crystallized from the oil and was removed by filtration, affording an additional 13 g (16%) of **14**, mp 98–100°. Recrystallization from toluene–pentane gave an analytical sample: mp 101–102°; ir ($CHCl_3$) 2987 (CH), 1496 (C=C), 1440 (C=C), and 695 cm^{-1}; nmr ($CDCl_3$) δ 8.32–8.03 (m, 2 H), 7.94 (s, 1 H), 7.53–7.00 (m, 8 H), and 5.17 (s, 2 H); mass spectrum (70 eV) *m/e* (rel intensity) 235 (100) and 91 (66).

Anal. Calcd for $C_{15}H_{13}N_3$: C, 76.57; H, 5.57; N, 17.86. Found: C, 76.54; H, 5.60; N, 17.92.

1-Benzyl-3,α,α-triphenyl-1,2,4-triazole-5-methanol. A solution of phenyllithium (0.25 mol, prepared as above) in 200 ml of anhydrous ether was cooled to −20° and treated over 1 hr with a solution of 52 g (0.22 mol) of **14** in 200 ml of tetrahydrofuran–anhydrous ether (1:1 v/v). The mixture was stirred for 2 hr without external cooling and a solution of 41.9 g (0.23 mol) of benzophenone in 100 ml of tetrahydrofuran was added dropwise over 1 hr. After stirring for 18 hr at 30°, water (300 ml) was added dropwise and the resulting layers were separated. The organic layer was washed with water (2 × 50 ml), dried ($MgSO_4$), and filtered and the solvent was evaporated *in vacuo* to give 49 g (53%) of the alcohol, mp 118–121°.

An analytical sample was obtained upon recrystallization from benzene: mp 120–122°; ir ($CHCl_3$) 3380 (OH), 3060, 3000, 1595, 1487, 1483, and 687 cm^{-1}; nmr (DMSO-d_6) δ 8.14–7.78 (m, 2 H), 7.67–6.88 (m, 18 H), and 5.47 (s, 2 H); mass spectrum (70 eV) *m/e* (rel intensity) 417 (21), 326 (10), 235 (100), 182 (84), 105 (79), 91 (90).

Anal. Calcd for $C_{28}H_{23}N_3O$: C, 80.55; H, 5.55; N, 10.07. Found: C, 80.62; H, 5.64; N, 10.08.

3(5),α,α-Triphenyl-1,2,4-triazole-5(3)-methanol (15). A stirred solution of 47 g (0.11 mol) of the above alcohol in 300 ml of liquid ammonia (−50°) was treated portionwise over 1.5 hr with 6.2 g (0.26 mol) of sodium metal. After the addition was complete, the reaction mixture was stirred for 2.5 hr and quenched by the addition of 15.5 g (0.29 mol) of solid ammonium chloride. The ammonia was allowed to evaporate and the residue was partitioned between ether and water. The ether layer was washed with water (2 × 100 ml), dried ($MgSO_4$), filtered, and concentrated to 50 ml on a steam bath. Upon diluting with pentane, a precipitate formed which was removed by filtration and dried *in vacuo* to give 21 g (58%) of **15**, mp 228–230° dec. The mother liquors were then evaporated to dryness to give an additional 16 g (34%). The carbinol **15** was recrystallized twice from toluene to afford an analytical sample: mp 232–233° dec; ir (KBr) 3043 (NH), 3263 (OH), 1490, 1468, 746, and 691 cm^{-1}; nmr (DMSO-d_6) δ 8.12–7.82 (m, 2 H) and 7.58–6.82 (m, 13 H); mass spectrum (70 eV) *m/e* (rel intensity) 327 (20), 310 (67), 209 (100), 281 (12), 250 (21), 182 (23), 178 (51), 105 (43) and 103 (44).

Anal. Calcd for $C_{21}H_{17}N_3O$: C, 77.04; H, 5.23; N, 12.84. Found: C, 77.22; H, 5.38; N, 12.89.

4(5)-Phenyl-5(4)-chlorodiphenylmethyl-1,2,3-triazole Hydrochloride. To a solution of 40 ml of thionyl chloride in 60 ml of benzene was added 21 g (0.095 mol) of the alcohol **8c**. The mixture was stirred for 3 hr at 30°, heated to reflux for 1 hr, and then stirred at 30° for 18 hr. Upon diluting with anhydrous ether a solid separated which was collected by filtration to give 24 g (66%) of the salt, mp 228–230° dec. An additional 9 g (24%), mp 222–226° dec, was recovered by evaporating the filtrate and diluting the residue with ether. A sample recrystallized from tetrahydrofuran–ether had mp 229–230° dec; ir (KBr) 3270, 2340, and 1852 (NH), 759 cm^{-1} (CCl); mass spectrum (70 eV) *m/e* (rel intensity 345 (7), 281 (100), 282 (100), 283 (89), and 204 (46).

Anal Calcd for $C_{21}H_{16}ClN_3 \cdot HCl$: C, 65.97; H, 4.48; N, 10.99. Found: C, 65.90; H, 4.40; N, 11.12.

5(4)-Chlorodiphenylmethyl-1,2,3-triazole Hydrochloride. To a stirred solution of 40 ml of thionyl chloride in 60 ml of benzene was added portionwise 24.5 g (0.097 mol) of the solid alcohol **8b**. The mixture was stirred for 1 hr at 30°, during which time complete solution occurred, followed by formation of a heavy precipitate. The reaction mixture was diluted with ether and the solid was removed by filtration and dried *in vacuo* to give 25.8 g (84%) of the salt, mp 136–140°. An analytically pure sample could not be prepared, as this salt was very hydroscopic: ir (KBr) 3310, 2560, and 1845 (NH^+), 1579 (C=N), 1483 (C=C), 1443 (C=C), 750 (CCl), and 698 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 233 (100), 205 (44), and 128 (24).

4(5)-*p*-Chlorophenyl-5(4)-chlorodiphenylmethyl-1,2,3-triazole Hydrochloride. To a solution of 15 ml of thionyl chloride in 30 ml of benzene was added 9.05 g (0.025 mol) of the alcohol **8c**. The mixture was stirred at 30° for 18 hr and then refluxed for 4 hr. Upon dilution with ether a precipitate formed which was removed by filtration and dried *in vacuo* to give 9.1 g (87%) of the salt, mp 245–248° dec. Two recrystallizations from tetrahydrofuran–ether afforded the analytical sample: mp 250–252°; ir (KBr) 3310, 2520, and 1830 (NH · HCl), 1602 (C=N), 1490 and 1443 (C=C), 750 (CCl), and 698 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 345 (30), 343 (100), 268 (50), and 266 (20).

Anal. Calcd for $C_{21}H_{15}Cl_2N_3 \cdot HCl$: C, 60.52; H, 3.87; N, 10.08. Found: C, 60.47; H, 3.92; N, 10.19.

3(5)-Chlorodiphenylmethyl-1,2,4-triazole Hydrochloride. To a solution of 60 ml of thionyl chloride in 100 ml of benzene was added 38 g (0.15 mol) of the solid alcohol **11** portionwise. After the exothermic reaction ceased, the mixture was stirred for 18 hr at 30°. The solid which formed was removed by filtration and dried *in vacuo* to give 33 g (73%) of the salt, mp 184–187°. Two recrystallizations from tetrahydrofuran–ether afforded a sample which had mp 186–188°. An analytically pure sample could not be prepared, as this salt was very hydroscopic: ir (KBr) 3300, 2460, and 1890 (NH^+) and 760 cm^{-1} (CCl); mass spectrum (70 eV) *m/e* (rel intensity) 233 (100), 205 (40), and 128 (35).

3(5)-Phenyl-5(3)-chlorodiphenylmethyl-1,2,4-triazole Hydrochloride. A stirred solution of 9.8 g (0.03 mol) of the alcohol **15** in 100 ml of anhydrous ether was saturated with dry hydrogen chloride. The solvent was evaporated *in vacuo* and the residue was treated with a solution of 15 ml of thionyl chloride in 30 ml of benzene. The resulting mixture was refluxed for 1 hr and then stirred at 30° for 18 hr. Upon dilution with anhydrous ether, the crystals which formed were collected by filtration and dried *in vacuo* to give 10.8 g (93%) of the salt, mp 174–176° dec. Two recrystallizations from tetrahydrofuran–ether afforded an analytical sample: mp 175–177°; ir (KBr) 3300, 2380, and 1840 (NH^+) and 780 cm^{-1} (CCl); mass spectrum (70 eV) *m/e* (rel intensity) 309 (100).

Anal. Calcd for $C_{21}H_{16}ClN_3 \cdot HCl$: C, 65.97; H, 4.48; N, 10.99. Found: C, 65.91; H, 4.54; N, 11.12.

1,6-Diphenyl-5,5,10,10-bisdiphenylene-5*H*,10*H*-ditriazolo[1,2-*a*:1′,2′-*d*]pyrazine (16). To a stirred solution of 10 ml of thionyl chloride in 50 ml of dry benzene was added 3.25 g (0.01 mol) of the alcohol **10**. The solution was heated to reflux in order to complete solution, and after 10 min a heavy precipitate formed. Heating was continued for 0.5 hr and the suspension was then stirred for 18 hr at 30°. The reaction was diluted with dry ether, and the solid was removed by filtration, washed with ether, and dried *in vacuo* to give 3 g (97%) of **16**: mp >330°; ir (KBr) 1450 (C=C), 1280, 943, 900, 745, and 700 cm^{-1}; nmr (DMSO-d_6) δ 7.81–6.98 (m, 26 H); mass spectrum (70 eV) *m/e* (rel intensity) 279 (100).

Anal. Calcd for $C_{42}H_{26}N_6$: C, 82.06; H, 4.26; N, 13.67. Found: C, 82.14; H, 4.22; N, 13.81.

Attempted Synthesis of 4(5)-Benzhydrylidene-4*H*(5*H*)-1,2,3-triazole (17a). To a chilled solution (−78°) of 1.16 g (0.0037 mol) of 5(4)-chlorodiphenylmethyl-1,2,3-triazole hydrochloride in 200 ml of benzene–tetrahydrofuran (1:1 v/v) was added 0.75 g (0.0074 mol) of triethylamine. A deep orange solution formed during the addition of the second equivalent of triethylamine but began to fade immediately at −78°. The resulting colorless solution (after 5 min) was filtered through Celite to remove the triethylamine hydrochloride (0.92 g, 91%), and from the filtrate only 0.85 g (91%) of **8b**, mp 184–186°,[14] could be isolated.

Attempted Synthesis of 3(5)-Benzhydrylidene-3*H*(5*H*)-1,2,4-triazole (18a). To a chilled suspension (−78°) of 3.06 g (0.01 mol) of 3(5)-chlorodiphenylmethyl-1,2,4-triazole hydrochloride in 300

ml of benzene–tetrahydrofuran (1:1 v/v) was added 2.02 g (0.02 mol) of triethylamine. The resulting intense yellow solution at −78° faded over 4 hr and the resulting colorless solution was filtered through Celite to remove the triethylamine hydrochloride (2.35 g, 85%). The solvent from the filtrate was evaporated *in vacuo*, yielding a gummy residue of which only 2.25 g (89%) of **11**, mp 218–220°,[14] could be isolated.

2,5,5,7,10,10-Hexaphenyl-5*H*,10*H*-ditriazolo[1,2-*a*:1′,2′-*d*]pyrazine (20). A chilled solution (−78°) of 1.91 g (0.005 mol) of 3(5)-phenyl-5(3)-chlorodiphenylmethyl-1,2,4-triazole hydrochloride in 200 ml of anhydrous tetrahydrofuran was treated with 1.01 g (0.01 mol) of triethylamine. An intense red-orange color formed during the addition of the second equivalent of triethylamine and the solution was allowed to warm to room temperature, during which time the color faded. The reaction mixture was diluted with 200 ml of anhydrous ether and filtered through Celite to remove 1.25 g (91%) of triethylamine hydrochloride. The solvent was evaporated *in vacuo* to give 1.26 g (84%) of pure **20**: mp 291–293°; ir 1501 and 1456 (C=C), 905, and 701 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 590 (17), 562 (30), 281 (100), and 204 (48).

Anal. Calcd for $C_{42}H_{30}N_6$: C, 81.53; H, 4.89; N. 13.58. Found: C, 81.23; H, 4.99; N, 13.45.

Attempted Photolysis of 20. A solution of 1.55 g (0.0025 mol) of the pyrazine **20** in 400 ml of benzene–tetrahydrofuran (1:1 v/v) was photolyzed for 4 hr using a Hanovia 450-W high-pressure mercury discharge lamp in a quartz probe. There was no nitrogen evolution and, upon evaporating the solvent *in vacuo*, starting material was recovered quantitatively.[14]

Hydrolysis of 20. To a suspension of 0.618 g (0.001 mol) of the pyrazine **20** in 200 ml of ethanol was added 50 ml of 5% hydrochloric acid. The mixture was refluxed for 18 hr and evaporated *in vacuo*. The residue was dissolved in ether, washed with water, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give 0.56 g (91%) of crystalline **15**, mp 232–233°.[14]

3(5)-Phenyl-5(3)-methoxydiphenylmethyl-1,2,4-triazole. A solution of 3.83 g (0.01 mol) of 3(5)-phenyl-5(3)-chlorodiphenylmethyl-1,2,4-triazole hydrochloride in 250 ml of anhydrous tetrahydrofuran was cooled to −78° and treated dropwise with 2.02 g (0.02 mol) of anhydrous triethylamine, during which time a deep red-orange color developed. After stirring for 10 min at −78°, the reaction mixture was diluted with hexane and filtered under a dry nitrogen atmosphere to remove 2.58 g (94%) of triethylamine hydrochloride. The resulting clear red-orange solution was treated with 40 ml of anhydrous methanol at −78° and allowed to warm gradually to room temperature. As the reaction mixture warmed, there was a gradual discharge of color until a clear, colorless solution resulted from which the solvent was evaporated *in vacuo*. The solid residue was recrystallized from toluene to give 2.9 g (89%) of the ether: mp 134–135°; ir ($CHCl_3$) 3444 (NH), 1490, 1468, and 1443 (C=C), 1100 (broad, COC), and 698 cm^{-1}; nmr ($CDCl_3$) δ 8.28–7.92 (m, 2 H), 7.77–7.06 (m, 13 H), and 3.22 (s, 3 H); mass spectrum (70 eV) *m/e* (rel intensity) 341 (70) and 310 (100).

Anal. Calcd for $C_{22}H_{19}N_{30}$: C, 77.39; H, 5.61; N, 12.31. Found: C, 77.42; H, 5.80; N, 12.15.

1,5,5,6,10,10-Hexaphenyl-5*H*,10*H*-ditriazolo[1,2-*a*:1′,2′-*d*]pyrazine (19a). A solution of 2 g (0.0052 mol) of 4(5)-phenyl-5(4)-chlorodiphenylmethyl-1,2,3-triazole hydrochloride in 200 ml of anhydrous tetrahydrofuran was chilled to −78° and treated with 1.05 g (0.01 mol) of triethylamine. An intense blood-red color formed during the addition of the second equivalent of triethylamine. The solution was allowed to warm to room temperature and the color faded gradually. The reaction was diluted with 200 ml of anhydrous ether and filtered through Celite to remove 1.22 g (89%) of triethylamine hydrochloride. The solvent was evaporated *in vacuo* to give 1.6 g (87%) of **19a**: mp 277–280°; λ_{max} (THF) 216 nm (ε 30,282); ir (KBr) 1494 and 1449 (C=C) and 895 and 698 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 590 (15), 562 (23), 281 (100), and 204 (50).

Anal. Calcd for $C_{42}H_{30}N_6$: C, 81.53; H, 4.89; N, 13.58. Found: C, 81.29; H, 4.93; N, 13.57.

Attempted Photolysis of 19a. A solution of 1.55 g (0.0025 mol) of pyrazine **19a** in 400 ml of benzene–tetrahydrofuran (1:1) was photolyzed for 3 hr using a Hanovia 450-W high-pressure mercury discharge lamp in a quartz probe. There was no nitrogen evolution and upon evaporating the solvent *in vacuo*, starting material was recovered quantitatively.[14]

Hydrolysis of 19a. To a suspension of 0.618 g (0.001 mol) of the pyrazine **19a** in 200 ml of ethanol was added 50 ml of 5% hydrochloric acid. The mixture was refluxed for 18 hr and the solvent was evaporated *in vacuo*. The residue was dissolved in ether, washed with water, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Upon diluting with pentane 0.52 g (87%) of **8a** precipitated.[14]

4(5)-Phenyl-5(4)-diphenylpiperidinomethyl-1,2,3-triazole. A solution of 1 g (0.0025 mol) of 4(5)-phenyl-5(4)-chlorodiphenylmethyl-1,2,3-triazole hydrochloride in 200 ml of anhydrous tetrahydrofuran was chilled to −78° and treated with 0.5 g (0.005 mol) of triethylamine. There was an immediate red color and precipitate formation and the solution was filtered through Celite under a dry nitrogen atmosphere to remove 0.65 g (94%) of triethylamine hydrochloride. When the resulting clear blood-red solution was treated with 8.5 g (0.1 mol) of piperidine there resulted an immediate discharge of color. The solvent was evaporated *in vacuo* and the solid residue was recrystallized from benzene–hexane to give 0.85 g (95%) of colorless needles of the amine: mp 148–149°; ir ($CHCl_3$) 3410 (NH), 2935 (CH), 1445, 1490, and 695 cm^{-1}; nmr ($CDCl_3$) δ 7.55–6.68 (m, 15 H), 3.01–2.49 (m, 4 H), and 1.69–1.38 (m, 6 H); mass spectrum (70 eV) *m/e* (rel intensity) 281 (100), 85 (29), and 84 (41).

Anal. Calcd for $C_{23}H_{26}N_4$: C, 77.06; H, 7.31; N, 15.63. Found: C, 77.24; H, 7.28; N, 15.82.

4(5)-Phenyl-5(4)-methoxydiphenylmethyl-1,2,3-triazole. A solution of 3.83 g (0.01 mol) of 4(5)-phenyl-5(4)-chlorodiphenylmethyl-1,2,3-triazole hydrochloride in 250 ml of anhydrous tetrahydrofuran was cooled to −78° and treated dropwise with 2.02 g (0.02 mol) of anhydrous triethylamine, during which time a deep red color developed. After stirring for 10 min the reaction mixture was diluted with hexane and filtered under a dry nitrogen atmosphere to remove 2.70 g (100%) of triethylamine hydrochloride. The resulting clear deep-red solution was treated with 20 ml of anhydrous methanol at −78° and allowed to warm gradually to 30°. As the reaction mixture warmed, there was a gradual discharge of color until a clear colorless solution resulted from which the solvent was evaporated *in vacuo*. The solid residue was crystallized from benzene–hexane to afford 3.2 g (94%) of the ether: mp 101–102°; ir ($CHCl_3$) 3437 (NH) and 1075 cm^{-1} (COC); nmr ($CDCl_3$) δ 7.66–6.98 (m. 15 H) and 3.07 (s, 3 H); mass spectrum (70 eV) *m/e* (rel intensity) 341 (60) and 310 (100).

Anal. Calcd for $C_{22}H_{19}N_3O$: C, 77.39; H, 5.61; N, 12.31. Found: C, 77.41; H, 5.68; N, 12.09.

Photolysis of 5(4)-Phenyl-4(5)-benzhydrylidene-4*H*(5*H*)-1,2,3-triazole (17b). A chilled solution (−78°) of 3.83 g (0.01 mol) of 4(5)-phenyl-5(4)-chlorodiphenylmethyl-1,2,3-triazole hydrochloride in 400 ml of benzene–tetrahydrofuran (1:1) was treated with 2.02 g (0.02 mol) of triethylamine. The resulting blood-red solution, λ_{max} (THF) 463 nm, of the fulvene **17b** was filtered through Celite to remove 1.35 g (98%) of triethylamine hydrochloride and then photolyzed at −78° for 5 hr using a 450-W Hanovia high-pressure mercury discharge lamp in a Pyrex probe. The solvent was evaporated *in vacuo* and the residue was triturated with benzene to give 0.73 g (26%) of **27a**, mp 225–230°. After recrystallization from ethanol an analytical sample was obtained: mp 230–232°; λ_{max} (EtOH) 258 nm (ε 42,150); λ_{max} (HCl–EtOH) 263 nm (ε 36,998); λ_{max} (concentrated H_2SO_4) 618 nm; ir ($CHCl_3$) 1618 (C=N), 1598 (C=C), 1577 (C=C), 1492, 1448, 1125 (broad), and 698 cm^{-1}; nmr ($CDCl_3$) δ 8.08–6.57 (m, 30 H); mass spectrum (70 eV) *m/e* (rel intensity) 563 (50), 562 (100), 483 (6), 459 (18), 383 (21), 281 (100), 204 (48), and 178 (14).

Anal. Calcd for $C_{42}H_{30}N_2$: C, 89.65; H, 5.37; N, 4.98. Found: C, 89.55; H, 5.39; N, 4.99.

The benzene triturate was concentrated *in vacuo* and the residue was chromatographed on 50 g of Florisil. Upon elution with hexane 0.87 g of diphenylacetylene was isolated.[14] Elution with hexane–benzene (1:1) afforded 0.53 g of benzonitrile.[14] Further elution with pure benzene gave 0.20 g (7%) of triphenylacrylonitrile **35**, mp 166–167°.[14,15] The last compound present, 0.31 g (11%), was isolated by elution with benzene–chloroform (8:2–7:3 v/v) and was identified as 2,3-diphenylquinoline **26a**, mp 90–91°.[14,16]

Photolysis of 3(5)-Phenyl-5(3)-benzhydrylidene-5*H*(3*H*)-1,2,4-triazole (18b). A chilled solution (−78°) of 3.83 g (0.01 mol) of 3(5)-phenyl-5(3)-chlorodiphenylmethyl-1,2,4-triazole hydrochloride in 400 ml of benzene–tetrahydrofuran (1:1) was treated with 2.02 g (0.02 mol) of triethylamine. The resulting red-orange solution, λ_{max} (THF) 442 nm, of the fulvene **18b** was filtered through Celite to remove 2.62 g (92%) of triethylamine hydrochloride and then photolyzed at −78° for 4.5 hr using a 450-W Hanovia high-pressure mercury discharge lamp in a Pyrex probe. The resulting colorless solution was allowed to warm to room temperature and was concentrated *in vacuo*. The residue was triturated

with benzene to give 0.338 g of **27a**, mp 225–230°. The benzene triturate was evaporated *in vacuo* and the residue was chromatographed on 50 g of Florisil. Upon elution with hexane 0.85 g of diphenylacetylene was isolated.[14] Elution with hexane–benzene (1:1) afforded 0.45 g of benzonitrile.[14] Further elution with benzene gave 0.30 g of triphenylacrylonitrile **35**, mp 166–167°.[14,15] Continued elution with benzene–chloroform (1:1) led to the isolation of 0.309 g of 1,3-diphenyl-5-diphenylmethyl-1,2,4-triazole (**30**), mp 188–190°.[14] The last compound present, 0.48 g, was isolated by eluting with benzene–chloroform (8:2–7:3 v/v) and was identified as 2,3-diphenylquinoline **26a**, mp 90–91°.[14,16]

Thermolysis of 27a. The dimer **27a** (0.56 g, 0.001 mol) was heated at 300° for 1 hr in a 100-ml flask. The residue was chromatographed on 15 g of Florisil and elution with hexane–benzene (1:1 v/v) gave 0.027 g (26%) of benzonitrile.[14] elution with benzene gave 0.059 g (13%) of pentaphenylpyridine, mp 244–245°.[14,17] Further elution with benzene afforded 0.326 g (58%) of the starting dimer **27a**.

Photolysis of 4(5)-*p*-Chlorophenyl-5(4)-benzhydrylidene-5*H*(4*H*)-1,2,4-triazole (17c). A chilled (−78°) solution of 4.17 g (0.01 mol) of 4(5)-*p*-chlorophenyl-5(4)-chlorodiphenylmethyl-1,2,3-triazole hydrochloride in 400 ml of benzene–tetrahydrofuran (1:1) was treated with 2.02 g (0.02 mol) of triethylamine. The resulting red-orange solution, λ_{max} (THF) 454 nm, of the fulvene **17c** was filtered to remove the triethylamine hydrochloride (2.43 g, 88%) and then photolyzed at −78° for 3.5 hr using a 450-W Hanovia high-pressure mercury discharge lamp in a Pyrex probe. The resulting colorless solution was concentrated *in vacuo* and the residue was triturated with benzene and allowed to stand for 24 hr, during which time 0.160 g of **27b** crystallized, mp 243–244°. After two recrystallizations from ethanol **27b** had λ_{max} (EtOH) 247 nm (ϵ 36,750); λ_{max} (HCl–EtOH) 263 nm (ϵ 19,163); λ_{max} (H_2SO_4) 525 nm; ir ($CHCl_3$) 1620 (C=N), 1592 and 1485 (C=C), 1445, 1140, 1125 (broad), 1090, and 695 cm^{-1}; nmr ($CDCl_3$) δ 8.05–6.84 (m, 30 H); mass spectrum (70 eV) *m/e* (rel intensity) 634 (21), 633 (38), 632 (82), 631 (60), 630 (100), 495 (7), 494 (10), 493 (16), 492 (14), 454 (6), 452 (13), 419 (21), 417 (46), 214 (15), 212 (40), and 178 (45).

Anal. Calcd for $C_{42}H_{28}Cl_2N_2$: C, 79.87; H, 4.47; N, 4.44. Found: C, 79.94; H, 4.52; N, 4.46.

The benzene triturate was evaporated *in vacuo* and the residue was chromatographed on 50 g of Florisil. Upon elution with hexane 1.17 g of diphenylacetylene was isolated.[14] Elution with hexane–benzene (1:1 v/v) afforded 0.938 g of *p*-chlorobenzonitrile.[14] Further elution with benzene gave 0.447 g of 1-*p*-chlorophenyl-2,2-diphenylacrylonitrile (**25b**), mp 142–143°.[14,21] Continued elution with benzene–chloroform (9:1–7:3) led to the isolation of 0.221 g of 2-*p*-chlorophenyl-3-phenylquinoline (**26b**), mp 93–95°.[14]

2-*p*-Chlorophenyl-3-phenylquinoline-4-carboxylic Acid. To a solution of 7.35 g (0.05 mol) of isatin and 12.7 g (0.055 mol) of 4-chloro-α-phenylacetophenone[34] in 60 ml of dry ethanol was added 12 g of sodium hydroxide in 25 ml of water. The mixture was refluxed for 18 hr and cooled and the solvent was evaporated *in vacuo*. The residue was dissolved in water, washed with ether, decolorized with Norite, filtered, and acidified with concentrated hydrochloric acid. The precipitate which formed was removed by filtration and dried *in vacuo* to give 16.5 g (92%) of the carboxylic acid, mp 305–308°. An analytical sample obtained by two recrystallizations from ethanol had mp 307–308°; ir (KBr) 3400 (OH) and 1715 cm^{-1} (C=O); nmr (DMSO-d_6) δ 8.33–7.08 (m, 13 H); mass spectrum (70 eV) *m/e* (rel intensity) 361 (27), 360 (48), 359 (73), 358 (92), 316 (14), 315 (23), 314 (38), 313 (35), 280 (22), 279 (84), 278 (100), and 277 (52).

Anal. Calcd for $C_{22}H_{14}ClNO_2$: C, 73.44; H, 3.92; N, 3.89. Found: C, 73.46; H, 4.04; N, 3.96.

2-*p*-Chlorophenyl-3-phenylquinoline (26b). In a 100-ml flask, 3.6 g (0.01 mol) of the above acid was heated at 320° until gas evolution ceased. The residue was chromatographed over 20 g of Florisil and elution with benzene gave 2.46 g (78%) of **26b**, mp 93–95°. One recrystallization from pentane afforded an analytical sample: mp 94–95°; ir ($CHCl_3$) 3060, 2975, 1597, 1488, 1095, 1018, 841, 701, and 597 cm^{-1}; nmr ($CDCl_3$) δ 8.33–7.10 (m, 14 H); mass spectrum (70 eV) *m/e* (rel intensity) 317 (21), 316 (47), 315 (61), and 314 (100).

Anal. Calcd for $C_{21}H_{14}ClN$: C, 79.87; H, 4.47; N, 4.44. Found: C, 79.76; H, 4.55; N, 4.44.

1,3-Diphenyl-5-diphenylmethyl-1,2,4-triazole (30). A 250-ml, three-necked, round-bottomed flask fitted with a reflux condenser, nitrogen inlet, and pressure-equalizing dropping funnel was charged with 9.24 g (0.04 mol) of benzoyl chloride phenylhydrazone[23] and 15.44 g (0.08 mol) of diphenylacetonitrile and then heated to 100°. The resulting solution was treated dropwise over 3 hr at 100° with a solution of 14.54 g (0.144 mol) of triethylamine in 30 ml of toluene. After the addition was complete, the reaction mixture was stirred at reflux for 18 hr, cooled, and diluted with benzene to 250 ml and the precipitated triethylamine hydrochloride was removed by filtration. The organic layer was washed with water (300 ml), dried ($MgSO_4$), decolorized with Norite, filtered, and evaporated *in vacuo*. The residue was dissolved in hot ethanol and diluted with water until turbid. After standing for 18 hr, needles formed and were removed by filtration and recrystallized from ethanol to give 10.4 g (67%) of **30**: mp 188–190°; ir ($CHCl_3$) 1600 (C=N), 1498 (C=C), 1448 (C=C), 1353, and 697 cm^{-1}; nmr ($CDCl_3$) δ 8.35–8.11 (m, 2 H), 7.87–6.98 (m, 18 H), and 5.49 (s, 1 H); mass spectrum (70 eV) *m/e* (rel intensity) 387 (100).

Anal. Calcd for $C_{27}H_{21}N_3$: C, 83,69; H, 5.46; N, 10.85. Found: C, 83.72; H, 5.39; N, 10.72.

Photolysis of Triphenyl-*v*-triazine (43). A solution of 3.09 g (0.01 mol) of triphenyl-*v*-triazine[28] in 400 ml of benzene–tetrahydrofuran (1:1 v/v) was photolyzed at 30° for 6 hr using a Hanovia 450-W high-pressure mercury discharge lamp in a Pyrex probe. After removing the solvent *in vacuo*, the residue was triturated with benzene–pentane to afford yellow crystals which were removed by filtration and dried *in vacuo* to give 0.51 g (18%) of **27a**, mp 232–234°.[14] The triturate was evaporated *in vacuo* and the residue was chromatographed over 40 g of Florisil. Upon elution with hexane 1.21 g of diphenylacetylene was isolated.[14] Elution with hexane–benzene (1:1 v/v) provided 0.68 g of benzonitrile.[14] Continued elution with benzene–chloroform (9:10–7:3) gave 0.170 g of 2,3-diphenylquinoline.[14,16]

3,5,α,α-Tetraphenylpyrazole-4-methanol (45). To a solution of phenyllithium (0.2 mol, prepared as above) and sodium in 250 ml of anhydrous ether was added portionwise 13 g (0.0468 mol) of solid methyl 3,5-diphenylpyrazole-4-carboxylate.[30] The suspension was stirred for 18 hr at reflux and decomposed with 100 ml of 5% aqueous hydrochloric acid. A solid separated and was removed by filtration to give 16.8 g of **45**, mp 207–209°. The organic layer of the filtrate was washed with water (2 × 75 ml), dried ($MgSO_4$), decolorized with Norite (2 g), filtered through Celite, and evaporated *in vacuo* to give an additional 1.4 g of **45**, mp 208–209°. The combined yield was 18.4 g (97%) and an analytical sample of **45** obtained by crystallization from toluene had mp 208–209°; ir (KBr) 3490 (broad OH) and 3230 cm^{-1} (broad NH); nmr (DMSO-d_6) δ 12.97 (broad s, 1 H), 7.52–6.61 (m, 20 H), and 6.19 (s, 1 H); mass spectrum (70 eV) *m/e* (rel intensity) 402 (40), 385 (100), and 325 (40).

Anal. Calcd for $C_{28}H_{22}N_2O$: C, 83.55; H, 5.51; N, 6.96. Found: C, 83.29; H, 5.61; N, 7.04.

3,5-Diphenyl-4-chlorodiphenylmethylpyrazole Hydrochloride. A solution of 8.04 g (0.02 mol) of the alcohol **45** in 100 ml of tetrahydrofuran was saturated with dry hydrogen chloride. The mixture was stirred for 15 min, the solvent was evaporated *in vacuo*, and the residue was treated with a solution of 15 ml of thionyl chloride in 30 ml of dry benzene. After heating at reflux for 0.5 hr the mixture was stirred at 30° for 18 hr. The precipitate that formed was removed by filtration, washed with ether, and dried *in vacuo* to give 6 g (66%) of the salt, mp 168–171°. A second crop crystallized, affording an additional 2 g (22%), mp 168–170°. An analytical sample obtained by crystallization from tetrahydrofuran ether had mp 170–171°; ir (KBr) 3060, 2400, and 1850 (NH–HCl), 1478 and 1442 (C=C), and 687 cm^{-1} (CCl); mass spectrum (70 eV) *m/e* (rel intensity) 384 (100) and 307 (27).

Anal. Calcd for $C_{28}H_{21}ClN_2 \cdot HCl$: C, 73.52; H, 4.85; N, 6.13. Found: C, 73.50; H, 4.97; N, 6.20.

3,5-Diphenyl-4-benzhydrylidene-4*H*-pyrazole (49). A cooled solution (−78°) of 6 g (0.013 mol) of 3,5-diphenyl-4-chlorodiphenylmethylpyrazole hydrochloride in 200 ml of anhydrous tetrahydrofuran was treated with 2.6 g (0.026 mol) of triethylamine. The mixture was stirred for 10 min and then diluted with isooctane and the solid which formed was removed by filtration at −78° to yield 3.6 g (100%) of triethylamine hydrochloride. The resulting red solution was allowed to warm to 30° and concentrated *in vacuo* until red, needle-like crystals began to separate. The crystals were removed by filtration to give 4.7 g (94%) of **49**: mp 155–156°; λ_{max} (THF) 382 nm; ir ($CHCl_3$) 1540 (C=C), 1468 (C=C), 1448 (C=C), 1120, and 700 cm^{-1}; nmr ($CDCl_3$) δ 7.55–6.81 (m, 20 H); mass spectrum (70 eV) *m/e* (rel intensity) 386 (34), 385 (100), 384 (49), and 307 (26).

Anal. Calcd for $C_{28}H_{20}N_2$: C, 87.47; H, 5.24; N, 7.29. Found: C, 87.26; H, 5.10; N, 7.13.

3,5-Diphenyl-4-methoxydiphenylmethylpyrazole. To 10 ml of

anhydrous methanol was added 0.1 g (0.00026 mol) of the fulvene **49**, resulting in an immediate color discharge. Upon standing for 1 hr the solution began to deposit colorless plates which were removed by filtration to give 0.11 g (100%) of the ether: mp 105° (resolidifies and then melts at 170–172° dec); ir ($CHCl_3$) 3442 (NH) and 1078 cm^{-1} (COC); nmr ($CDCl_3$) δ 7.47–6.84 (m, 20 H) and 3.20 (s, 3 H); mass spectrum (70 eV) *m/e* (rel intensity) 416 (25), 385 (100), and 339 (15).

Anal. Calcd for $C_{29}H_{24}N_2O$: C, 83.62; H, 5.81; N, 6.73. Found: C, 83.60; H, 5.76; N, 6.59.

3,5-Diphenyl-4-aminodiphenylmethylpyrazole. A chilled solution (5°) of 0.1 g (0.00026 mol) of the azafulvene **49** in 10 ml of anhydrous tetrahydrofuran was saturated with ammonia. The resulting colorless solution was evaporated *in vacuo* and the residue obtained was recrystallized from ether–hexane to give 0.097 g (93%) of the amine: mp 180–182°; ir ($CHCl_3$) 3442 (NH_2) and 3190 cm^{-1} (broad NH); nmr ($CDCl_3$) δ 7.32 (s, 2 H), 7.21 (s, 1 H), and 7.18–6.84 (m, 20 H); mass spectrum (70 eV) *m/e* (rel intensity) 401 (5), 387 (100), 386 (100), 220 (31), and 181 (25).

Anal. Calcd for $C_{28}H_{23}N_3$: C, 83.76; H, 5.77; N, 10.47. Found: C, 83.55; H, 5.53; N, 10.68.

3,4,α,α-Tetraphenylpyrazole-5-methanol (44). To a solution of phenyllithium (0.35 mol, prepared as above) in 500 ml of ether was added 27.8 g (0.1 mol) of solid methyl 3,4-diphenylpyrazole-5-carboxylate.[29] After the initial exothermic reaction was complete, the mixture was refluxed for 3 hr, then stirred for 18 hr at 30°. The reaction mixture was decomposed by the addition of 100 ml of saturated aqueous ammonium chloride solution and the ether layer after drying ($MgSO_4$) was evaporated *in vacuo* to give 39 g (97%) of **44**: mp 150–151°; ir (KBr) 3558 (OH), 3448 (NH), 1492 (C=C), 1450 (C=C), and 700 cm^{-1}; nmr ($CDCl_3$) δ 7.46–7.01 (m, 20 H); mass spectrum (70 eV) *m/e* (rel intensity) 402 (31), 384 (100), 325 (23), and 380 (18).

Anal. Calcd for $C_{28}H_{22}N_2O$: C, 83.55; H, 5.51; N, 6.96. Found: C, 83.47; H, 5.53; N, 6.93.

3,4-Diphenyl-5-chlorodiphenylmethylpyrazole Hydrochloride. A suspension of 12 g (0.03 mol) of the alcohol **44** in 300 ml of anhydrous ether was saturated with dry hydrogen chloride. During the addition there was complete solution followed by the formation of a heavy precipitate. The mixture was stirred for 30 min, the solvent was evaporated *in vacuo*, and the residue was treated with a solution of 15 ml of thionyl chloride in 30 ml of dry benzene. After heating at reflux for 0.5 hr the resulting solution was stirred at 30° for 18 hr. Upon diluting with ether (200 ml), a precipitate formed which was removed by filtration and dried *in vacuo* to give 13.4 g (98%) of the salt, mp 131–133°. Two recrystallizations from tetrahydrofuran–ether afforded the analytical sample: mp 134–136°; ir (KBr) 3058 and 2400 (NH^+), 1573 (C=C), 1478 (C=C), 1442, and 683 cm^{-1} (CCl); mass spectrum (70 eV) *m/e* (rel intensity) 384 (100).

Anal. Calcd for $C_{28}H_{21}ClN_2 \cdot HCl$: C, 73.52; H, 4.85; N, 6.13. Found: C, 73.64; H, 5.02; N, 5.97.

3,4-Diphenyl-5-benzhydrylidene-5*H*-pyrazole (47). To a chilled solution (5°) of 4.57 g (0.01 mol) of 3,4-diphenyl-5-chlorodiphenylmethylpyrazole hydrochloride in 250 ml of anhydrous tetrahydrofuran was added 2.02 g (0.02 mol) of triethylamine. An intense red solution formed during the addition of the second equivalent of triethylamine. The reaction mixture was stirred for 5 min at 5°, then warmed to 30°, and the solvent was evaporated *in vacuo*. The resulting residue was dissolved in benzene and filtered through Celite under a dry nitrogen atmosphere to remove the triethylamine hydrochloride. The filtrate was concentrated *in vacuo* and diluted with *n*-hexane. Red, needle-like crystals formed which were removed by filtration and dried *in vacuo* to give 3.6 g (94%) of **47**. Upon heating, the crystals turned to a white solid at 120–130° which then melted at 179–181° (an ir of the white solid showed it to be identical with **50**). **47** had λ_{max} (THF) 393 nm; ir ($CHCl_3$) 1543, 1463, and 1452 (C=C), 1134, and 698 cm^{-1}; nmr ($CDCl_3$) δ 7.74–6.91 (m, 20 H); mass spectrum (70 eV) *m/e* (rel intensity) 385 (100), 384 (73), and 307 (34).

Anal. Calcd for $C_{28}H_{20}N_2$: C, 87.47; H, 5.24; N, 7.29. Found: C, 87.42; H, 5.22; N, 7.44.

1,2,5,5,6,7,10,10-Octaphenyl-5*H*,10*H*-dipyrazolo[1,2-*a*:1′,2′-*d*]pyrazine (50). A solution of 1.12 g (0.00024 mol) of 3,4-diphenyl-5-chlorodiphenylmethylpyrazole hydrochloride in 100 ml of dry tetrahydrofuran was cooled to 5° and treated with 0.495 g (0.0048 mol) of triethylamine. The mixture was stirred at room temperature for an additional 18 hr, during which time the intense red color faded. The triethylamine hydrochloride was removed by filtration (0.638 g, 96%). The filtrate was concentrated *in vacuo* and the residue was chromatographed over 30 g of Florisil. Elution with benzene afforded 0.741 g (75%) of **50**: mp 179–181°; ir ($CHCl_3$) 1623 (C=N), 1605 (C=C), 1475 (C=C), and 700 cm^{-1}; nmr ($CDCl_3$) δ 7.64–6.68 (m, 40 H); mass spectrum (70 eV) *m/e* (rel intensity) 768 (100) and 384 (27).

Anal. Calcd for $C_{56}H_{40}N_2$: C, 87.47; H, 5.24; N, 7.29. Found: C, 87.24; H, 5.37; N, 7.14.

Attempted Photolysis of 49. To a chilled solution (5°) of 2.29 g (0.0005 mol) of 3,5-diphenyl-4-chlorodiphenylmethylpyrazole hydrochloride in 150 ml of dry tetrahydrofuran was added 1.01 g (0.01 mol) of triethylamine. The red solution was diluted with 150 ml of cold tetrahydrofuran and photolyzed for 6 hr at 5° using a 450-W Hanovia high-pressure mercury discharge lamp in a Pyrex probe. Tlc indicated no reaction and the red color still persisted.

Photolysis of 47. To a chilled solution (5°) of 4.57 g (0.01 mol) of 3,4-diphenyl-5-chlorodiphenylmethylpyrazole hydrochloride in 300 ml of dry tetrahydrofuran–benzene (1:1 v/v) was added 2.02 g (0.02 mol) of triethylamine. The reaction mixture was stirred for 5 min and filtered through Celite under a dry nitrogen atmosphere to remove triethylamine hydrochloride (2.32 g, 85%). The clear red solution was photolyzed at 5° using a quartz probe and a 450-W Hanovia high-pressure mercury discharge lamp. The color of the solution was discharged without noticeable gas evolution during 20 min, after which the solvent was evaporated *in vacuo* to give 3.11 g (81%) of **50**, mp 179–181°.[14]

α,α-Diphenyl-1*H*-phenanthro[9,10-*c*]pyrazole-3-methanol (46). To a stirred solution of 52.5 ml of phenyllithium (2.3 *M*) in 70:30 benzene–ether in 100 ml of anhydrous ether was added 11 g (0.04 mol) of solid methyl 3,4-diphenylenepyrazole-5-carboxylate.[31] After the addition was complete, the mixture was refluxed for 6 hr, stirred at 30° for 18 hr, and decomposed using 5% aqueous hydrochloric acid (125 ml). The organic layer was washed with water, dried ($MgSO_4$), and filtered and the solvent was evaporated *in vacuo* to give 14 g (87%) of **46**, mp 168–171°. Two recrystallizations from benzene afforded an analytical sample of **46**: mp 172–173°; ir (KBr) 3410 (OH) and 3160 cm^{-1} (NH); nmr (DMSO-d_6) δ 10.01–6.81 (m, 18 H); mass spectrum (70 eV) *m/e* (rel intensity) 400 (27) and 382 (100).

Anal. Calcd for $C_{28}H_{20}N_2O$: C, 83.97; H, 5.03; N, 7.00. Found: C, 83.78; H, 5.09; N, 6.90.

3-Chlorodiphenylmethyl-1*H*-phenanthro[9,10-*c*]pyrazole. To a stirred solution of 20 ml of thionyl chloride in 40 ml of benzene was added 12 g (0.03 mol) of the solid alcohol **46**. The mixture was stirred for 18 hr at 30° and then refluxed for 4 hr. The precipitate which formed was removed by filtration, washed with anhydrous ether, and dried *in vacuo* to give 12 g (88%) of the salt, mp 248–251°. Two recrystallizations from tetrahydrofuran–ether afforded a pure sample, mp 250–252°. An analytically pure sample could not be prepared, as the salt was very hydroscopic: ir (KBr) 3250 and 2500 (NH^+) and 790 cm^{-1} (CCl); mass spectrum (70 eV) *m/e* (rel intensity) 382 (100) and 305 (15).

Attempted Synthesis of 3-Benzhydrylidene-3*H*-phenanthro[9,10-*c*]pyrazole (48). To a solution of 2.28 g (0.005 mol) of 3-chlorodiphenylmethyl-1*H*-phenanthro[9,10-*c*]pyrazole in 400 ml of dry tetrahydrofuran–benzene (1:1 v/v) at −78° was added 1.01 g (0.01 mol) of triethylamine. The light orange solution faded after 20 min. The resulting colorless solution was filtered through Celite to remove 1.27 g (92%) of triethylamine hydrochloride and from the filtrate only 1.8 g (95%) of **46**, mp 172–173°,[14] could be isolated.

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Registry No.—**7a**, 40235-35-6; **7c**, 50561-42-7; **8a**, 50561-43-8; **8b**, 50561-44-9; **8c**, 50561-45-0; **9a**, 50561-43-8; **10**, 50561-47-2; **11**, 50561-48-3; **14**, 38345-37-8; **15**, 50561-50-7; **16**, 50561-51-8; **17b**, 40759-79-3; **17c**, 40759-80-6; **18b**, 40795-33-3; **19a**, 40759-87-3; **20**, 40759-81-7; **25b**, 35364-02-4; **26a**, 22514-82-5; **26b**, 24667-98-9; **27a**, 40759-84-0; **27b**, 40759-85-1; **30**, 50561-60-9; **35**, 50561-61-0; **43**, 39672-37-2; **44**, 50561-63-2; **45**, 50561-64-3; **46**, 50561-65-4; **47**, 50561-66-5; **49**, 50561-67-6; **50**, 50561-68-7; methyl *p*-chlorophenylpropiolate, 50561-69-8; ethyl 1,2,3-triazole-4(5)-carboxylate, 40594-98-7; triphenylcarbinol, 76-84-6; 3-phenyl-1,2,4-triazole, 3357-42-4; 1-benzyl-3,α,α-triphenyl-1,2,4-triazole-5-methanol, 50561-72-3; 4(5)-phenyl-5(4)-chlorodiphenylmethyl-1,2,3-triazole hydrochloride, 50561-73-4; 5(4)-chlorodiphenylmethyl-1,2,3-triazole hydrochloride, 50561-74-5; 4(5)-*p*-chlorophenyl-5(4)-chlorodiphenylmethyl-1,2,3-triazole hydrochloride, 50561-75-6; 3(5)-chlorodiphenylmethyl-1,2,4-triazole hydrochloride, 50561-76-7; 3(5)-phenyl-5(3)-chlorodiphenylmethyl-1,2,4-triazole hydrochloride,

50561-77-8; 3(5)-phenyl-5(3)-methoxydiphenylmethyl-1,2,4-triazole, 50561-78-9; 4(5)-phenyl-5(4)-diphenylpiperidinomethyl-1,2,3-triazole, 50561-79-0; 4(5)-phenyl-5(4)-methoxydiphenylmethyl-1,2,3-triazole, 40759-82-8; pentaphenylpyridine, 40249-26-1; 2-*p*-chlorophenyl-3-phenylquinoline-4-carboxylic acid, 50561-82-5; methyl 3,5-diphenylpyrazole-4-carboxylate, 50561-83-6; 3,5-diphenyl-4-chlorodiphenylmethylpyrazole hydrochloride, 50561-84-7; 3,5-diphenyl-4-methoxydiphenylmethylpyrazole, 50561-85-8; 3,5-diphenyl-4-aminodiphenylmethylpyrazole, 50561-86-9; methyl 3,4-diphenylpyrazole-5-carboxylate, 50561-87-0; 3,4-diphenyl-5-chlorodiphenylmethylpyrazole hydrochloride, 50561-88-1; 3-chlorodiphenylmethyl-1*H*-phenanthro[9,10-*c*]pyrazole, 50561-89-2.

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Reaction of Oxaziridine with Heterocumulene. A Ketene, Isocyanates, and a Carbodiimide

Mitsuo Komatsu,* Yoshiki Ohshiro, Hiroshi Hotta, Masa-aki Sato, and Toshio Agawa

Department of Petroleum Chemistry, Faculty of Engineering, Osaka University, Yamadakami, Suita, Osaka, 565, Japan

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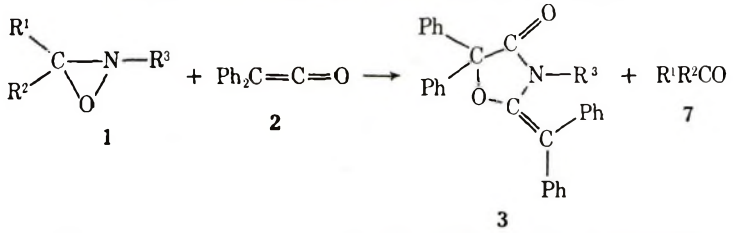
Reactions of oxaziridines I with a ketene, isocyanates, and a carbodiimide are studied, and the results are quite different from those of oxiranes, aziridines, or thiiranes. With diphenylketene (2), 2-*n*-alkyl- or *sec*-alkyloxaziridines give 3-alkyl-5,5-diphenyl-2-diphenylmethylidene-1,3-oxazolidin-4-ones (3), but 2-*tert*-butyloxaziridine **1f** rearranges to *N*-*tert*-butylbenzamide. In the reactions with isocyanates, cycloadditions forming 1,2,4-oxadiazolidin-5-ones **10** are exclusively observed. The reactions similar to that with the ketene **2** occur between 2-*n*-alkyloxaziridines and diphenylcarbodiimide, giving hexahydro-1,3,5-triazine derivatives **17** as a result of hydride shift. The oxaziridine **1f** undergoes 1:1 cycloaddition with the carbodiimide.

Many reactions of three-membered heterocycles containing one heteroatom with heterocumulenes have been reported. Oxiranes react with a ketene, an isocyanate, and a carbodiimide to give dioxolans[1] or γ-lactones,[2] oxazolidinones,[3] and imidazolidinones,[1] respectively; imidazolidinones are also given by the cycloaddition of aziridines to an isocyanate.[4] Thiiranes react with a ketene to afford thiolactones.[5]

On the other hand, the chemistry of three-membered rings containing two heteroatoms has not been so widely studied. In particular, there has been no report on the cycloadditions of such heterocycles to heterocumulenes.

In this study, the reactions of oxaziridines with a ketene, isocyanates, and a carbodiimide are presented. The accompanying report[6] describes the reactions of oxaziridines with sulfur-containing heterocumulenes.

Table I
Reaction of Oxaziridine with Diphenylketene

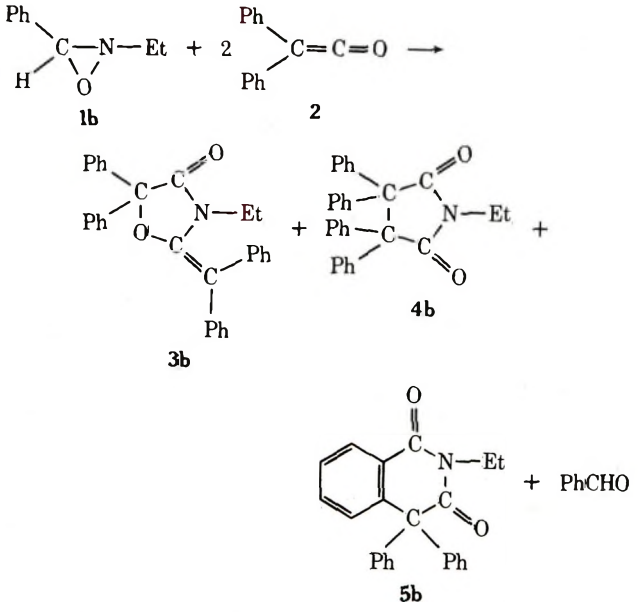


1 2 3 7

Registry no.	Oxaziridine (1)	R¹	R²	R³	Conditions[a] Temp, °C	Time,[b] hr	Registry no. of 3	Yield, % 3	7
3400-12-2	**1a**	C_6H_5	H	CH_3	60	0.5	50484-08-7	24	27[e]
7771-15-5	**1b**	C_6H_5	H	C_2H_5	60	0.5	50484-09-8	38	59
21710-99-6	**1c**	C_6H_5	H	n-C_4H_9	60	0.5	50484-10-1	40	62
7731-32-0	**1d**	C_6H_5	H	i-C_3H_7	80	4.5	50484-11-2	64	43
21711-00-2	**1e**	C_6H_5	H	c-C_6H_{11}	80	1.0	50484-12-3	28	75
7731-34-2	**1f**	C_6H_5	H	t-C_4H_9	80	5.0		c	
21711-01-3	**1g**	C_6H_5	CH_3	n-C_4H_9	60	0.5		80	d
21711-02-4	**1h**	C_2H_5	CH_3	n-C_4H_9	60	0.5		32	d

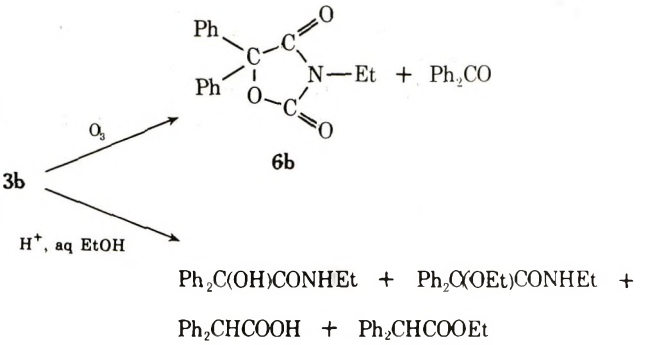
[a] Mole ratio of **1**:**2** was 0.8–1.0; benzene was employed as a solvent. [b] Allowed to react until ir absorption of C=C=O disappeared. [c] *t*-BuNHCOPh (**8**) was obtained in 97% yield. [d] Not determined exactly. [e] Registry no., 100-52-7.

Reaction with Diphenylketene. Reaction of 2-ethyl-3-phenyloxaziridine (**1b**) with diphenylketene (**2**) gave an oxazolidinone derivative **3b** (yield 38%) and small amounts of *N*-ethyltetraphenylsuccinimide (**4b**) and 2-ethyl-4,4-diphenyl-1,3-(2*H*,4*H*)-isoquinolinedione (**5b**) with benzaldehyde (yield 59%). Such a type of reaction has not been found for other three-membered heterocycles.



1b **2** **3b** **4b** **5b**

The ir spectrum of the major product **3b** shows strong absorption bands at 1726 and 1630 cm^{-1}, which are assigned to C=O and C=C stretching vibrations, respectively. The minor product **4b** has a very weak ir absorption band at 1765 cm^{-1} and a strong one at 1700 cm^{-1} whose pattern well coincides with those of other five-membered imides. The nmr spectra of **3b** and **4b** show the signals of the ethyl group of the oxazolidinone **3b** appearing at higher fields than those of the imide **4b** (by 0.26 ppm for the triplet due to the methyl protons and by 0.76 ppm for the quartet due to the methylene protons). This shift can be attributed to the phenyl ring located near the ethyl group in the oxazolidinone **3b** and to the two carbonyl groups adjacent to the nitrogen atom of the imide **4b**. That the signal of phenyl rings of **3b** is broad and that of **4b** is very sharp is also consistent with these structures. Further evidence for the structure **3b** was provided by ozonolysis and acidic hydrolysis of **3b**. The former gave benzophenone (85%) and an oxazolidinedione **6b** (40%) and the latter gave *N*-ethyl-2-hydroxy-2,2-diphenylethanamide (69%), *N*-ethyl-2-ethoxy-2,2-diphenylethanamide (23%), diphenylacetic acid (21%), and ethyl diphenylacetate (41%).



6b

$Ph_2C(OH)CONHEt$ + $Ph_2C(OEt)CONHEt$ +

$Ph_2CHCOOH$ + $Ph_2CHCOOEt$

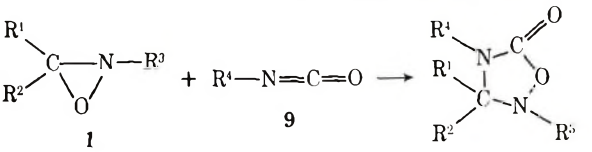
The ozonolysis product **6b** shows two strong ir absorption bands at 1812 and 1728 cm^{-1}. As for nmr spectra, the chemical shifts of the ethyl protons of **6b** are nearly equal to those of the imide **4b**.

In this reaction, another minor product **5b** was isolated; elemental analysis and the mass spectrum show that the compound was formed with loss of two hydrogens from a 1:1 adduct of the oxaziridine **1b** and the ketene. Absorptions characteristic of imido carbonyl groups are found in the ir spectrum (1706 and 1658 cm^{-1}). The nmr spectrum indicates substitution on a phenyl ring and the pattern of the signal of H-8, a complex multiplet at δ 8.2–8.3, is completely consistent with the computed one for H-6 of benzocyclobuten-1-ol.[7]

The thermal rearrangement of **3b** to **4b** was not observed when the compound **3b** was heated directly above 180° for 25 hr or in refluxing solvents (xylene or chloroform) for a long period.

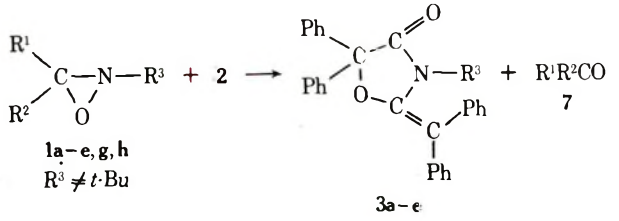
Other 2-*n*-alkyl- or *sec*-alkyloxaziridines, **1a,c–e,g,h**, similarly reacted with the ketene **2** to give oxazolidinone derivatives **3** and ketones (or aldehydes) **7**. Substituents on the oxaziridine carbon do not change the course of the reaction but do influence the yield of oxazolidinones **3**.[25] The results are shown in Table I.

Table II
Reaction of Oxaziridine with Isocyanates



	Oxaziridine (1) R¹	R²	R³	Isocyanate (9) R⁴	Conditions: Mole ratio 1:9	Solvent	Temp, °C	Time,[a] hr	Registry no.	Yield, %
1c	C_6H_5	H	*n*-C_4H_9	C_6H_5[f]	1.0	C_6H_6	85	25[b]	50484-14-5	36
1d	C_6H_5	H	*i*-C_3H_7	C_6H_5	1.2	C_6H_6	85	13	50484-15-6	95
1d	C_6H_5	H	*i*-C_3H_7	C_6H_5	0.5	$C_6H_5OCH_3$	81	25		53
1d	C_6H_5	H	*i*-C_3H_7	C_6H_5	0.5	CH_3CN	75	12		5[c]
1d	C_6H_5	H	*i*-C_3H_7	*n*-C_4H_9[g]	1.4	C_6H_6	90	17	50506-96-2	24
1f	C_6H_5	H	*t*-C_4H_9	C_6H_5	1.0	C_6H_6	80	2	2289-83-0	94
1i[e]	$-(CH_2)_5-$		COC_6H_5	C_6H_5	1.0	$C_6H_5CH_3$	115	7		*d*

[a] Allowed to react until ir absorption of $-N=C=O$ (*ca.* 2300 cm^{-1}) disappeared. [b] In a sealed tube. [c] Unreacted **1d** was recovered (88%) and most of the unreacted isocyanate was recovered in trimeric form. [d] Rearranged to dioxazoline **15** in 60% yield. [e] Registry no., 50484-16-7. [f] Registry no., 103-71-9. [g] Registry no., 111-36-4.

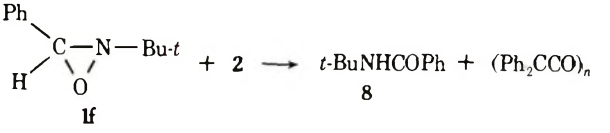


1a–e,g,h
$R^3 \neq t$-Bu

3a–e

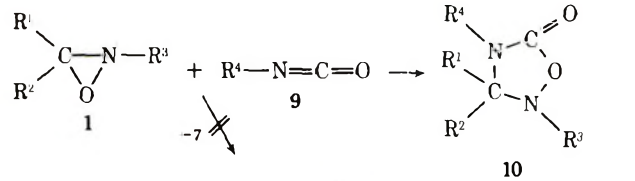
The tetraphenylsuccinimide, which was mistakenly reported to be the major product in a preliminary report,[8] is not a well-known compound[9] and the imide **4b**, the by-product, may be the only N-substituted tetraphenylsuccinimide except for its azomethine derivative.[9b]

Oxazolidinone formation was not observed when 2-*tert*-butyloxaziridine **1f** was treated with diphenylketene; instead **1f** rearranged to *N*-*tert*-butylbenzamide (**8**) quantitatively.



1f

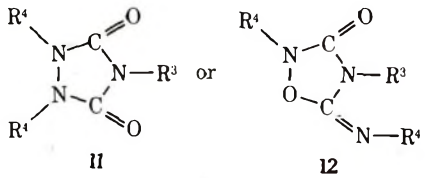
Reaction with Isocyanates. Reaction of oxaziridines with isocyanates **9** did not yield triazolidinediones **11** or oxadiazolidiones **12**. The reaction gave a 1:1 cycloadduct, an oxadiazolidinone **10**, and was independent of the *N*-alkyl substituent. For the N-unsubstituted oxaziridine **1′**, it has been reported that the oxaziridine acts as an active hydrogen compound and gives 2-aminoformyloxaziridine **13**.[10] The results are listed in Table II.



1

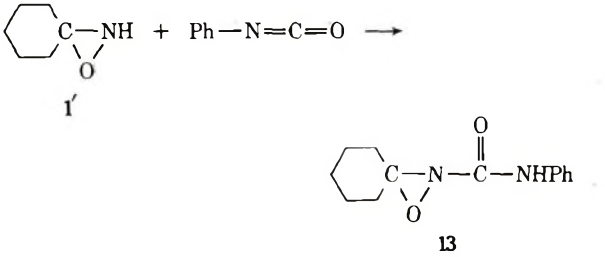
9

10



11

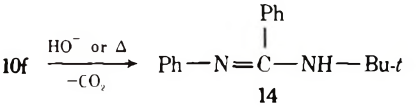
12



1′

13

The ir spectrum of oxadiazolidinone **10** shows an absorption band at *ca.* 1740 cm^{-1} and the spectrum of **10f** was identical with that of an authentic sample prepared from α-phenyl-*N*-*tert*-butylnitrone and phenyl isocyanate.[11] The fragmentation in the mass spectrum also well explains the structure of **10**. Alkaline hydrolysis and pyrolysis of the oxadiazolidinone **10f** gave *N*-*tert*-butyl-*N*′-phenylbenzamidine (**14**).

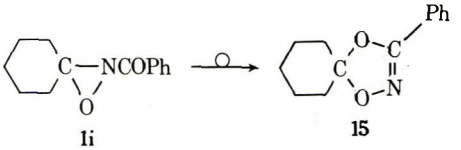


14

Lability of the oxaziridine may have lowered the yield of the product **10c** in the case of 2-*n*-butyloxaziridine **1c**.

The use of polar solvents did not change the product in these reactions, but the yields of **10c** and **10d** decreased with an increase in polarity of solvents. Polar solvents seem to prohibit the addition of an oxaziridine to the isocyanate and to promote, rather, the trimerization of the isocyanate. In anisole, 2-ethyloxaziridine **1b**, less stable than *N*-isopropyloxaziridine **1d**, gave no adduct.

The *N*-acyloxaziridine **1i** did not form any product with the isocyanate **9** but instead isomerization to dioxazoline **15**[12] was observed.



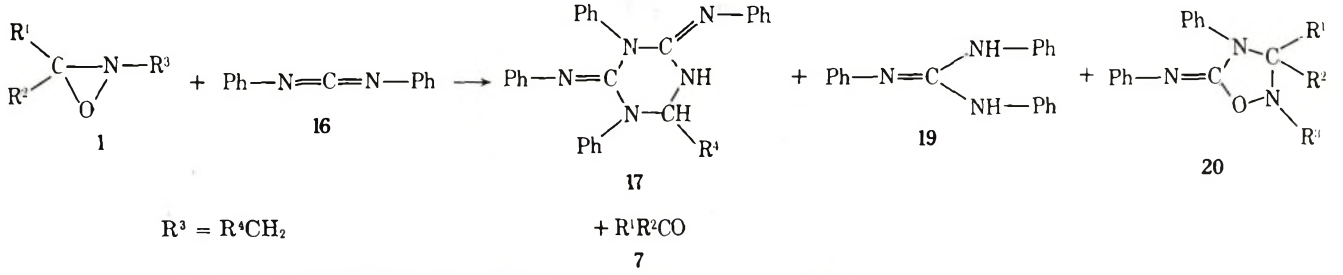
1i **15**

The use in one instance of *n*-butyl isocyanate in place of phenyl isocyanate also gave, when treated with **1d**, the oxadiazolidinone **10′d**.

Reaction with Carbodiimide. The reactions of *N*-*n*-alkyloxaziridines **1a–c,g,h** with diphenylcarbodiimide (**16**) gave hexahydro-1,3,5-triazine derivatives **17a–c** unexpectedly and ketones (Table III).

The ir spectrum of the hexahydro-1,3,5-triazine **17b** shows characteristic absorption bands at 1660, 1622 (C=N), 3400, and 1581 cm^{-1} (NH). The nmr spectrum of the compound **17b** has a doublet (δ 1.84, J = 6.0 Hz, 3 H),

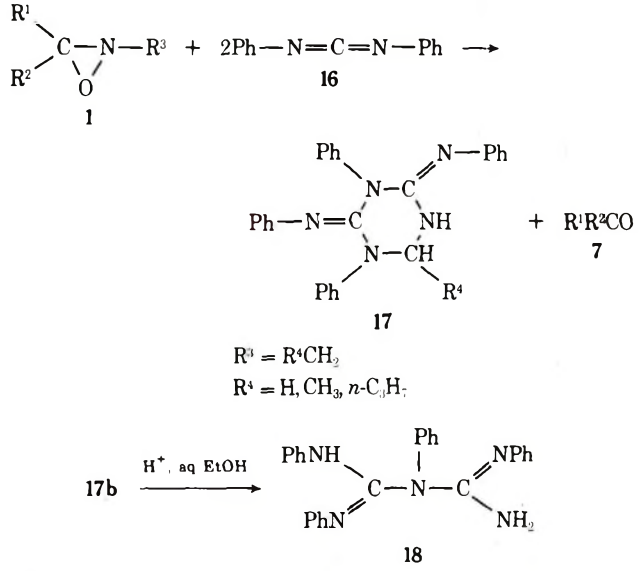
Table III
Reaction of Oxaziridine with Diphenylcarbodiimide

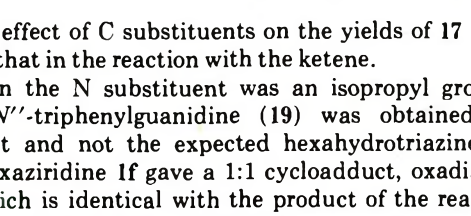


Oxaziridine (1)				Conditions: Mole ratio 1:16	Temp, °C	Time,[a] hr	Yield, % 17	19	20	7
	R^1	R^2	R^3							
1a	C_6H_5	H	CH_3	0.5	110	1.5	61[b,f]			97
1b	C_6H_5	H	C_2H_5	0.5	110	1.0	88[c,g]			*e*
1c	C_6H_5	H	*n*-C_4H_9	1.0	100	1.5	58[d,h]			76
1c	C_6H_5	H	*n*-C_4H_9	0.5	110	1.5	85[d]			92
1g	C_6H_5	CH_3	*n*-C_4H_9	0.5	110	1.5	100[d]			79[i]
1h	C_2H_5	CH_3	*n*-C_4H_9	0.5	110	1.5	52[d]			78[j]
1d	C_6H_5	H	*i*-C_3H_7	0.5	110	3.0		56[k]		*e*
1f	C_6H_5	H	*t*-C_4H_9	1.0	115	3.0			72[l]	

[a] Allowed to react until ir absorption of –N=C=N– disappeared. [b] R^4 = H. [c] R^4 = CH_3. [d] R^4 = *n*-C_3H_7. [e] Not determined exactly. [f] Registry no., 50484-19-0. [g] Registry no., 50600-52-7. [h] Registry no., 50600-53-8. [i] Registry no. 98-86-2. [j] Registry no., 78-93-3. [k] Registry no., 101-01-9. [l] Registry no., 35105-50-1.

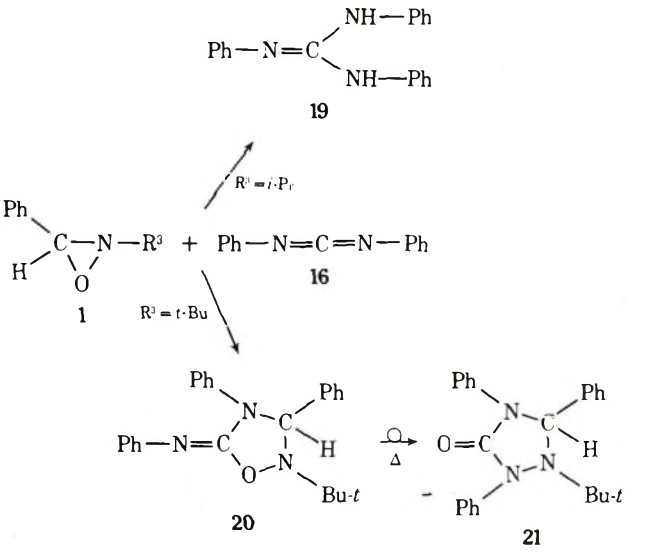
a quartet (δ 5.14, J = 6.0 Hz, 1 H), and a broad singlet at δ 4.8–5.3 that rapidly disappears upon addition of deuterium oxide, and these signals are assigned to the methyl, the methine, and the amino protons, respectively. In the mass spectrum of **17b** (R^4 = CH_3), the fragment ion peak corresponding to the elimination of a methyl group from the molecular ion appears at m/e 416 with the absence of the fragment corresponding to the elimination of an ethyl fragment. In addition, acidic hydrolysis of **17b** gave 1,2,3,4-tetraphenylbiguanide (**18**).





The effect of C substituents on the yields of **17** was similar to that in the reaction with the ketene.

When the N substituent was an isopropyl group (**1d**), *N,N′,N″*-triphenylguanidine (**19**) was obtained as the product and not the expected hexahydrotriazine. 2-*tert*-Butyloxaziridine **1f** gave a 1:1 cycloadduct, oxadiazolidine **20**, which is identical with the product of the reaction between α-phenyl-*N*-*tert*-butylnitrone and diphenylcarbodiimide.[13] As the oxadiazolidine **20** readily rearranges to the triazolidinone **21** upon heating,[13] the formation of **21** was observed at higher temperatures. With *N,N′*-dicyclohexylcarbodiimide (**16′**), however, the oxaziridine **1f** gave no adduct but rearranged to α-phenyl-*N*-*tert*-butylnitrone, and the carbodiimide **16′** was recovered quantitatively.



Discussion

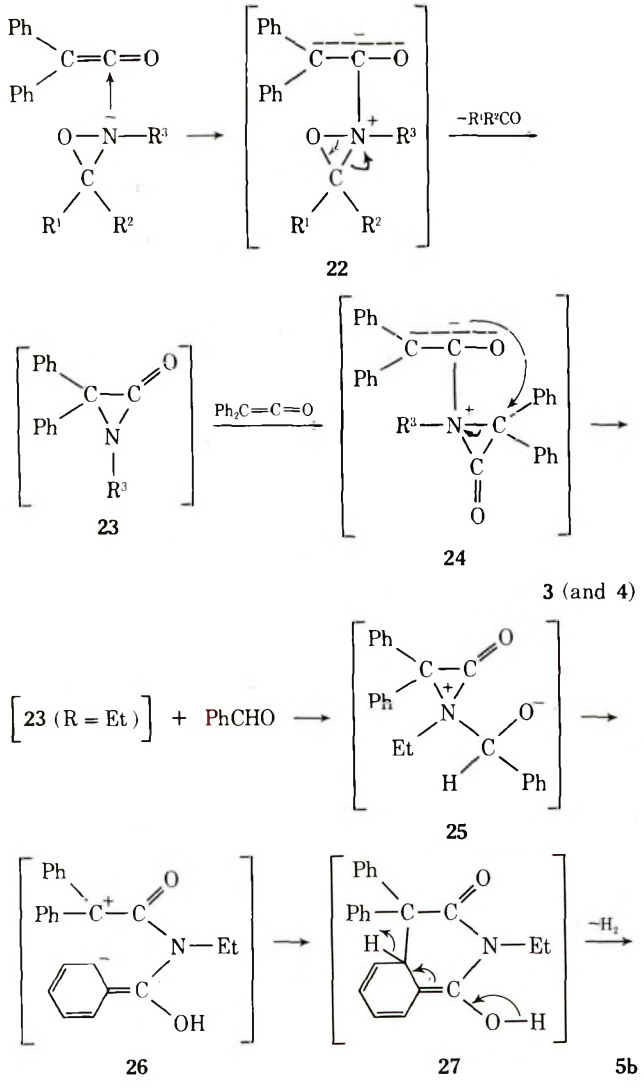
These reactions are classified into two types, the one initiated by the nucleophilic attack of a nitrogen atom of an oxaziridine to a center carbon atom of a heterocumulene and the other initiated by that of an oxygen atom. The reaction with the ketene belongs to the former and the reaction with isocyanates to the latter, and the both types were observed in the reactions with the carbodiimide.

In the reaction with the ketene **2**, the formation of the cycloadduct **3** is assumed to proceed *via* an α-lactam intermediate **22** as shown in Scheme I. The reaction is initiated by a nucleophilic attack of a nitrogen atom of an oxaziridine followed by the release of a carbonyl compound to give a highly strained intermediate **23**, which immediately reacts with an additional ketene molecule to afford an intermediate **24**. Ring closure of the intermediate **24** gives an oxazolidinone **3** and a succinimide **4**, but the former is predominant because of steric hindrance of phenyl groups against ring closure. The observed influence

of C substituents on the yield of oxazolidinones **3** correlates with carbonyl character of the leaving molecule.

The formation of a small amount of the isoquinolinedione **5b** in the reaction of **1b** is perhaps caused by the recombination of the intermediate **23** and the released

Scheme I



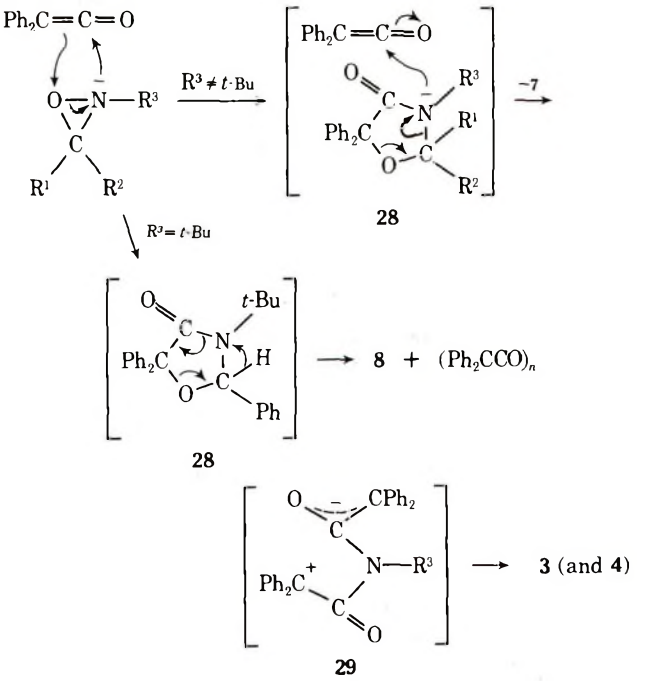
benzaldehyde. The dehydrogenation from **27** giving **5b** may be promoted by the oxaziridine, as it is an oxidizing agent.

Though generation of a nitrene in photolysis of some oxaziridines is reported,[14] the initial step of the reaction is not the formation of nitrenes because the reactions with isocyanates under similar conditions can never be understood by the formation of nitrenes.

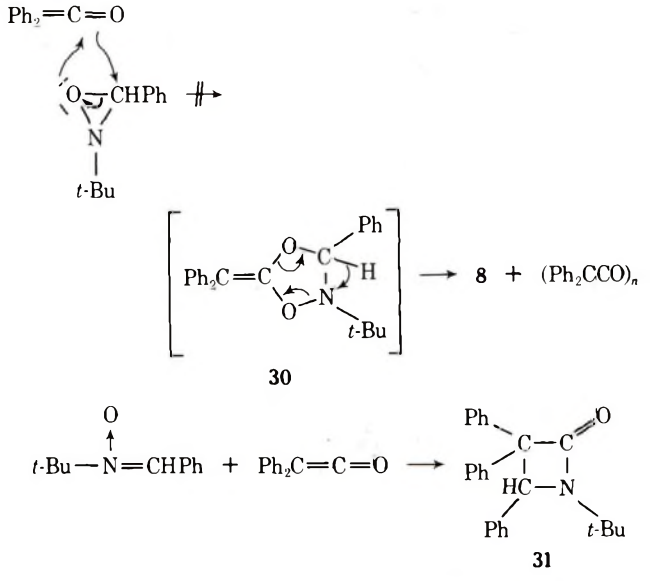
The oxaziridine **1f** rearranges to the isomeric nitrone on heating.[15] Therefore rearrangement to the amide **8** suggests participation of the ketene in this isomerization. To explain the whole reaction including this isomerization, an alternative mechanism *via* an intermediate **28**, a 1:1 cycloadduct of an oxaziridine and the ketene, can also be assumed (Scheme II). It seems that the bulky substituent inhibits the nucleophilic attack to an additional ketene by the nitrogen atom of the intermediate **28**, which in turn decomposes thermally into the amide and the ketene. Nevertheless, it is less likely that the intermediate **28** further reacts with the ketene to form betaine intermediate **29** with the release of a carbonyl compound **7**.

As another possibility, the steric hindrance of the *N*-*tert*-butyl group can be assumed in the initial cyclization.

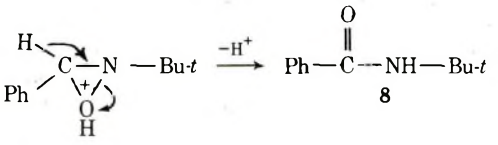
Scheme II



In this case, a nucleophilic attack by an oxygen atom results exclusively in an acetal-type intermediate **30**, which is expected to be formed from its isomeric nitrone and the ketene. This mechanism, however, is excluded by the reaction of α-phenyl-*N*-*tert*-butylnitrone with the ketene under the same conditions, giving no rearranged amide but the β-lactam **31**.

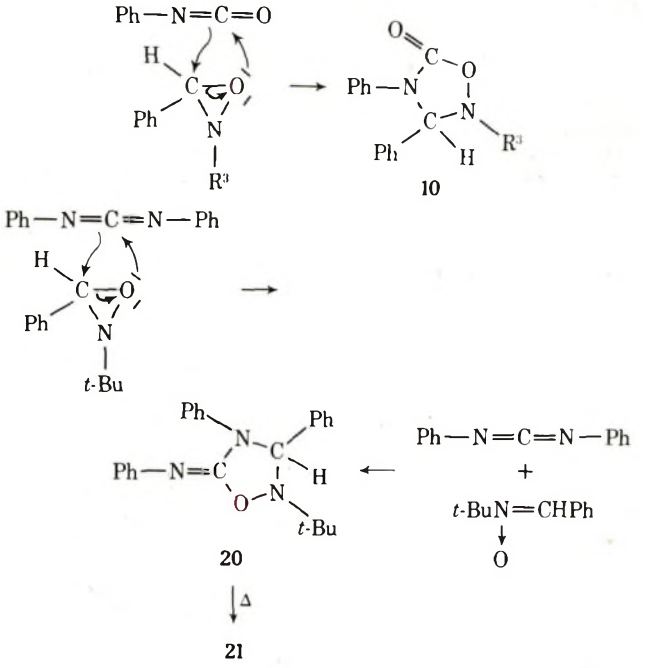


The rearrangement of the oxaziridine **1f**, whose nucleophilic attack to the ketene is sterically restricted, is thus considered to be promoted by trace amounts of diphenylacetic acid derived from the ketene.



On the other hand, oxaziridines undergo 1:1 cycloadditions with isocyanates which are similar in nature to reactions of other three-membered heterocycles with heterocumulenes. The adducts, oxadiazolidinone derivatives, have been reported in the reaction of a nitrone with an isocyan-

Scheme III



ate,[11] but there was no evidence for isomerization of oxaziridines to nitrones in the course of the reactions. If this isomerization would occur under the employed conditions, the reaction of the oxaziridine **1f** with the ketene **2** or the reaction of the oxaziridine **1a** with the carbodiimide **16** should have given such products as obtained in the reaction of the corresponding isomeric nitrone.[13] Thus the reaction may proceed as shown in Scheme III.

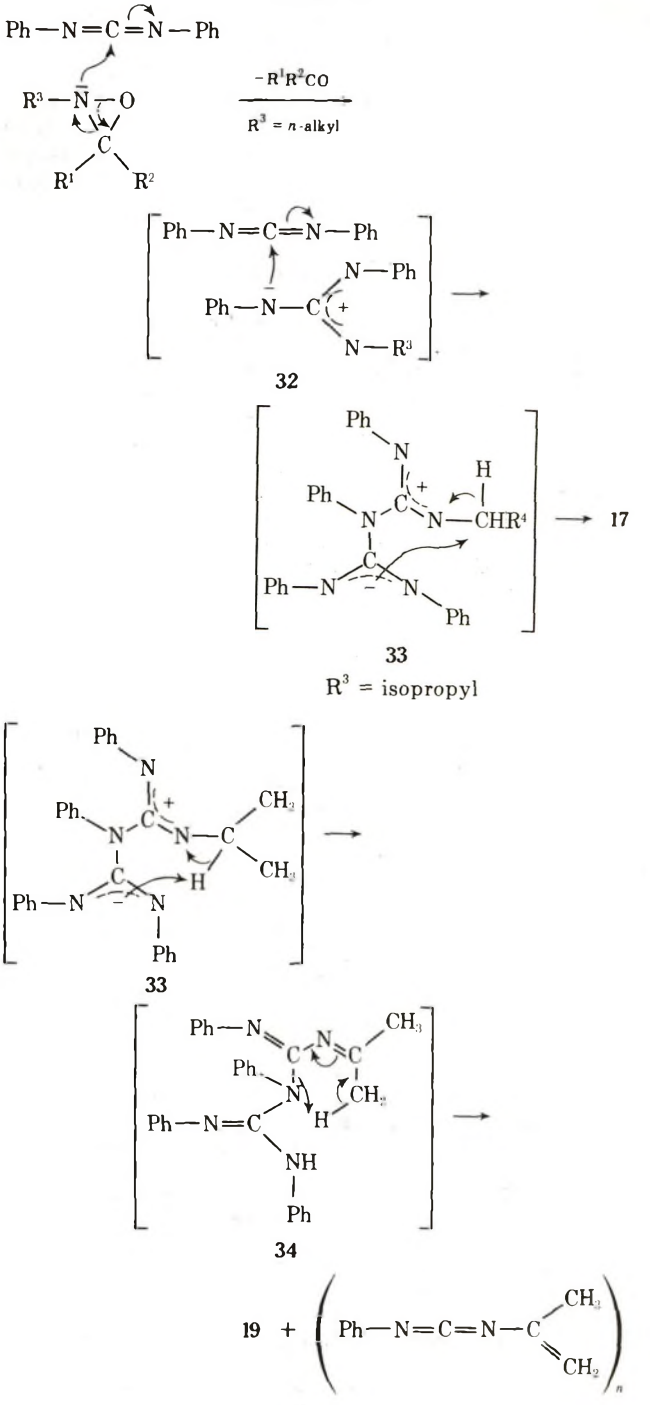
The nucleophilic attack by an oxygen atom, which is quite different from the reaction with the ketene **2**, was also observed to take place in the reaction of **1f** with diphenylcarbodiimide (**16**) and was evidenced to cause the nitrone-type 1,3 cycloaddition. The adduct **20** readily rearranges to the triazolidinone **21** upon heating. Similar rearrangement of an acetal-type intermediate, which is reported in the reactions of oxiranes with isocyanates,[3] formed by cycloaddition of an oxaziridine across the C=O bond of an isocyanate might have given the oxadiazolidinone **10**. In contrast to the reaction with the ketene, the nucleophilic attack by the nitrogen atom of an oxaziridine cannot lead to the product in these reactions.

The difference of the initial nucleophilic attacks among these reactions should be attributed to the balance of steric hindrance of N substituents and electrophilicity of heterocumulenes. Thus it may well be concluded that sufficient electrophilicity of a center carbon atom of a cumulative bond can cause a nucleophilic attack by the oxygen atom which is less nucleophilic but also less hindered. This is consistent with the fact that an attack by a nitrogen atom was observed in the reaction of the oxaziridine **1′** whose nitrogen atom is not sterically hindered and in the reaction with the ketene whose center carbon is considered to be less electrophilic.

In this regard, a nucleophilic attack by a nitrogen atom of an oxaziridine to the carbodiimide **16**, whose center carbon has poor electrophilicity compared with the isocyanate **9**, is expected. The results are consistent with this prediction. As for the low reactivity of dicyclohexylcarbodiimide **16′**, a cyclohexyl group cannot delocalize the negative charges on the nitrogen atoms and rather inhibits such polarization with their electron donation.

In the reaction of 2-*n*-alkyl- or *sec*-alkyloxaziridine with the carbodiimide **16**, the initial step is similar to that of the reaction with the ketene. A betaine intermediate **32**

Scheme IV



(Scheme IV) is expected instead of an iminodiaziridine intermediate, which corresponds to the α-lactam intermediate **23**, because of the smaller N-N bond energy. This is compatible with the reversible isomerization of such iminodiaziridines.[16] The intermediate **32** attacks an additional corbodiimide to give an intermediate **33**, whose negatively charged nitrogen atom is located rather nearer to the carbon atom than to the positive nitrogen atom because of the repulsion between the two nitrogens. 1,2-Hydride shift therefore occurs to give the hexahydrotriazine **17**. An alternative mechanism *via* an oxadiazolidinimine, a 1:1 cycloadduct of an oxaziridine and the carbodiimide, is also possible. In the case of the isopropyl-substituted oxaziridine **1d**, approach of the negative nitrogen atom of the intermediate **33** to the carbon atom is sterically hindered and the proton abstraction occurs. The resultant intermediate **34** is thermally decomposed to the guanidine **19** and polymer of vinylcarbodiimide.

Another possible mechanism for these reactions may involve the intermediacy of diradicals. This mechanism is based on the stimulating concept of diradical intermediates in 1,3-dipolar cycloadditions suggested by Firestone,[18] applying Linnet electron theory.[19] The concept aroused much interest but has not been well established yet.[20] Furthermore, the reaction of the oxaziridine **1b** with the ketene in the presence of chloranil showed no essential difference from that without chloranil.

Experimental Section

All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Ir, nmr, and mass spectra were obtained on a JASCO IR-E spectrophotometer, JEOL LNM-3H-60 and JEOL JNM-PS-100 spectrometers, and a Hitachi RMU-6E spectrometer, respectively. Carbonyl compounds contained in the distillates of the reaction mixtures were identified and determined by glpc using a 10% Apiezon L on Diasolid L (60–80 mesh, 4 mm × 2 m) column.

All reactions were carried out under nitrogen stream in a 50-ml four-necked flask equipped with a stirrer, a reflux condenser, a dropping funnel, and a thermometer, and products were isolated by column chromatography (basic aluminum oxide–benzene).

Materials. Diphenylketene (2) and diphenylcarbodiimide (**16**) were prepared according to known methods.[21,22] Phenyl isocyanate and *n*-butyl isocyanate were purchased from a commercial source.

Preparations of 2-alkyloxaziridines **1a–h** were done with perbenzoic acid according to Pews' method.[23] 2-Benzoyl-3,3-pentamethyleneoxaziridine (**1i**) was prepared by the benzoylation of 3,3-pentamethyleneoxaziridine.[12,24] Boiling points or melting point and yields are as follows: 2-methyl-3-phenyloxaziridine (**1a**), 67° (5 mm), 70%; 2-ethyl-3-phenyloxaziridine (**1b**), 74–75° (0.2 mm), 66%; 2-*n*-butyl-3-phenyloxaziridine (**1c**), 74–75° (0.5 mm), 75%; 2-isopropyl-3-phenyloxaziridine (**1d**), 73–74° (1.5 mm), 60%; 2-cyclohexyl-3-phenyloxaziridine (**1e**), 90° (0.2 mm), 50%; 2-*tert*-butyl-3-phenyloxaziridine (**1f**), 78–79° (1.5 mm), 75%; 2-*n*-butyl-3-methyl-3-phenyloxaziridine (**1g**), 60° (0.35 mm), 61%; 2-*n*-butyl-3-methyl-3-ethyloxaziridine (**1h**), 76° (13 mm), 46%; 2-benzoyl-3,3-pentamethyleneoxaziridine (**1i**), mp 68°,,28%.

The purities [active oxygen content (AO)] were determined by iodometry.

A. Reaction with Diphenylketene. All reactions were carried out by the same procedure as the reaction of the oxaziridine **1b.**

Reaction of the Oxaziridine 1b. To a solution of the ketene **2** (9.7 g, 50 mmol) in benzene (10 ml), a solution of the oxaziridine **1b** (4.2 g, 25 mmol, AO 90%) in benzene (5 ml) was added dropwise with stirring at such a rate as the temperature did not rise above 60°. Half an hour later, the characteristic ir absorption of the ketene disappeared. The reaction mixture was distilled and 1.58 g (59%) of benzaldehyde was obtained. The residue was chromatographed to give 4.12 g (38%) of 3-ethyl-5,5-diphenyl-2-diphenylmethylidene-1,3-oxazolidin-4-one (**3b**), 0.46 g (4%) of *N*-ethyltetraphenylsuccinimide (**4b**), and 0.31 g (4%) of 2-ethyl-4,4-diphenyl-1,3-(2*H*,4*H*)-isoquinolinedione (**5b**). The major product **3b** was recrystallized (benzene–hexane) to afford colorless granules: mp 144–144.5°; ir (Nujol) 1726 (C=O) and 1630 cm^{-1} (C=C); nmr ($CDCl_3$) δ 0.83 (t, 3, J = 6.9 Hz, CH_3), 3.14 (q, 2, J = 6.9 Hz, CH_2), 7.0–7.7 (m, 20, 4 Ph); mass spectrum (70 eV) m/e 431 (M^+, calcd 431), 332 ($Ph_2C{=}CPh_2^+$), 221 ($Ph_2C{=}C{=}NEt^+$), 194 (Ph_2CCO^+).

Anal. Calcd for $C_{30}H_{25}NO_2$: C, 83.50; H, 5.84; N, 3.25. Found: C, 83.39; H, 5.83; N, 3.13.

Recrystallization of one of the minor products **4b** yielded colorless plates: mp 216–218°; ir (Nujol) 1765 (C=O, weak) and 1700 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.09 (t, 3, J = 7.0 Hz, CH_3), 3.81 (q, 2, J = 7.0 Hz, CH_2), 6.9–7.2 (m, 20, 4 Ph); mass spectrum (70 eV) m/e 431 (M^+, calcd 431), 332 ($Ph_2C{=}CPh_2^+$), 221 ($Ph_2C{=}C{=}NEt^+$), 194 (Ph_2CCO^+).

Anal. Calcd for $C_{30}H_{25}NO_2$: C, 83.50; H, 5.84; N, 3.25. Found: C, 83.50; H, 5.66; N, 3.40.

The last compound **5b** was recrystallized from benzene–hexane to give colorless granules: mp 230–231°; ir (Nujol) 1706 and 1658 cm^{-1} (C=O); nmr ($CDCl_3$, 100 MHz) δ 1.11 (t, 3, J = 7.1 Hz, CH_3), 4.03 (q, 2, J = 7.1 Hz, CH_2), 6.7–7.6 (m, 13, aromatic protons), 8.2–8.3 (m, 1, H-8); the last signal of a complex multiplet well agreed with the computed pattern for the proton of the 6 position of benzocyclobuten-1-ol[7]; mass spectrum (70 eV) m/e 341 (M^+, calcd 341), 312 (M^+ − Et), 270 (M^+ − EtNCO), 241 (270 − COH), 239 ($Ph_2CHCONHEt^+$), 119 (M^+ − Ph_2CCO − $CH_2{=}CH_2$).

Anal. Calcd for $C_{23}H_{19}NO_2$: C, 80.92; H, 5.61; N, 4.10. Found: C, 80.98; H, 5.50; N, 4.19.

Reaction of the Oxaziridine 1a. The same treatment of the ketene **2** (9.5 g, 50 mmol) and the oxaziridine **1a** (9.5 g, 49 mmol, AO 70%) as the above reaction gave 2.6 g (26%) of 3-methyl-5,5-diphenyl-2-diphenylmethylidene-1,3-oxazolidin-4-one (**3a**) and 0.69 g (27%) of benzaldehyde. Recrystallization (benzene–hexane) of the compound **3a** gave colorless granules: mp 131–131.5°; ir (Nujol) 1730 (C=O) and 1660 cm^{-1} (C=C).

Anal. Calcd for $C_{29}H_{23}NO_2$: C, 83.43; H, 5.55; N, 3.36. Found: C, 83.39; H, 5.31; N, 3.33.

Reaction of the Oxaziridine 1c. From 12.7 g (67 mmol, AO 94%) of the oxaziridine **1c** and 11.8 g (61 mmol) of the ketene **2**, 5.5 g (40%) of 3-*n*-butyl-5,5-diphenyl-2-diphenylmethylidene-1,3-oxazolidin-4-one (**3c**) and 2.0 g (62%) of benzaldehyde were obtained, and 3.3 g of the oxaziridine **1c** was recovered. The product **3c** was recrystallized from benzene–hexane to give colorless granules: mp 125–126°; ir (Nujol) 1732 (C=O) and 1660 cm^{-1} (C=C); nmr (CCl_4) δ 0.68 (t, 3, CH_3), 0.8–1.5 (m, 4, 2 CH_2), 3.12 (t, 2, NCH_2), 6.8–7.7 (m, 20, 4 Ph); the triplets are considerably deformed; mass spectrum (70 eV) m/e 459 (M^+, calcd 459), 402 (M^+ − Bu), 332 ($Ph_2CCPh_2^+$).

Anal. Calcd for $C_{32}H_{29}NO_2$: C, 83.63; H, 6.36; N, 3.05. Found: C, 83.63; H, 6.38; N, 3.04.

Reaction of the Oxaziridine 1d. The reaction between the oxaziridine **1d** (4.6 g, 27 mmol, AO 95%) gave 3.8 g (64%) of 3-isopropyl-5,5-diphenyl-2-diphenylmethylidene-1,3-oxazolidin-4-one (**3d**), 0.61 g (43%) of benzaldehyde, and 1.05 g (23%) of *N*-isopropylbenzamide. The oxazolidinone **3d** was recrystallized from benzene–hexane to afford colorless granules: mp 163–164.5°; ir (Nujol) 1726 (C=O) and 1642 cm^{-1} (C=C); mass spectrum (70 eV) m/e 445 (M^+, calcd 445), 403 (M^+ − $CH_3CH{=}CH_2$), 375 (403 − CO), 332 ($Ph_2CCPh_2^+$).

Anal. Calcd for $C_{31}H_{27}NO_2$: C, 83.57; H, 6.14; N, 3.14. Found: C, 83.71; H, 5.94; N, 3.31.

Reaction of the Oxaziridine 1e. After the treatment as above, the oxaziridine **1e** (10.2 g, 45 mmol, AO 90%) and the ketene **2** (10.0 g, 52 mmol) gave 2.0 g (75%) of benzaldehyde and 3.5 g (28%) of 3-cyclohexyl-5,5-diphenyl-2-diphenylmethylidene-1,3-oxazolidin-4-one (**5e**). Recrystallization of the latter from benzene–hexane gave colorless granules: mp 208°; ir (Nujol) 1726 (C=O) and 1640 cm^{-1} (C=C); mass spectrum (70 eV) m/e 485 (M^+, calcd 485), 402 (M^+ − C_6H_{11}), 374 (402 − CO), 332 ($Ph_2CCPh_2^+$).

Anal. Calcd for $C_{34}H_{31}NO_2$: C, 84.09; H, 6.43; N, 2.88. Found: C, 84.58; H, 6.29; N, 2.85.

Reaction of the Oxaziridine 1f. After the reaction of the oxaziridine **1f** (3.0 g, 17 mmol, AO 98%) with the ketene **2** (3.3 g, 17 mmol), 2.7 g (92%) of *N*-*tert*-butylbenzamide (**8**) was obtained. The amide **8** was identical with the authentic sample from benzoyl chloride and *tert*-butylamine, mmp 140–141.5°.

Reactions of the Oxaziridines 1g and 1h. From 10.1 g (43 mmol, AO 81%) of the oxaziridine **1g** and 10.3 g (53 mmol) of the ketene **2**, 9.7 g (80%) of the oxazolidinone **3c** was obtained. The compound **3c** was also yielded in the reaction of the oxaziridine **1h** (10.0 g, 52 mmol, AO 74%) with the ketene **2** (10.0 g, 52 mmol) in 32% yield (3.8 g).

Ozonolysis of the Oxazolidinone 3b. A mixture of ozone–air (generated by a Nippon Ozone Model 0-1-2 ozone generator operated at 60 V at a flow rate of 150 ml/min) was passed through a solution of the compound **3b** (440 mg, 1.0 mmol) in 15 ml of methanol–carbon tetrachloride (2:1 mixture) cooled in an ice bath for 30 min. Then the mixture was refluxed for 3 hr. The ir spectrum of the mixture showed the formation of benzophenone and the yield was determined by glpc, 157 mg, 85%. The mixture was chromatographed to afford 114 mg (40%) of 3-ethyl-5,5-diphenyl-1,3-oxazolidine-2,4-dione (**6b**) as colorless granules (from benzene–hexane): mp 93.5–94.5°; ir (Nujol) 1818 and 1730 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.26 (t, 3, J = 7.2 Hz, CH_3), 3.65 (q, 2, J = 7.2 Hz, CH_2), 7.2–7.6 (m, 10, 2 Ph); mass spectrum (70 eV) m/e 281 (M^+, calcd 281), 210 (M^+ − EtNCO), 182 (Ph_2CO^+).

Anal. Calcd for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.75; H, 5.28; N, 5.07.

Acidic Hydrolysis of the Oxazolidinone 3b. To a solution of 880 mg (2.0 mmol) of the compound **3b** in 30 ml of ethanol, 3 ml of concentrated hydrochloric acid and 1 ml of water were added. The mixture was refluxed for 20 hr, extracted (benzene), dried (Na_2SO_4), concentrated *in vacuo*, and chromatographed to give

355 mg (69%) of 2-hydroxy-2,2-diphenylethanamide, 133 mg (23%) of 2-ethoxy-2,2-diphenylethanamide, 90 mg (21%) of diphenylacetic acid, and 200 mg (41%) of ethyl diphenylacetate.

2-Hydroxy-2,2-diphenylethanamide was obtained as colorless needles (from benzene–hexane): mp 105–106°; ir (Nujol) 3340, 3200 (OH and NH), 1650 (C=O), and 1055 cm^{-1} (CO); nmr ($CDCl_3$) δ 1.06 (t, 3, J = 7.5 Hz, CH_3), 3.23 (double q, 2, $J(CH_3)$ = 7.5 Hz, J(NH) = 6.0 Hz, CH_2), 6.4 (broad, 1, OH), 7.0–7.6 (m, 11, Ph and NH); the signal assigned to the hydroxy proton appeared very near that of 2-hydroxy-2-phenylacetic acid and was not completely removed by addition of deuterium oxide, showing the existence of strong hydrogen bonding; mass spectrum (70 eV) m/e 255 (M^+, calcd 255), 183 (Ph_2COH^+), 105 ($PhCO^+$).

Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.46; H, 6.73; N, 5.57.

2-Ethoxy-2,2-diphenylethanamide was obtained as colorless needles (from benzene–hexane): mp 86.5–87.5°; ir (Nujol) 3300 (NH). 1648 (C=O), and 1068 cm^{-1} (CO); nmr ($CDCl_3$) δ 1.15 (t, 3, J = 7.1 Hz, CH_3), 1.19 (t, 3, J = 6.8 Hz, CH_3), 3.09 (q, 2, J = 7.1 Hz, OCH_2), 3.32 (double q, 2, $J(CH_3)$ = 6.8 Hz, J(NH) = 7.8 Hz, NCH_2), 7.0–7.7 (m, 11, Ph and NH); mass spectrum (70 eV) m/e 283 (M^+, calcd 283), 211 (Ph_2COEt^+), 183 (Ph_2COH^+), 105 ($PhCO^+$).

Anal. Calcd for $C_{18}H_{21}NO_2$: C, 76.29; H, 7.47; N, 4.94. Found: C, 76.28; H, 7.52; N, 5.01.

Diphenylacetic acid and ethyl diphenylacetate were identified with authentic samples.

Reaction of α-Phenyl-*N*-*tert*-butylnitrone. To a solution of the ketene **2** (3.0 g, 15 mmol) in benzene (5 ml), a solution of the nitrone (2.7 g, 15 mmol) in benzene (10 ml) was added dropwise over 20 min at 80°. The mixture was maintained at 80° for another 5 hr, just as the conditions in the reaction of the oxaziridine **1f**. An ir spectrum of the mixture did not show the formation of *N*-*tert*-butylbenzamide. Then the mixture was concentrated and chromatographed to give 2.1 g (43%) of 1-*tert*-butyl-3,3,4-triphenylazetidin-2-one (**31**) as colorless plates (from benzene–ethanol): mp 131–132°; ir (Nujol) 1730 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.33 (s, 9, *t*-Bu), 5.34 (s, 1, CH), 6.8–7.7 (m, 15, 3 Ph); mass spectrum (70 eV) m/e 355 (M^+, calcd 355), 298 (M^+ − Bu), 256 (M^+ − BuNCO), 194 (Ph_2CCO^+), 178 ($PhCCPh^+$).

Anal. Calcd for $C_{25}H_{25}NO$: C, 84.47; H, 7.09; N, 3.94. Found: C, 84.60; H, 7.09; N, 3.89.

The azetidinone was also given by the reaction of the ketene with an excess amount of *N*-*tert*-butylbenzylidenamine under similar conditions.

B. Reaction with Isocyanate. Reaction of the Oxaziridine 1c. A mixture of the oxaziridine **1c** (6.2 g, 38 mmol, AO 92%), phenyl isocyanate (**9**, 4.5 g, 38 mmol), and 8 ml of benzene was sealed in a 50-ml glass tube and allowed to stand for 25 hr at 85°. The reaction mixture was concentrated *in vacuo* and chromatographed to give 3.8 g (36%) of 2-*n*-butyl-3,4-diphenyl-1,2,4-oxadiazolidin-5-one (**10c**). When the reaction was carried out according to the same procedure as the following runs, the yield of **10c** was slightly low. The oxadiazolidinone **10c** was recrystallized from benzene–hexane to give colorless needles: mp 114–115°; ir (Nujol) 1738 cm^{-1} (C=O); mass spectrum (70 eV) m/e 296 (M^+, calcd 296), 252 (M^+ − CO_2 or $CH_3CH{=}CH_2$), 180 ($PhN{=}CPh^+$).

Anal. Calcd for $C_{18}H_{20}N_2O_2$: C, 72.94; H, 6.80; N, 9.45. Found: C, 72.65; H, 6.72; N, 9.47.

Reaction of the Oxaziridine 1d. To a solution of the oxaziridine **1d** (6.0 g, 30 mmol, AO 90%) in the same portion of benzene, the isocyanate **9** (3.1 g, 26 mmol) was added dropwise with stirring and the mixture was refluxed for 13 hr until the characteristic ir absorption of the isocyanate at about 2300 cm^{-1} disappeared. The mixture was cooled and the precipitate was recrystallized to give 7.05 g (95%) of 2-isopropyl-3,4-diphenyl-1,2,4-oxadiazolidin-5-one (**10d**) as colorless needles (from benzene–hexane): mp 140–141.5°; ir (Nujol) 1738 cm^{-1} (C=O); mass spectrum (70 eV) m/e 282 (M^+, calcd 282), 239 (M^+ − Pr), 238 (M^+ − CO_2 or $CH_3CH{=}CH_2$), 180 ($PhN{=}CPh^+$), 163 (M^+ − PhNCO).

Anal. Calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.45; H, 6.39; N, 9.86.

The reaction between the oxaziridine **1d** (3.9 g, 22 mmol, AO 91%) and the isocyanate **9** (5.1 g, 43 mmol) in anisole for 25 hr gave 3.05 g (53%) of the oxadiazolidinone **10d** and considerable amounts of phenyl isocyanate trimer, *N*,*N*′-diphenylurea, and unreacted isocyanate 9.

In acetonitrile, the oxaziridine **1d** (5.2 g, 30 mmol, AO 91%) and the isocyanate **9** (7.2 g, 30 mmol) gave 0.45 g (5%) of the oxadiazolidinone **10d**. Unreacted oxaziridine **1d** (4.15 g, 22 mmol, AO 88%) and the isocyanate **9** (1.20 g) were recovered by distillation and 4.12 g of isocyanate trimer and 1.20 g of the mixture of *N*,*N*′-diphenylurea and the trimer.

Reaction of the Oxaziridine 1d with *n*-Butyl Isocyanate (9′). After a solution of the oxaziridine **1d** (6.0 g, 36 mmol, AO 98%) and the isocyanate **9′** (2.5 g, 25 mmol) in benzene was refluxed for 17 hr, the mixture was distilled under reduced pressure to give 1.7 g of excess oxaziridine **1d** and a small amount of benzaldehyde. The residue was chromatographed to give 1.55 g (24%) of 2-isopropyl-4-*n*-butyl-3-phenyl-1,2,4-oxadiazolidin-5-one (**10′d**) as colorless needles (from benzene–hexane): mp 73–74°; ir (Nujol) 1742 cm^{-1} (C=O); mass spectrum (70 eV) m/e 262 (M^+, calcd 262), 218 (M^+ − CO_2 or $CH_3CH{=}CH_2$), 163 (M^+ − PhNCO).

Anal. Calcd for $C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.45; N, 10.68. Found: C, 68.45; H, 8.46; N, 10.53.

Reaction of the Oxaziridine 1f. The reaction of 5.0 g (28.5 mmol, AO 99%) of the oxaziridine **1f** and 3.4 g (28.5 mmol) of the isocyanate **9** was carried out by the same procedure as above. Upon cooling, 7.95 g (94%) of 2-*tert*-butyl-3,4-diphenyl-1,2,4-oxadiazolidin-5-one (**10f**) was isolated. The oxadiazolidinone **10f** was identical with the adduct of α-phenyl-*N*-*tert*-butylnitrone and the isocyanate **9**.[11] The compound **10f** was recrystallized from benzene–hexane to afford colorless needles: mp 201–202°; ir (Nujol) 1738 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.28 (s, 9, *t*-Bu), 5.90 (s, 1, CH), 7.0–7.8 (m, 10, 2 Ph); mass spectrum (70 eV) m/e 296 (M^+, calcd 296), 252 (M^+ − CO_2), 240 (M^+ − $Me_2C{=}CH_2$), 180 ($PhN{=}CPh^+$), 177 (M^+ − PhNCO).

Anal. Calcd for $C_{18}H_{20}N_2O_2$: C, 72.94; H, 6.80; N, 9.45. Found: C, 72.69; H, 6.72; N, 9.40.

Reaction of the Oxaziridine 1i. To a solution of the oxaziridine **1i** (7.0 g, 30 mmol, AO 93%) in toluene (20 ml), the isocyanate **9** (3.57 g, 30 mmol) was added dropwise and the mixture was refluxed for 7 hr. The isocyanate **9** was recovered quantitatively. The residue was chromatographed to give 4.2 g (60%) of 2,2-pentamethylene-5-phenyl-1,3,4-dioxazoline (**15**): bp 95° (0.005 mm); ir (neat) 1618 (C=N), 1112 and 1072 cm^{-1} (CO); mass spectrum (70 eV) m/e 217 (M^+, calcd 217), 188 (M^+ − Et), 174 (M^+ − Pr), 119 (M^+ − $C_6H_{10}O$), 98 ($C_6H_{10}O^+$).

Hydrolysis and Pyrolysis of the Oxadiazolidinone 10f. To a solution of the oxadiazolidinone **10f** (1.0 g, 3.4 mmol) in ethanol (40 ml), aqueous potassium hydroxide solution was added. The mixture was refluxed for 5 hr, followed by extraction (benzene), drying (Na_2SO_4), and concentration, which gave 0.50 g (59%) of *N*-*tert*-butyl-*N*′-phenylbenzamidine (**14**). Recrystallization (benzene–hexane) gave colorless needles: mp 113.5–114°; ir (Nujol) 3520 (NH) and 1614 cm^{-1} (C=N); mass spectrum (70 eV) m/e 252 (M^+, calcd 252), 196 [$PhC(NH_2){=}NPh^+$], 180 ($PhN{=}CPh^+$); nmr ($CDCl_3$) δ 1.55 (s, 9, *t*-Bu), 4.0–4.6 (broad, 1, NH), 6.4–7.2 (m, 10, 2 Ph).

When the oxadiazolidinone **10f** was pyrolyzed under nitrogen stream, CO_2 evolved, which was detected with an aqueous solution of barium hydroxide, and the ir spectrum of the residue showed the formation of the amidine **14** with some other materials.

C. Reaction with Carbodiimide. All reactions were carried out by the same procedure as the reaction of the oxaziridine **1a**.

Reaction of the Oxaziridine 1a. To a solution of diphenylcarbodiimide (**16**, 15.5 g, 80 mmol) in a small portion of benzene, the oxaziridine **1a** (5.4 g, 36 mmol, AO 90%) was added dropwise at 110° until ir absorption of N=C=N disappeared. After 1.5 hr, the reaction mixture was distilled to give 3.7 g (97%) of benzaldehyde. The residue was chromatographed to give 9.2 g (62%) of 1,3-diphenyl-2,4-bis(phenylimino)hexahydro-1,3,5-triazine (**17a**). The hexahydrotriazine **17a** was recrystallized from methanol to give colorless needles: mp 148°; ir (Nujol) 1640 and 1611 (C=N), 3340 and 1580 cm^{-1} (NH); nmr ($CDCl_3$) δ 4.93 (broad s, 2, CH_2), 5.3–5.8 (broad, 1, NH), 6.2–7.6 (m, 20, 4 Ph); the second signal disappeared upon addition of deuterium oxide: mass spectrum (70 eV) m/e 417 (M^+, calcd 417), 387 (M^+ − NH_2CH_2), 325 (M^+ − PhNH), 311 (M^+ − $PhNCH_2NH$), 297 [$PhN(C{=}NPh)_2^+$], 249 (M^+ − Ph − PhN), 223 (M^+ − PhNCNPh).

Elemental analysis of **17a** did not give a satisfactory result, as it was very hygroscopic.

Reaction of the Oxaziridine 1b. The reaction mixture of the oxaziridine **1b** (4.6 g, 29 mmol, AO 94%) and the carbodiimide **16** (7.5 g, 39 mmol) was poured into ether to separate 7.3 g (88%) of 6-methyl-1,3-diphenyl-2,4-bis(phenylimino)hexahydro-1,3,5-triazine (**17b**), which was recrystallized from benzene–ethanol to give colorless needles: mp 174–174.5°; ir (Nujol) 1660 and 1622 (C=N), 3440 and 1585 cm^{-1} (NH); nmr ($CDCl_3$) δ 1.84 (d, 3, J = 6.0 Hz, CH_3), 5.14 (q, 1, J = 6.0 Hz, CH), 4.8–5.3 (broad, 1, NH), 6.1–7.8 (m, 20, 4 Ph); the third signal disappeared upon addition of deu-

terium oxide; mass spectrum (70 eV) *m/e* 431 (M^+, calcd 431), 416 ($M^+ - CH_3$), 388 ($M^+ - NHCHCH_3$), 339 ($M^+ - PhNH$), 313 ($M^+ - PhNCNH$), 286 [$PhNHC(NPh)=NPh^+$], 237 ($M^+ - PhNCNPh$).

Anal. Calcd for $C_{28}H_{25}N_5$: C, 77.93; H, 5.84; N, 16.23. Found: C 78.20; H, 5.89; N, 16.10.

Reaction of the Oxaziridine 1c. From the oxaziridine **1c** (5.0 g, 24 mmol, AO 87%) and the carbodiimide **16** (4.8 g, 24 mmol), 1.0 g (76%) of benzaldehyde and 3.3 g (58%) of 6-*n*-propyl-1,3-diphenyl-2,4-bis(phenylimino)hexahydro-1,3,5-triazine (**17c**) were obtained. In the case of the mole ratio of the oxaziridine **1c** to the carbodiimide **16** of 0.5, the yield of the hexahydrotriazine **17c** increased. The reaction of **1c** (4.4 g, 22 mmol, AO 84%) with the carbodiimide **16** (9.7 g, 50 mmol) gave 8.1 g (85%) of the crude product **17c**. The filtrate was distilled to give 2.1 g (92%) of benzaldehyde. The compound **17c** was recrystallized from methanol to afford colorless needles: mp 154°; ir (Nujol) 1660 and 1616 (C=N), 3480 and 1580 cm^{-1} (NH); nmr ($CDCl_3$) δ 1.34 (t, 3, J = 6.0 Hz, CH_3), 1.5–2.4 (m, 4, 2 CH_2), 4.6–5.2 (broad, 2, CH and NH), 6.3–7.6 (m, 20, 4 Ph); mass spectrum (70 eV) *m/e* 459 (M^+, calcd 459), 416 ($M^+ - Pr$), 312 ($M^+ - PhNHCHPr$), 265 ($M^+ - PhNCNPh$).

Anal. Calcd for $C_{30}H_{29}N_5$: C, 78.40; H, 6.30; N, 15.24. Found: C, 78.30; H, 6.55; N, 15.27.

Reaction of the Oxaziridine 1d. By the same treatment of the oxaziridine **1d** (3.1 g, 19 mmol, AO 98%) and the carbodiimide **16** (3.7 g, 19 mmol), 1.53 g (56%) of *N,N',N''*-triphenylguanidine (**19**) was obtained. The guanidine was identical with an authentic sample prepared from the carbodiimide **16** and aniline, mmp 147.5–149°.

Reaction of the Oxaziridine 1f. A mixture of the oxaziridine **1f** (8.9 g, 50 mmol, AO 99%) and the carbodiimide **16** (9.8 g, 51 mmol) was allowed to react for 3 hr at 110°. The ir spectrum of the reaction mixture showed neither the absorption of N=C=N nor that of benzaldehyde. The mixture was then chromatographed to give 15.8 g (72%) of 2-*tert*-butyl-3,4-diphenyl-5-phenylimino-1,2,4-oxadiazolidine (**20**) and 0.25 g (2%) of the oxadiazolidinone **10f**. The former was identical with the adduct of α-phenyl-*N*-*tert*-butylnitrone and diphenylcarbodiimide.[13] The latter probably arose as a result of hydrolysis of the azomethine function during chromatography.

Reactions of the Oxaziridines 1g and 1h. The oxaziridine **1g** (7.4 g, 35 mmol, AO 90%) reacted with the carbodiimide **16** (15.0 g, 77 mmol) to give 17.4 g (100%) of the crude hexahydrotriazine **17c**. The filtrate was distilled to give 3.3 g (79%) of benzaldehyde. The same triazine was obtained in 52% yield (6.0 g) in the reaction of the oxaziridine **1h** (5.7 g, 25 mmol, AO 63%) with the carbodiimide **16** (9.7 g, 50 mmol). In this reaction, 1.4 g (78%) of methyl ethyl ketone was obtained by distillation.

Acidic Hydrolysis of the Hexahydrotriazine 17b. To a solution of 2.0 g (4.6 mmol) of the compound **17b** in 30 ml of ethanol, 6 ml of 6 *N* hydrochloric acid was added and the mixture was refluxed for 4.5 hr. The mixture was then allowed to stand overnight to precipitate colorless crystals. The solid was filtered off (0.78 g) and the filtrate was concentrated to give the same solid (0.90 g). The combined solid was recrystallized (ethanol–benzene) to give 1.19 g (58%) of 1,2,3,4-tetraphenylbiguanide hydrochloride and 0.16 g (8%) of *N,N'*-diphenylurea. The hydrochloride was treated with aqueous potassium hydroxide in refluxing ethanol to afford 1,2,3,4-tetraphenylbiguanide (**18**) and a small amount of *N,N'*-diphenylurea.

Biguanide **18** was obtained as colorless needles (from benzene): mp 138.5–140°; ir (Nujol) 3380 (NH), 1605, 1575 (sh), and 1560 cm^{-1} (NH and C=N); mass spectrum (70 eV) *m/e* 405 (M^+, calcd 405), 313 ($M^+ - PhNH$), 287 ($M^+ - PhNCNH$), 211 [$PhNHC(NH_2)NPh^+$], 194 ($PhNCNPh^+$).

Anal. Calcd for $C_{26}H_{23}N_5$: C, 77.01; H, 5.72; N, 17.27. Found: C, 76.91; H, 5.68; N, 16.92.

Biguanide hydrochloride was obtained as colorless granules (from ethanol–benzene): mp 204–208°; ir (Nujol) 3600–3300 (broad), 3180, 1634, 1610, 1565 (strong), and 1530 cm^{-1}.

Anal. Calcd for $C_{26}H_{24}N_5Cl$: C, 70.67; H, 5.47; N, 15.91. Found: C, 70.34; H, 5.27; N, 15.81.

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Registry No.—**2**, 525-06-4; **4b**, 50484-22-5; **5b**, 50484-23-6; **5e**, 50484-12-3; **6b**, 50484-25-8; **14**, 50484-26-9; **15**, 2290-00-8; **16**, 622-16-2; **18**, 50484-28-1; **18** HCl, 50484-29-2; **31**, 50484-30-5; 2-hydroxy-2,2-diphenylethanamide, 10012-56-3; 2-ethoxy-2,2-diphenylethanamide, 50484-13-4; α-phenyl-*N*-*tert*-butylnitrone, 3376-24-7.

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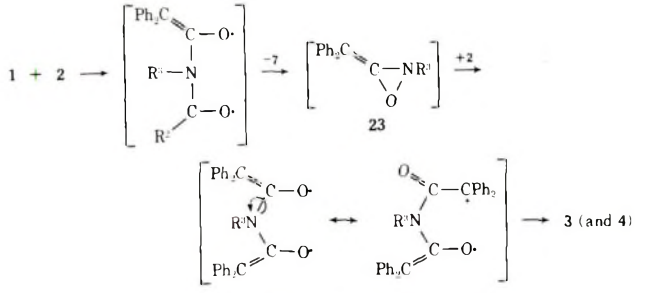

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Reaction of Oxaziridine with Sulfur-Containing Heterocumulenes

Mitsuo Komatsu,* Yoshiki Ohshiro, Kiyoshi Yasuda, Seiji Ichijima, and Toshio Agawa

Department of Petroleum Chemistry, Faculty of Engineering, Osaka University, Yamadakami, Suita, Osaka, 565, Japan

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The reactions of oxaziridines **1** with carbon disulfide (**2**) and phenyl isothiocyanate (**8**) have been studied. With carbon disulfide, 2-*n*-alkyl- or *sec*-alkyloxaziridines give alkyl isothiocyanates (quantitatively), carbonyl compounds, and sulfur. Similar reactions between **1** and **8** form carbodiimides **9**, but under mild experimental conditions **1** and **8** react to yield considerable amounts of either and/or the thiadiazolidinethione isomers **10** and **11**. 2-*tert*-Butyloxaziridine **1f** does not react with **2**, but reacts with **8** to afford oxadiazolidinethione **12** and oxadiazolidinone **13**.

In the preceding paper,[1] we reported the reactions of oxaziridines with a ketene, isocyanates, and a carbodiimide, showing that the results are quite different from those of oxiranes and of aziridines. In the reactions, oxaziridines gave 1:1 cycloadducts or unstable three-membered intermediates, which further reacted with the cumulenes to give stable heterocycles, with the release of carbonyl compounds.

In the present study, the reactions with sulfur-containing heterocumulenes such as carbon disulfide and an isothiocyanate are described. From one heterocumulene, in these reactions, another heterocumulene was obtained along with a carbonyl compound and sulfur *via* unstable intermediates. The further reactions of the intermediates giving heterocycles were also observed.

Such a characteristic difference caused by a sulfur atom, which is generally a good leaving group or easily exchangeable with an oxygen atom, can be expected from the following reactions of the cumulenes. In the reactions with ethylene oxide, for example, carbon disulfide gives ethylene carbonate and ethylene trithiocarbonate[2,3] and phenyl isothiocyanate gives 1,3-oxazolidin-2-one[4,5] or isocyanate trimer,[4,6] though 1:1 cycloadditions are observed in the reactions of propylene oxide,[3] ethylene sulfide,[3] or aziridines[7,8] with carbon disulfide, aziridines with phenyl isothiocyanate,[8] and ethylene oxide with *N*-acyl isothiocyanate.[5]

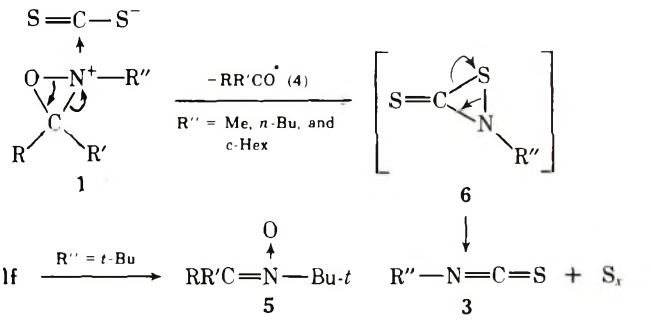
Results and Discussion

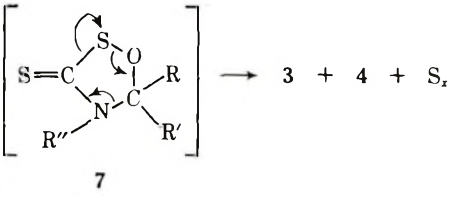
Reaction with Carbon Disulfide. In the reaction of 2-*n*-alkyl- or 2-cycloalkyloxaziridine **1a,c,e,g,j** with carbon disulfide (**2**), an isothiocyanate **3** was quantitatively obtained. The results are shown in Table I.

The products were characterized by the strong infrared absorption band at 2120 cm^{-1} (N=C=S). They were identified and determined by glpc or by converting them into thiourea derivatives. No reaction was observed for 2-*tert*-butyloxaziridine **1f** in refluxing carbon disulfide; and the rearrangement of the oxaziridine **1f** to α-phenyl-*N*-*tert*-butylnitrone (**5**) occurred under severe conditions, but a small quantity of *tert*-butyl isothiocyanate was detected by ir and glpc.

The reaction is assumed to proceed *via* a thiaziridinethione intermediate **6** (Scheme I), which readily decomposes into an isothiocyanate **3** and sulfur. A similar assumption has been proposed for the reactions of the oxaziridines with diphenylketene and with diphenylcarbodiimide. The decomposition of the intermediate **6** occurs much faster than its further reaction with carbon disulfide because of the poor stability of the intermediate **6** caused by the sulfur atom in the ring and because of the low electrophilicity of carbon disulfide. In this reaction, an unstable thioperoxy intermediate **7**, a 1:1 cycloadduct of an oxaziridine and carbon disulfide, is also possible, taking into account the strong affinity of sulfur and oxygen along with a large ring strain of the intermediate **6**. Such intermediates having a sulfur–oxygen bond are known in many reactions, for example, synthesis of sulfinylimine from *p*-toluenesulfonamide and a sulfoxide *via* a 1,3-dioxa-2,4,6,5-trithiazine intermediate.[9]

Scheme I





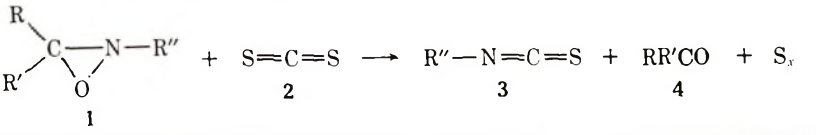
The reason for no reaction of the oxaziridine **1f** with carbon disulfide other than the rearrangement of **1f** to an isomeric nitrone is apparently due to a combination of factors involving both the steric hindrance to addition by the bulky *N*-*tert*-butyl moiety and the low electrophilicity of carbon disulfide.

Reaction with Phenyl Isothiocyanate. It is very interesting to observe whether an isothiocyanate will behave like carbon disulfide or an isocyanate in the reaction with oxaziridines. A carbodiimide should be given in the former case and a 1:1 cycloadduct in the latter.

At 110°, the reaction of 2-cyclohexyl-3-phenyloxaziridine (**1e**) gave *N*-cyclohexyl-*N*′-phenylcarbodiimide (**9e**) with benzaldehyde and sulfur, showing that the reaction surely proceeded by such a mechanism as assumed in the reaction with carbon disulfide. Though carbonyl compounds and sulfur were quantitatively obtained in the reactions of other 2-*n*-alkyl- or *sec*-alkyloxaziridines **1a–d,k**, none of the corresponding carbodiimides were isolated. This was because of polymerization of the resulting carbodiimides.

The reaction was remarkably changed with a decrease in the reaction temperature. At 90°, the reaction of these oxaziridines gave thiadiazolidinethione derivatives **10**, **11**, and benzaldehyde. That not only a considerable amount of sulfur was isolated but also benzaldehyde was obtained in more than 100% yield (calculated based on the reaction

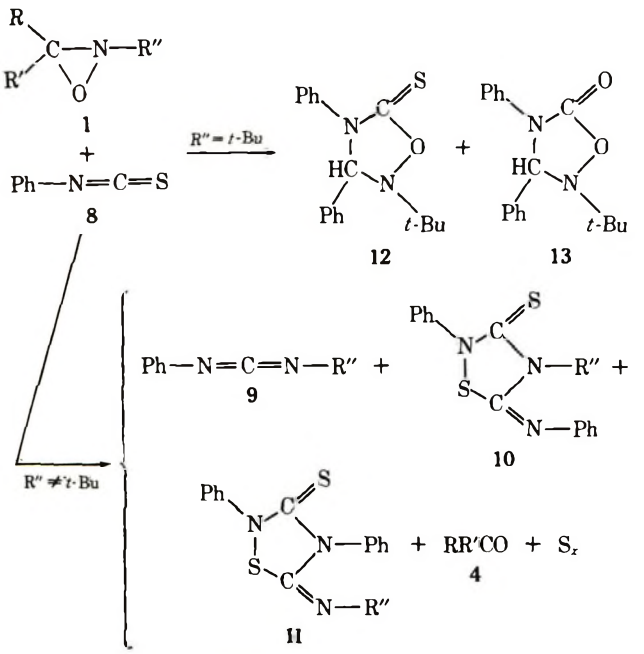
Table I
Reaction of Oxaziridine with Carbon Disulfide



Oxaziridine (1)				Reaction[a] time, hr	Yield, %[d]			
	R	R′	R″		3	4	S_x	RR′C=N—R″ (O)
1a	C_6H_5	H	CH_3	6.0	97	100	92	
1c	C_6H_5	H	n-C_4H_9	7.0	55[e]	61[e]	84	
1e	C_6H_5	H	c-C_6H_{11}	7.5	84	90	82	
1g	C_6H_5	CH_3	n-C_4H_9	5.0	84	98	100	
1j	$-(CH_2)_5-$		CH_3	5.0	94	100	93	
1f	C_6H_5	H	t-C_4H_9	30.0				*f*
1f	C_6H_5	H	t-C_4H_9	33.0[b]				38[g]
1f	C_6H_5	H	t-C_4H_9	7.0[c]	*h*	*h*		95

[a] Refluxed with excessive amount of **2**. [b] At 70° in a sealed tube. [c] At 100° in a sealed tube. [d] Yields of **3** and **4** were determined by glpc. [e] Determined by distillation. [f] Unreacted **1f** was recovered quantitatively. [g] Unreacted **1f** was recovered. [h] t-BuNCS, PhCHO, and t-BuN=CHPh were detected by ir and glpc but not isolated.

between 1 mol of **1** and 2 mol of **8**) indicates that the reactions include the path leading to a carbodiimide **9**.



2-*tert*-Butyloxaziridine **1f**, on the other hand, gave the 1:1 cycloadduct, oxadiazolidinethione **12**, in a good yield with a small amount of oxadiazolidinone **13**.

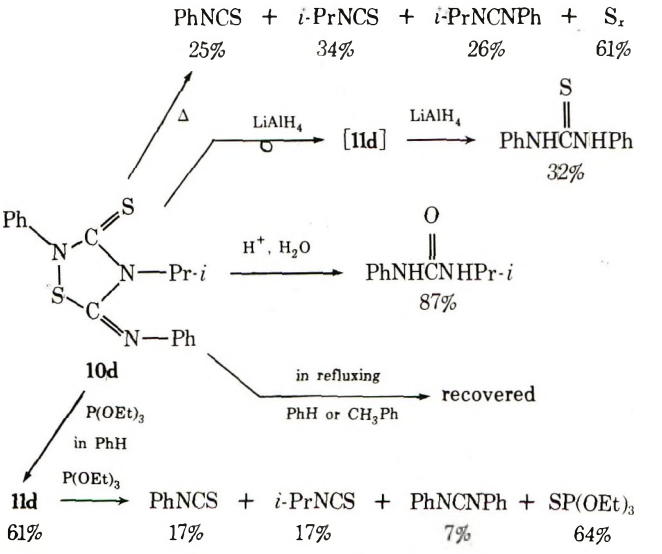
No reaction was observed between the isothiocyanate and 2-benzoyloxaziridine **1i**, which rearranged to 2,2-pentamethylene-5-phenyl-1,3,4-dioxazoline.[10]

The results are given in Table II.

The carbodiimide **9e** showed a strong infrared absorption band at *ca.* 2150 cm^{-1} and was confirmed as *N*-cyclohexyl-*N*′-phenylurea by hydration.

The structures of the two thiadiazolidine isomers **10** and **11** were determined by the spectral and analytical data and pyrolysis. The infrared absorption of the C=N stretching vibration of **10** appears at 1610–1615 cm^{-1}, *ca.* 20 cm^{-1} lower than that of **11**. In nmr spectra, the signals of the *N*-methylene or *N*-methine proton of **10** were observed in higher field than those of **11** by 0.7–2.0 ppm. Such a thidiazolidine ring system seems to be relatively stable and, for example, 2,4-diphenyl-3,5-bis(phenylimino)-1,2,4-thiadiazolidine is readily formed by acidic oxidation of *N,N*′-diphenylthiourea.[11]

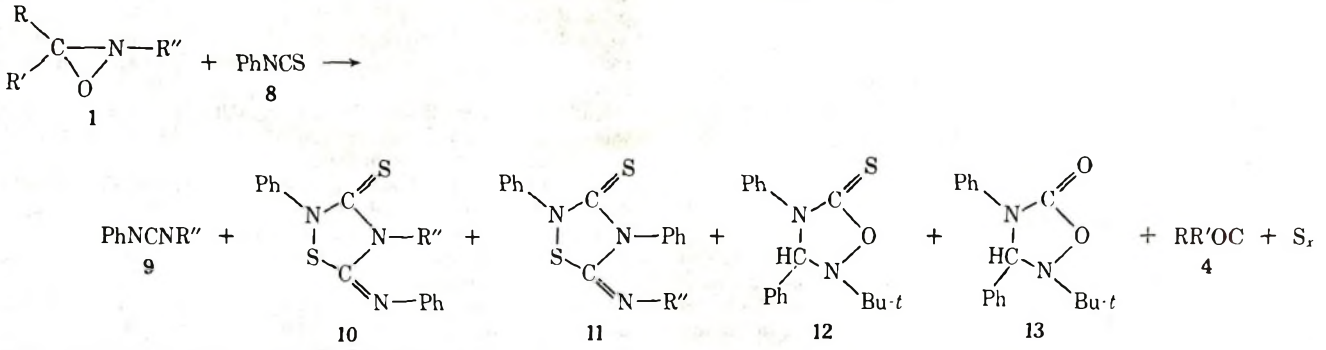
Pyrolysis of **10d** at 185° under a nitrogen stream gave isopropyl isothiocyanate, phenyl isothiocyanate, *N*-isopropyl-*N*′-phenylcarbodiimide, and sulfur. These products well supported the structure of **10d**. The compound **10d** was unchanged when it was heated in refluxing benzene or toluene, but rearranged to the isomer **11d** (61% yield) when a catalytic amount of triethyl phosphite was added to the solution. A large amount of the phosphite caused desulfurization to give phenyl isothiocyanate (17%), isopropyl isothiocyanate (17%), diphenylcarbodiimide (7%), the rearranged isomer **11d** (trace), and triethyl phosphite (64%). Reduction with $LiAlH_4$ and acidic hydrolysis of the compound **10d** gave *N,N*′-diphenylthiourea and *N*-isopropyl-*N*′-phenylurea, respectively. The former may be formed *via* the rearranged isomer **11d**.



The strucure of the major product of the reaction of the oxaziridine **1f** with phenyl isothiocyanate, namely 2-*tert*-butyl-3,4-diphenyl-1,2,4-oxadiazolidine-5-thione (**12**), was also determined by spectral and analytical data. The minor product, 2-*tert*-butyl-3,4-diphenyl-1,2,4-oxadiazolidin-5-one (**13**), is identical with the cycloadduct of the oxaziridine and phenyl isocyanate.[1]

A possible reaction scheme to explain the products of the reaction of oxaziridines with phenyl isothiocyanate involves the formation of a thiaziridineimine intermediate **14** with the release of a carbonyl compound **4**. At higher temperatures the intermediate **14** thermally decomposes into a carbodiimide **9** and sulfur (Scheme II) as postulated for the reaction of oxaziridines with carbon disulfide. At

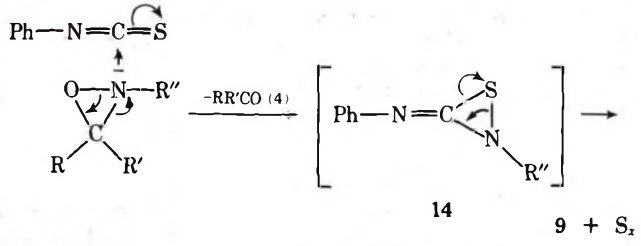
Table II
Reaction of Oxaziridine with Phenyl Isothiocyanate



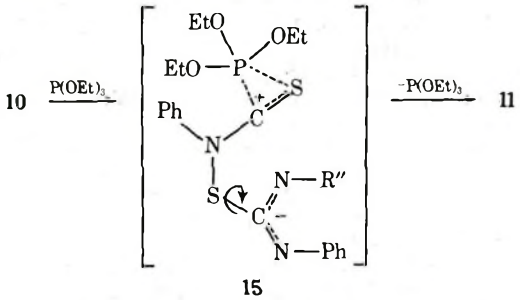
Oxaziridine (1)				Conditions[a]			Yield, %						
	R	R′	R″	Mole ratio 1:8[b]	Temp, °C	Time,[c] hr	9[d]	10[e]	11[e]	12[d]	13[d]	4[e]	S_x[d]
1a	C_6H_5	H	CH_3	1.0	110	3.0						191	90
1e	C_6H_5	H	c-C_6H_{11}	1.0	110	3.0	58					192	82
1a	C_6H_5	H	CH_3	1.0	100	1.2		6				188	69
1b	C_6H_5	H	C_2H_5	0.6	85	2.6		22	4			119	19
1c	C_6H_5	H	n-C_4H_9	1.0	90	3.0		8	28			122	30
1d	C_6H_5	H	i-C_3H_7	0.7	90	5.5		36	1			98	1
1e	C_6H_5	H	c-C_6H_{11}	1.0	90	5.5		*g*	58			117	2
1f	C_6H_5	H	t-C_4H_9	1.0	105	2.0				68	19		
1i	$-(CH_2)_5-$		COC_6H_5	1.0	115[f]	7.0							*h*
1k	C_6H_5	H	$CH_2C_6H_5$	1.0	100	1.4		7				143	67

[a] Relatively small amount of benzene was added. [b] **8:** phenyl isothiocyanate. [c] Allowed to react until ir absorption of **8** disappeared. [d] Based on equimolar reactions. [e] Based on reaction between 1 mol of **1** and 2 mol of **8**. Hence, the yield of **4** is 200% when the reaction is completely equimolar. [f] Toluene was employed as a solvent. [g] The product corresponding to **10e** was detected by ir but could not be purified. [h] The oxaziridine **1i** rearranged to 2,2-pentamethylene-5-phenyl-1,3,4-dioxazoline in 53% yield.

Scheme II

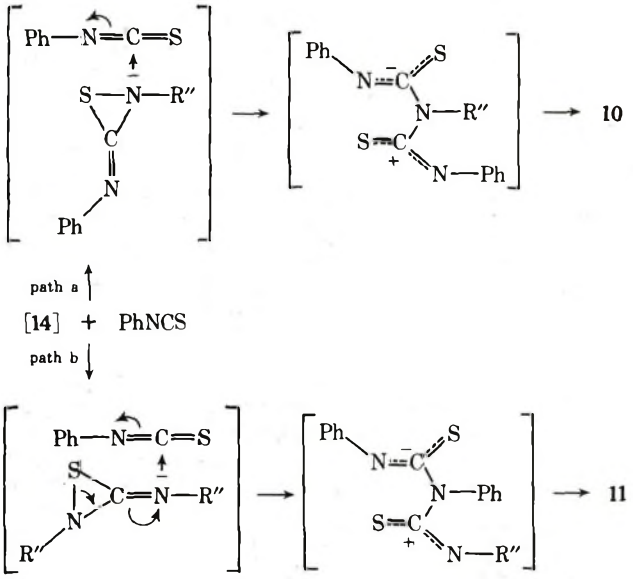


lower temperatures, the intermediate **14** is somewhat more stable and it reacts with an additional molecule of the isothiocyanate, giving thiadiazolidinethiones. The formation of two isomers can be explained in terms of the two paths shown in Scheme III. The one is formed by the nucleophilic attack of the ring nitrogen atom to an isothiocyanate (path a) and the other is formed by the attack of the imino nitrogen atom (path b). According to the fact that the thiadiazolidine **10d** rearranged to the isomer **11d** in the presence of triethyl phosphite, possibility of the rearrangement of **10** to **11** during the reactions may not be excluded. The rearrangement is considered to be promoted by stabilization of the intermediate **15**.



In the reaction giving thiadiazolidinethiones, the equimolar reaction forming a carbodiimide occurs simultaneously. Therefore, it is reasonable that a carbonyl compound was obtained in more than 100% yield when it is

Scheme III



calculated on the basis of the reaction giving thiadiazolidinethiones.

As an alternative mechanism, a 1:1 cycloadduct intermediate instead of the three-membered intermediate cannot be excluded for these reactions. This possibility is already mentioned in the reaction with carbon disulfide. Thermal decomposition and the further reaction of this intermediate will also lead to the reaction products.

The reaction of 2-*tert*-butyloxaziridine **1f** with phenyl isothiocyanate to yield the oxadiazolidinethione **12** can be rationalized by invoking the steric arguments used to explain the reaction of **1f** with isocyanates and a carbodiimide.[1] The formation of the minor product **13** is ascribed to the replacement of a sulfur atom by an oxygen atom of an oxaziridine during the reaction, as the ir spectrum of

the reaction mixture showed the formation of **13**, and partly to the replacement during column chromatography.

The difference from the reaction with carbon disulfide is due partly to the greater electrophilicity of the center carbon of an isothiocyanate, which is less than that of an isocyanate and comparable with that of a carbidiimide or a ketene, and partly to slightly larger stability of the intermediate **14** compared with the intermediate **6**.

Experimental Section

Melting points (uncorrected), ir, nmr, and mass spectra, and glpc data were obtained on the same apparatus reported in the preceding paper.[1] Mass spectrometry was performed at 70 eV. All the reactions were carried out under a nitrogen stream in the apparatus reported previously.[1]

Materials. Phenyl isothiocyanate was purchased from a commercial source.

2-Alkyloxaziridine **1a–g,k** and 2-benzoyloxaziridine **1i** were prepared by the procedures reported in the preceding paper[1] and the oxaziridine **1j** by Schmitz's method.[12] Boiling point and yields of 2-methyl-3,3-pentamethyleneoxaziridine (**1j**) and 2-benzyl-3-phenyloxaziridine (**1k**), which was used without distillation, are as follows: **1j**, bp 63–64° (13 mm), 50%; **1k**, 84%. The data on the other oxaziridines are described in the preceding paper.[1] The purities (active oxygen content: AO) were determined by iodometry.

A. Reaction with Carbon Disulfide. Reactions of the Oxaziridines 1a, 1g, and 1j. A mixture of the oxaziridine **1a** (8.1 g, 54 mmol, AO 90%) and carbon disulfide (**2**, 13.5 g, 178 mmol) was refluxed for 6 hr. After removal of the excess of **2**, 1.62 g (93%) of sulfur precipitated and was filtered off. The filtrate was distilled, but *N*-methyl isothiocyanate (**3a**) and benzaldehyde were not separated satisfactorily; infrared spectra of the distillates indicated absorption bands at about 2120 (N=C=S) and 1700 cm^{-1} (CHO). Determination of the yields and identification were made by glpc on the combined distillates.

The other two runs were carried out by the same procedure, starting with the oxaziridine **1g** (6.0 g, 28 mmol, AO 90%) and carbon disulfide (**2**, 10.0 g, 132 mmol), the oxaziridine **1j** (5.0 g, 34 mmol, AO 86%), and **2** (8.7 g, 114 mmol), respectively. The amount of sulfur precipitated was 0.91 (100%) and 1.0 g (93%), respectively.

Retention times of the products were identical with those of an authentic sample.[13] Operating conditions of glpc were as follows: column, 4 mm × 2 m Apiezon Grease L 10% on Diazolid L 60–80 mesh; carrier gas H_2, 34 ml/min; column temperature, 103 (CH_3NCS) and 145° (C_4H_9NCS); retention time, 1.6 min (CH_3NCS) and 3.7 min (C_4H_9NCS).

Reaction of Oxaziridine 1c and 1e. A mixture of the oxaziridine **1c** (10.2 g, 54 mmol, AO 94%) and carbon disulfide (**2**, 12.9 g, 170 mmol) was refluxed for 7 hr. After removal of the excess of **2** and of sulfur (1.45 g, 84%), the filtrate was treated with 40% $NaHSO_3$ and extracted (ether). The aqueous layer was treated with NaOH, extracted (ether), dried (Na_2SO_4), and distilled to give benzaldehyde (3.8 g, 66%). The ethereal solution was dried (Na_2SO_4) and distilled to afford *n*-butyl isothiocyanate (**3c**, 3.4 g, 55%), bp 76° (26 mm), ir (neat) 2120 cm^{-1} (-NCS). Furthermore, the compound **3c** was allowed to react with *n*-butylamine to give *N,N'*-di-*n*-butylthiourea: mp 64.5–65.5°; ir (Nujol) 3290 (NH), 1418 and 1215 (C=S), 1520 cm^{-1} (NH, CN).

Anal. Calcd for $C_9H_{20}N_2S$: C, 57.40; H, 10.70; N, 14.87. Found: C, 57.68; H, 10.79; N, 14.70.

The reaction of the oxaziridine **1e** (10.0 g, 44 mmol, AO 89%) with **2** (10.0 g, 132 mmol) was carried out as described above, and cyclohexyl isothiocyanate (**3e**, 5.2 g, 84%), benzaldehyde (4.2 g, 90%), and sulfur (1.15 g, 82%) were obtained. The isothiocyanate **3e** was treated with cyclohexylamine to give *N,N'*-dicyclohexylthiourea (**3e**), bp 85° (7.5 mm), ir (neat) 2120 cm^{-1} (-NCS), and thiourea, mp 185.5–187°, ir (Nujol) 3210 (NH), 1413 and 1226 (C=S), and 1505 cm^{-1} (NH, CN).

Anal. Calcd for $C_{13}H_{24}N_2S$: C, 64.95; H, 10.06; N, 11.65. Found: C, 64.94; H, 10.36; N, 11.79.

Reaction of the Oxaziridine 1f. A mixture of the oxaziridine **1f** (8.2 g, 45 mmol, AO 98%) and carbon disulfide (**2**, 11.0 g, 144 mmol) was refluxed for 30 hr. The oxaziridine was recovered quantitatively by distillation.

In a 25-ml glass tube, a mixture of the oxaziridine **1f** (8.0 g, 44 mmol, AO 98%) and **2** (5.4 g, 71 mmol) was sealed and allowed to stand at 70° for 33 hr. The excess of **2** was removed and the resultant solid was filtered and recrystallized (hexane) to give α-phenyl-*N*-*tert*-butylnitrone (3.0 g, 38%): mp 74–75° (mixture melting point of the mixture of the product and an authentic sample[14] was not depressed); ir (Nujol) 1562 (C=N), 1192, and 1120 cm^{-1} (NO); the spectrum was identical with that of the authentic sample.

Under severe conditions (100°, 7 hr), 6.8 g (95%) of the nitrone was obtained from the oxaziridine **1f** (8.1 g, 40 mmol, AO 88%) and the sulfide **2** (6.1 g, 80 mmol).

B. Reaction with Isothiocyanate. Reaction of the Oxaziridine 1a. To a solution of phenyl isothiocyanate (**8**, 10.0 g, 74 mmol) in benzene (10 ml), the oxaziridine **1a** (10.0 g, 52 mmol, AO 70%) was added dropwise with stirring and allowed to react for 2 hr. The temperature of the mixture was maintained at 110°. The mixture was distilled to give 7.5 g (191%) of benzaldehyde and a small amount of unreacted **8**. The residue was chromatographed (basic aluminum oxide–benzene) to give 1.5 g (90%) of sulfur.

At 100°, 3.6 g (188%) of benzaldehyde, 0.8 g (69%) of sulfur, and 0.30 g (6%) of 4-methyl-2-phenyl-5-phenylimino-1,2,4-thiadiazolidine-3-thione (**10a**) were obtained from the reaction between the oxaziridine **1a** (6.1 g, 37 mmol, AO 81%) and the isothiocyanate **8** (4.9 g, 36 mmol) for 1.2 hr.

Thiadiazolidinethione **10a** was obtained as pale yellow needles (from EtOH): mp 131–132.5°; ir (Nujol) 1610 cm^{-1} (C=N); mass spectrum *m/e* 299 (M^+, calcd 299), 226 ($M^+ - CH_3NCS$), 194 ($PhNCNPh^+$), 164 ($M^+ - PhNCS$), 132 ($PhNCNCH_3^+$), 135 ($PhNCS^+$).

Anal. Calcd for $C_{15}H_{13}N_3S_2$: C, 60.17; H, 4.37; N, 14.03. Found: C, 59.85; H, 4.10; N, 13.73.

Reaction of the Oxaziridine 1e. The reaction of the oxaziridine **1e** (11.0 g, 49 mmol, AO 91%) with the isothiocyanate **8** (7.7 g, 57 mmol) in 7 ml of benzene was carried out by the same procedure as above for 3 hr. The reaction mixture was distilled to give benzaldehyde (5.0 g, 96%) and *N*-cyclohexyl-*N'*-phenylcarbodiimide (**9e**, 5.7 g, 58%), bp 80° (1 mm), ir (neat) 2140 cm^{-1} (-N=C=N-). The residue was chromatographed (basic aluminum oxide–benzene) to give 1.3 g (82%) of sulfur. The compound **9e** was treated with sodium methoxide in water–methanol to afford *N*-cyclohexyl-*N'*-phenylurea as colorless needles (from EtOH): mp 190–191°; ir (Nujol) 3330 (NH), 1628 (C=O), 1547, 1320, and 1308 cm^{-1} (NH, CN); mass spectrum *m/e* 218 (M^+, calcd 218), 135 ($M^+ - C_6H_{11}$), 119 ($PhNCO^+$).

Anal. Calcd for $C_{13}H_{18}N_2O$: C, 71.53; H, 8.31; N, 12.83. Found: C, 71.31; H, 8.25; N, 12.76.

Under milder conditions, 90° (5.5 hr), the oxaziridine **1e** (11.1 g, 51 mmol, AO 93%) was allowed to react with the isothiocyanate **8** (6.75 g, 50 mmol). The mixture was distilled to give 3.1 g (117%) of benzaldehyde, but none of the carbodiimide **9e**. The residue was chromatographed (basic aluminum oxide–benzene) to give 5.30 g (58%) of 2,4-diphenyl-5-cyclohexylimino-1,2,4-thiadiazolidine-3-thione (**11e**) and 0.03 g (2%) of sulfur. The former was recrystallized from ethanol to give colorless needles: mp 208–209°; ir (Nujol) 1630 cm^{-1} (C=N); mass spectrum *m/e* 367 (M^+, calcd 367), 285 ($M^+ - C_6H_{10}$), 194 ($PhNCNPh^+$), 141 ($C_6H_{11}NCS^+$).

Anal. Calcd for $C_{20}H_{21}N_3S_2$: C, 65.36; H, 5.76; N, 11.43. Found: C, 65.13; H, 5.81; N, 11.31.

Reaction of the Oxaziridine 1b. The reaction of the oxaziridine **1b** (8.0 g, 48 mmol, AO 90%) and the isothiocyanate **8** (10.9 g, 81 mmol) was carried out by the same procedure as above at 85° for 2 hr. The solvent and benzaldehyde (5.1 g, 119%) were distilled off and addition of hexane to the residue precipitated crystalline solid. The solid was filtered and recrystallized (benzene–ethanol) to afford 0.2 g of sulfur and 2.8 g (22%) of 4-ethyl-2-phenyl-5-phenylimino-1,2,4-thiadiazolidine-3-thione (**10b**). The filtrate was chromatographed (basic aluminum oxide–benzene) to give 0.3 g of sulfur and 0.5 g (4%) of 2,4-diphenyl-5-ethylimino-1,2,4-thiadiazolidine-3-thione (**11b**). The combined yield of sulfur was 19%.

10b was obtained as colorless needles (from ethanol–benzene): mp 171–172°; ir (Nujol) 1615 cm^{-1} (C=N); nmr ($CDCl_3$) δ 1.15 (t, 3, J = 6.75 Hz, CH_3), 3.31 (q, 2, J = 6.75 Hz, CH_2), 6.7–7.5 (m, 10, 2 Ph); mass spectrum *m/e* 313 (m^+, calcd 313), 285 ($M^+ - CH_2{=}CH_2$), 226 ($M^+ - EtNCS$), 194 ($PhNCNPh^+$), 178 ($M^+ - PhNCS$), 167 ($M^+ - 146$), 146 ($PhNCNEt^+$), 135 ($PhNCS^+$).

Anal. Calcd for $C_{16}H_{15}N_3S_2$: C, 61.31; H, 4.82; N, 13.41. Found: C, 61.25; H, 4.78; N, 13.35.

11b was obtained as colorless flakes (from ethanol): mp 153–154° ir (Nujol) 1635 cm^{-1} (C=N); nmr ($CDCl_3$) δ 1.29 (t, 3, J = 6.75 Hz, CH_3), 4.03 (q, 2, J = 6.75 Hz, CH_2), 6.7–7.5 (m, 10, 2 Ph); mass spectrum *m/e* 313 (M^+, calcd 313), 285, 225 (285 –

NCS), 194, 178, 167, 145 (PhNCNEt$^+$ − H), 135. Unassigned fragments correspond to those from **10b**.

Anal. Calcd for $C_{16}H_{15}N_3S_2$: C, 61.31; H, 4.82; N, 13.41. Found: C, 61.29; H, 4.83; N, 13.41.

Reaction of the Oxaziridine 1c. From the oxaziridine **1c** (7.3 g, 37 mmol, AO 90%) and the isothiocyanate **8** (5.0 g, 37 mmol), 2.4 g (122%) of benzaldehyde, 0.35 g (30%) of sulfur, 0.50 g (8%) of 4-*n*-butyl-2-phenyl-5-phenylimino-1,2,4-thiadiazolidine-3-thione (**10c**), and 1.75 g (28%) of 2,4-diphenyl-5-*n*-butylimino-1,2,4-thiadiazolidine-3-thione (**11c**) were obtained. The latter three compcunds were separated by chromatography.

10c was obtained as pale yellow needles (from ethanol): mp 95–96°; ir (Nujol) 1610 cm^{-1} (C=N); mass spectrum *m/e* 341 (M$^+$, calcd 341), 285 (M$^+$ − EtCH=CH$_2$), 226 (M$^+$ − BuNCS), 206 (M$^+$ − PhNCS), 194 (PhNCNPh$^+$), 174 (PhNCNBu$^+$), 167 (M$^+$ − 174), 135 (PhNCS$^+$).

Anal. Calcd for $C_{18}H_{19}N_3S_2$: C, 63.31; H, 5.61; N, 12.30. Found: C, 63.10; H, 5.53; N, 12.11.

11c was obtained as colorless needles (from ethanol): mp 115–116°; ir (Nujol) 1635 cm^{-1} (C=N); mass spectrum *m/e* 341 (M$^+$, calcd 341), 285, 226, 206, 194, 174, 167, 135. The assignments for these fragments correspond to those for **10c**.

Anal. Calcd for $C_{18}H_{19}N_3S_2$: C, 63.31; H, 5.61; N, 12.30. Found: C, 63.54; H, 5.39; N, 12.16.

Reaction of the Oxaziridine 1d. A mixture of the oxaziridine **1d** (6.5 g, 38 mmol, AO 95%) and phenyl isothiocyanate (**8**, 7.27 g, 54 mmol) in benzene (10 ml) was allowed to react at 90° for 5.5 hr. Removal of the solvent precipitated 1.5 g of 4-isopropyl-2-phenyl-5-phenylimino-1,2,4-thiadiazolidine-3-thione (**10d**). The filtrate was distilled to give 2.8 g (97%) of benzaldehyde and small amounts of **1d** and **8**. The residue was chromatographed (basic aluminum oxide–benzene) to give 1.6 g of the compound **10d** and 0.1 g (1%) of 2,4-diphenyl-5-isopropylimino-1,2,4-thiadiazolidine-3-thione (**11d**). The total yield of the compound **10d** was 3.1 g (36%).

10d was obtained as colorless needles (from ethanol): mp 166.5–167°; ir (Nujol) 1612 cm^{-1} (C=N); nmr ($CDCl_3$) δ 1.07 (d, 6, J = 6.5 Hz, 2 CH_3), 3.4 (m, 1, J = 6.5 Hz, CH), 6.7–7.5 (m, 10, 2 Ph); mass spectrum *m/e* 327 (M$^+$, calcd 327), 285 (M$^+$ − MeCH=CH$_2$), 226 (M$^+$ − PrNCS), 194 (PhNCNPh$^+$), 192 (M$^+$ − PhNCS), 167 (M$^+$ − 160), 160 (PhNCNPr$^+$), 150 (285 − 135), 135 (PhNCS$^+$), 101 (PrNCS$^+$).

Anal. Calcd for $C_{17}H_{17}N_3S_2$: C, 62.35; H, 5.23; N, 12.83. Found: C. 62.20; H, 5.17; N, 12.89.

11d was obtained as colorless needles (from ethanol): mp 196.5–197°; ir (Nujol) 1635 cm^{-1} (C=N); nmr ($CDCl_3$) δ 1.37 (d, 6, J = 6.6 Hz, 2 CH_3), 5.4 (m, 1, J = 6.6 Hz, CH), 6.8–7.8 (m, 10, 2 Ph); mass spectrum *m/e* 327 (M$^+$, calcd 327), 285, 226, 194, 192, 167, 160, 150, 135, 101. These fragments correspond to those from **10d**.

Anal. Calcd for $C_{17}H_{17}N_3S_2$: C, 62.35; H, 5.23; N, 12.83. Found: C, 62.63; H, 5.15; N, 12.68.

Reaction of the Oxaziridine 1f. The oxaziridine **1f** (8.13 g, 46 mmol, AO 98%) and the isothiocyanate **8** (6.2 g, 46 mmol) were allowed to react at 105° for 2 hr. Then the mixture was cooled to give a quantitative amount (14.5 g) of crystalline solid. A part (3.0 g) of the filtered solid was chromatographed (basic aluminum oxide–benzene) and 2.04 g (62%) of 2-*tert*-butyl-3,4-diphenyl-1,2,4-oxadiazolidine-5-thione (**12**) and 0.57 g (19%) of 2-*tert*-butyl-3,4-diphenyl-1,2,4-oxadiazolidin-5-one (**13**) were obtained. The filtrate was proved to contain small amounts of benzaldehyde and *N,N'*-di-*tert*-butylcarbodiimide by ir and glpc. The oxadiazolidinethione **12** was recrystallized from ethanol to afford colorless needles: mp 129–130°; ir (Nujol) 1295 and 1157 cm^{-1}; nmr (CCl_4) δ 1.32 (s, 9, *t*-Bu), 5.93 (s, 1, CH), 7.1–7.4 (m, 10, 2 Ph); mass spectrum *m/e* 312 (M$^+$, calcd 312), 252 (M$^+$ − COS), 180 (PhN=CPh$^+$), 161 (PhCH=NBu-*t*$^+$).

Anal. Calcd for $C_{18}H_{20}NOS$: C, 69.19; H, 6.45; N, 8.97. Found: C, 69.27; H, 6.39; N, 8.95.

The oxadiazolidinone **13** was identical with an authentic sample.[1]

Reaction of the Oxaziridine 1i. A solution of the oxaziridine **1i** (2.05 g, 6.5 mmol, AO 93%) and the isothiocyanate **8** (1.22 g, 9.0 mmol) in toluene (10 ml) was refluxed for 7 hr. The ir spectrum of the mixture showed the strong absorption of unreacted **8** and no absorption of the benzoyl group. The mixture was distilled to give 0.65 g of **8** and 1.08 g (53%) of 2,2-pentamethylene-5-phenyl-1,3,4-dioxazoline, which is reported in the preceding paper.[1]

Reaction of the Oxaziridine 1k. The reaction between the oxaziridine **1k** (12.7 g, 50 mmol, AO 83%) and the isothiocyanate **8** (6.7 g, 50 mmol) at 100° for 1.4 hr gave 3.8 g (143%) of benzaldehyde, 1.05 g (67%) of sulfur, and 0.65 g (7%) of 2-phenyl-4-benzyl-5-phenylimino-1,2,4-thiadiazolidine-3-thione (**10k**). The last compound was recrystallized from benzene–ethanol to give pale yellow needles: mp 151.5–153.5°; ir (Nujol) 1612 cm^{-1} (C=N); mass spectrum *m/e* 375 (M$^+$, calcd 375), 343 (M$^+$ − S), 240 (M$^+$ − PhNCS), 208 (PhNCNCH$_2$Ph$^+$), 167 (M$^+$ − 208), 135 (PhNCS$^+$).

Anal. Calcd for $C_{21}H_{17}N_3S_2$: C, 67.17; H, 4.56; N, 11.19. Found: C, 66.89; H, 4.56; N, 10.99.

Pyrolysis of the Thidiazolidinethione 10d. The compound **10d** (800 mg, 2.45 mmol) was heated at 180–190° (10 mm) in an apparatus equipped with a trap cooled with Dry Ice. The trapped liquid (600 mg) was identified and determined by glpc to contain 165 mg (25%) of phenyl isothiocyanate, 84 mg (34%) of isopropyl isothiocyanate, and 99 mg (26%) of *N*-isopropyl-*N'*-phenylcarbodiimide. From the residue, 95 mg (61%) of sulfur was obtained.

Treatment of the Compound 10d with Triethyl Phosphite. The thiadiazolidinethione **10d** (1.0 g, 3.1 mmol) and triethyl phosphite (50 mg, 0.31 mmol) in benzene (7 ml) was refluxed for 1 hr. The solvent was removed *in vacuo* and the residue was solidified. Recrystallization (ethanol) gave 610 mg (61%) of the rearranged product **11d**.

When the compound **10d** (500 mg, 1.5 mmol) was treated with the phosphite (300 mg, 1.8 mmol) in benzene under similar conditions, an ir spectrum of the mixture indicated the formation of an isothiocyanate (*ca.* 2120 cm^{-1}). The mixture was distilled and determined by glpc; phenyl isothiocyanate (42 mg, 17%), isopropyl isothiocyanate (30 mg, 17%), and triethyl thiophosphite (226 mg, 64%) were obtained. The residue showed the ir absorptions of a carbodimide (2150 cm^{-1}) and the rearranged product **11d**. The treatment of the residue with water gave 21 mg of *N,N'*-diphenylurea, which showed the formation of *N,N'*-diphenylcarbodiimide (7%) and 15 mg (3%) of **11d**.

Hydrolysis of the Compound 10d. To a solution of the compound **10d** (400 mg, 1.2 mmol) in ethanol (15 ml), 3 ml of 12 *N* hydrochloric acid was added and the solution was refluxed for 5 hr, extracted (ether), dried (Na_2SO_4), and concentrated. The resultant solid was recrystallized (methanol) to give 190 mg (87%) of *N*-isopropyl-*N'*-phenylurea, which was identical with an authentic sample from phenyl isocyanate and isopropylamine.

Reduction of the Thiadiazolidinethione 10d. The compound **10d** (500 mg, 1.5 mmol) was treated with $LiAlH_4$ (1.0 g) in refluxing ether for 5 hr, followed by hydrolysis, extraction (ether), drying (Na_2SO_4), and concentration. The resultant solid was recrystallized (ethanol–benzene) to give 110 mg (32%) of *N,N'*-diphenylthiourea, which was identical with an authentic sample.

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Registry No.—**1a**, 3400-12-2; **1b**, 7771-15-5; **1c**, 21710-99-6; **1d**, 7731-32-0; **1e**, 21711-00-2; **1f**, 7731-34-2; **1g**, 21711-01-3; **1i**, 2289-83-0; **1j**, 3400-13-3; **1k**, 7731-37-5; **2**, 75-15-0; butyl isothiocyanate, 592-82-5; *N,N'*-dicyclohexylthiourea, 1212-29-9; phenyl isothiocyanate, 103-72-0; **9e**, 3878-67-9; **10a**, 50506-86-0; **10b**, 50506-87-1; **10c**, 50506-88-2; **10d**, 50506-89-3; **10k**, 50506-90-6; **11b**, 50506-91-7; **11c**, 50506-92-8; **11d**, 50506-93-9; **11e**, 50506-94-0; **12**, 50506-95-1; **13**, 50506-96-2; *N,N'*-di-*n*-butylthiourea, 109-46-6; α-phenyl-*N*-*tert*-butylnitrone, 3376-24-7; *N*-cyclohexyl-*N'*-phenylurea, 886-59-9.

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Nitrile Sulfides. Synthesis of 1,2,4-Thiadiazoles

Robert K. Howe* and John E. Franz

Research Department, Agricultural Division, Monsanto Company, St. Louis, Missouri 63166

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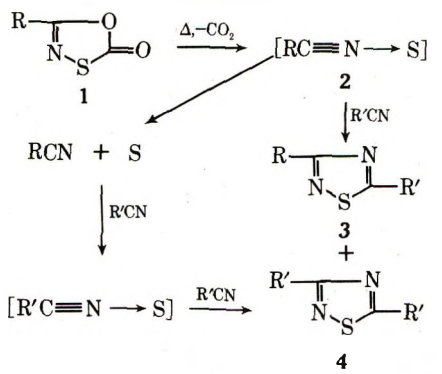
Reaction of nitriles with nitrile sulfide intermediates, generated by thermolysis of 1,3,4-oxathiazol-2-ones, resulted in 1,2,4-thiadiazoles. The scope of this new synthesis of thiadiazoles was explored; highest yields are obtained with electrophilic nitriles and with aromatic nitrile sulfides.

1,3-Dipolar cycloaddition reactions of nitrile oxides have been employed repeatedly in syntheses of heterocyclic compounds.[1,2] Until recently,[3,4] nitrile sulfides have been unavailable for syntheses of N-S heterocycles *via* cycloadditions. We have provided evidence that nitrile sulfides may be generated as reactive intermediates by thermolysis of 1,3,4-oxathiazol-2-ones and may be trapped in 1,3-dipolar cycloaddition reactions with acetylenes such as dimethyl acetylenedicarboxylate and ethyl propiolate.[3,4] We report here a new synthesis of 1,2,4-thiadiazoles *via* cycloaddition of nitrile sulfides to nitriles.

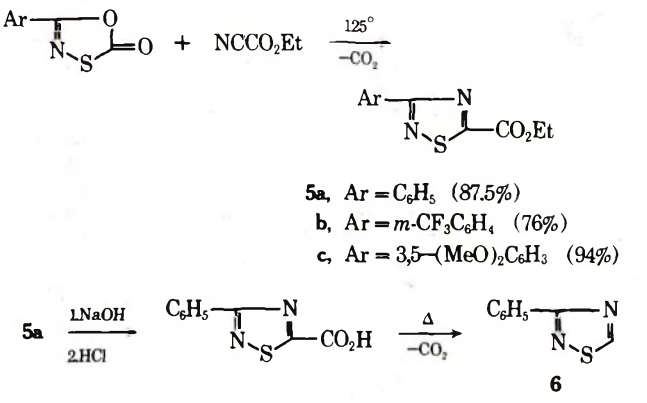
Thermolysis of 5-substituted 1,3,4-oxathiazol-2-ones (**1**) in excess nitrile led to thiadiazoles **3** and, in several cases, to lesser amounts of by-products **4** (Scheme I, Table I). Competitive decomposition of the intermediate nitrile sulfides produced sulfur and the nitrile derived from the oxathiazolone. Although the thiadiazole reaction proceeds less readily than the analogous 1,3-dipolar cycloaddition of nitrile oxides to nitriles to give 1,2,4-oxadiazoles,[5,6] under certain conditions reasonable yields of thiadiazoles may be obtained (Tables I and II). Thus, decarboxylation of 5-phenyl-1,3,4-oxathiazol-2-one in 35 equiv of benzonitrile at 190° gave 3,5-diphenyl-1,2,4-thiadiazole in 50% yield. The product and authentic material, prepared by iodine oxidation of thiobenzamide,[7] gave identical ir spectra and gave an undepressed mixture melting point. Products **3** and **4** were further characterized by mass spectrometry; the major fragmentation routes result in loss of RCN and R'CN (see Experimental Section), as found previously[8] for 3,5-disubstituted 1,2,4-thiadiazoles.

Scheme I



The cycloadditions of aromatic nitrile sulfides to ethyl cyanoformate proceeded especially well to give the ethyl 3-aryl-1,2,4-thiadiazole-5-carboxylates **5a**, **5b**, and **5c** (Scheme II; the indicated yields are for isolated pure products). Hydrolysis of **5a** and decarboxylation of the resultant acid gave the known[9] 3-phenyl-1,2,4-thiadiazole (**6**) in 99% yield.

Scheme II



By-product **4** (Scheme I) probably occurs *via* cycloaddition of R'CNS to R'CN. The R'CNS could form from reaction of atomic sulfur with R'CN[10] (Scheme I) or from direct sulfur atom transfer between RCNS and R'CN. Yields of **3** were found to increase with greater excesses of nitrile, as expected, and with higher temperatures (Tables I and II). Evidently, the rate of cycloaddition reaction to form thiadiazole increases more rapidly with temperature than the competing decomposition of nitrile sulfide to nitrile and sulfur. The data of Table I reveal that the yields of thiadiazoles increase with more electrophilic nitriles and decrease with less electrophilic nitriles.[11] Substituent effects in the oxathiazolones are similar. Because the yield of cycloaddition product **3** depends on the relative rates of cycloaddition and decomposition of the substituted nitrile sulfide, the absolute effects of substituents in the oxathiazolones on the cycloaddition rate are not readily determined. Thermolysis of 5-phenyl-1,3,4-oxathiazol-2-one at 125° in chlorobenzene in the presence of 1 equiv of boron trifluoride etherate showed an eightfold rate enhancement, but the presence of boron trifluoride etherate resulted in lower yields of thiadiazole (Table II) in the cycloaddition reaction.[12]

Our new synthesis of 1,2,4-thiadiazoles allows ready preparation of 3,5-unsymmetrically substituted derivatives with no uncertainty about the position of the substituents. Thus, both 3-phenyl-5-*p*-tolyl-1,2,4-thiadiazole, mp 115–116°, and 5-phenyl-3-*p*-tolyl-1,2,4-thiadiazole, mp 77.5–79°, were prepared unambiguously. A previous report[13] of the preparation of 3- (or 5-) phenyl-5- (or 3-) *p*-tolyl-1,2,4-thiadiazole, mp 56°, did not allow an exact

Table I
Thiadiazole Preparations *via* Nitrile Sulfides[a] at 190°

R	R′	Mole ratio,[b] 1:2	Yield[c] of 3, %	Yield[c] of 4, %
C_6H_5	C_6H_5	0.0287	50 (41)	
C_6H_5	p-$CH_3C_6H_4$	0.0287	33	2.3
C_6H_5	p-$CH_3C_6H_4$	0.0324	30 (10)	1.7
C_6H_5	p-ClC_6H_4	0.0287	56	8.6
p-$CH_3C_6H_4$	C_6H_5	0.0287	30 (8)	4.8
p-$CH_3C_6H_4$	p-$CH_3C_6H_4$	0.0287	28 (12)	
p-ClC_6H_4	C_6H_5	0.0287	57 (36)	7
p-ClC_6H_4	p-ClC_6H_4	0.0287	73	
p-ClC_6H_4	p-ClC_6H_4	0.0383	71 (62)	
CH_3	C_6H_5	0.0500[d]	6.9 (2.7)	3.7
p-ClC_6H_4	EtO_2CCH_2	0.0287	15.7 (6)	

[a] See Scheme I. [b] Unless otherwise indicated, **1** was added in three equal portions at 5-min intervals to **2** stirred at 190°. [c] Yields determined by gc analysis. Yields in parentheses are yields of isolated pure products. [d] The liquid oxathiazolone was added dropwise during 35 min to the nitrile.

structural assignment and very probably led to a mixture, based on the reported melting point.

Experimental Section

Melting points were taken in open capillaries in a Mel-Temp apparatus and are corrected. All nitriles were redistilled and checked for purity by gc prior to use, as impurities present in the commercial nitriles resulted in lower product yields. The 1,3,4-oxathiazol-2-ones were prepared by reaction of acid amides with chlorocarbonylsulfenyl chloride according to reported procedures.[14]

General Procedure for 3,5-Diaryl-1,2,4-thiadiazoles. To 1.0 mol of aromatic nitrile stirred at 190° was added in three equal portions at 5-min intervals a total of 0.0287 mol of 5-aryl-1,3,4-oxathiazol-2-one. The solution was stirred for another 10 min at 190°, cooled, analyzed by gc on a 2-ft column of 10% SE-30 programmed from 70 to 250°, and concentrated under vacuum to remove excess nitrile. The residue was boiled with methanol or ethanol, undissolved sulfur was removed by filtration, and the filtrate was concentrated somewhat and cooled to give solid product, which then was recrystallized from an appropriate solvent.

3,5-Diphenyl-1,2,4-thiadiazole. Pure product, mp 86–88° (lit.[7] mp 90°), was obtained from ethanol: uv max (CH_3CN) 219 nm (log ϵ 4.20), 255 (4.59); mass spectrum m/e (rel intensity, fragment) 238 (2, M^+), 135 (100, $M^+ - C_6H_5CN$), 103 (22, $C_6H_5CN^+$), 77 (23, $C_6H_5^+$).

5-*p*-Chlorophenyl-3-phenyl-1,2,4-thiadiazole. The product mixture was crystallized from ethanol and from acetonitrile to give a 90:10 mixture (gc assay), mp 145–147°, of 5-p-chlorophenyl-3-phenyl-1,2,4-thiadiazole and 3,5-bis(*p*-chlorophenyl)-1,2,4-thiadiazole (identified by gc retention time and gc–mass spectral data). A pure sample of product, mp 152°, was obtained by gas chromatographic purification, mass spectrum m/e (rel intensity, fragment) 272 (17, M^+), 169 (6, $M^+ - C_6H_5CN$), 135 (100, $M^+ - ClC_6H_4CN$), 111 (2, $C_6H_4Cl^+$), 103 (18, $C_6H_5CN^+$), 77 (18, $C_6H_5^+$). This isomer is distinguished from 3-*p*-chlorophenyl-5-phenyl-1,2,4-thiadiazole by ir absorptions ($CHCl_3$ solvent) at 11.96 (s) and 12.18 μ (w, shoulder) whereas the 5-phenyl isomer has absorption at 11.88 μ (s), with no shoulder at 12.18 μ.

Anal. Calcd for $C_{14}H_9ClN_2S$: C, 61.65; H, 3.33. Found: C, 61.80; H, 3.44.

3-*p*-Chlorophenyl-5-phenyl-1,2,4-thiadiazole. The product was recrystallized from acetonitrile to give 100% pure (gc assay) product, mp 118–119°. This isomer has weak ir absorptions ($CHCl_3$ solvent) at 7.40, 10.00, and 10.88 μ that are not present in the 3-phenyl isomer.

Anal. Calcd for $C_{14}H_9ClN_2S$: C, 61.65; H, 3.33. Found: C, 61.45; H, 3.33.

3,5-Bis(*p*-chlorophenyl)-1,2,4-thiadiazole. Pure product, mp 163–164° (lit.[15] mp 161–162°), was obtained from ethanol: mass spectrum m/e (rel intensity, fragment) 306 (18, M^+), 169 (100, $M^+ - ClC_6H_4CN$), 137 (30, $ClC_6H_4CN^+$), 111 (10, $C_6H_4Cl^+$), 102 (15, $C_6H_4CN^+$).

3-Phenyl-5-*p*-tolyl-1,2,4-thiadiazole. Gc and gc–mass spectral analyses of the reaction mixture revealed that 0.3% 3,5-diphenyl-1,2,4-thiadiazole, 33.2% 3-phenyl-5-*p*-tolyl-1,2,4-thiadiazole, and 2.3% 3,5-di-*p*-tolyl-1,2,4-thiadiazole had formed. Crystallization of the product mixture from methanol and then methylcyclohexane gave pure 3-phenyl-5-*p*-tolyl-1,2,4-thiadiazole: mp 115–116°; mass spectrum m/e (rel intensity, fragment) 252 (25, M^+), 149 (34, $M^+ - C_6H_5CN$), 135 (100, $M^+ - CH_3C_6H_4CN$), 117 (5, $CH_3C_6H_4CN^+$), 103 (24, $C_6H_5CN^+$), 91 (11, $C_7H_7^+$), 77 (29, $C_6H_5^+$); nmr ($CDCl_3$) δ 7.2–8.5 (m, 9, ArH), 2.40 (s, 3, CH_3). This isomer has a strong ir absorption ($CHCl_3$ solvent) at 12.20 μ that is absent in the isomeric 5-phenyl-3-*p*-tolyl-1,2,4-thiadiazole.

Anal. Calcd for $C_{15}H_{12}N_2S$: C, 71.40; H, 4.79. Found: C, 71.63; H, 4.84.

5-Phenyl-3-*p*-tolyl-1,2,4-thiadiazole. The product was recrystallized from hexane to give 100% pure material, mp 77.5–79°, which has a medium-intensity ir absorption ($CHCl_3$ solvent) at 6.65 μ that is absent in the 3-phenyl isomer.

Anal. Calcd for $C_{15}H_{12}N_2S$: C, 71.40; H, 4.79. Found: C, 71.32; H, 4.79.

3,5-Di-*p*-tolyl-1,2,4-thiadiazole. Pure product, mp 127–129° (lit.[13] mp 129°), was obtained from aqueous ethanol: mass spectrum m/e (rel intensity, fragment) 266 (22, M^+), 149 (100, $M^+ - CH_3C_6H_4CN$), 117 (23, $CH_3C_6H_4CN^+$), 91 (16, $C_7H_7^+$); nmr ($CDCl_3$) δ 8.27 (d, 2, ArH), 7.93 (d, 2, ArH), 7.27 (d, 4, ArH), 2.40 (s, 6, CH_3).

3-Methyl-5-phenyl-1,2,4-thiadiazole. To 86.8 g (0.842 mol) of redistilled benzonitrile at reflux was added dropwise 4.92 g (0.0421 mol) of 5-methyl-1,3,4-oxathiazol-2-one[14] during 35 min. The solution was held at reflux for another 10 min, cooled, analyzed by gc (see Table I), and concentrated under vacuum to remove excess benzonitrile. The residue was triturated with 30 ml of methanol, and the mixture was filtered free of sulfur. The filtrate was cooled in Dry Ice to give 0.24 g of 97% pure (gc assay) 3,5-diphenyl-1,2,4-thiadiazole, mp 82–87°. Recrystallization of this solid from methanol gave 0.12 g of solid, mp 87–89° (mmp 87–89° with authentic material), that gave the same ir spectrum as authentic 3,5-diphenyl-1,2,4-thiadiazole.

The filtrate from the first crystallization was distilled under vacuum; 86% pure product, 0.32 g of oil that solidified, was collected at bp 100–125° (2 mm). This solid was recrystallized from cold aqueous methanol to give 0.20 g of 100% pure 3-methyl-5-phenyl-1,2,4-thiadiazole (2.7% yield): mp 54–55.5° (lit.[16] mp 50°); nmr ($CDCl_3$) δ 8.00 (m, 2, ArH), 7.53 (m, 3, ArH), 2.73 (s, 3, CH_3).

3-(*p*-Chlorophenyl)-1,2,4-thiadiazole-5-acetic Acid Ethyl Ester. The general procedure was employed. The product was crystallized from aqueous ethanol and from hexane to give pure product: mp 127.5–129°; ir ($CHCl_3$) 5.78 μ; nmr ($CDCl_3$) δ 8.23 (m, 2, ArH), 7.43 (m, 2, ArH), 4.33 (q, 2, J = 7 Hz, OCH_2CH_3), 4.27 (s, 2, CH_2CO), 1.35 (t, 3, J = 7 Hz, OCH_2CH_3).

Anal. Calcd for $C_{12}H_{11}ClN_2O_2S$: C, 50.98; H, 3.92. Found: C, 50.98; H, 3.87.

Ethyl 3-Phenyl-1,2,4-thiadiazole-5-carboxylate (5a). A solution of 14.0 g (0.0783 mol) of 5-phenyl-1,3,4-oxathiazol-2-one and 31.0 g (0.313 mol) of ethyl cyanoformate in 150 ml of dodecane was held at reflux under N_2 (pot temperature was 138° at start) for 12.75 hr, at which time gc analysis revealed that the reaction was complete and that the product had formed in 89% yield. Removal of the solvent and crystallization of the residue from ethanol gave 15.97 g (87.5%) of white needles: mp 70–71°; ir ($CHCl_3$) 5.72, 5.81 μ; uv max (CH_3CN) 242 nm (log ϵ 4.24), 293 (3.44);

Table II
Effect of Mole Ratio, Temperature, and Boron Trifluoride Etherate on Yield of 3,5-Diphenyl-1,2,4-thiadiazole[a]

Mole ratio,[b] 1:2	Equiv of $BF_3 \cdot Et_2O$	Temp, °C	Yield of 3,[c] %
0.100	0	190	74
0.0287	0	190	39
0.10	0	190	14
0.0287	0	160	35
0.0287	0	130	25
0.0287	2[d]	190	10
0.0287	1	130	0

[a] See Scheme I. [b] All the **1** was added in one portion to **2** at the indicated temperature. [c] Determined by gc analysis. [d] Some of the boron trifluoride etherate was lost through the air-cooled condenser.

mass spectrum m/e (rel intensity, fragment) 234 (46, M^+), 189 (4, (M^+ − OEt), 161 (3, M^+ − CO_2Et), 135 (100, $C_6H_5CNS^+$), 103 (32, $C_6H_5CN^+$), 77 (16, $C_6H_5^+$).

Anal. Calcd for $C_{11}H_{10}N_2O_2S$: C, 56.40; H, 4.30. Found: C, 56.21; H, 4.45.

Ethyl 3-(α,α,α-Trifluoro-*m*-tolyl)-1,2,4-thiadiazole-5-carboxylate (5b). Use of a similar procedure to that above (92.5-hr reaction time) gave product thiadiazole in 76% yield (isolated product) as a white solid, mp 79–80.5° (from heptane), ir ($CHCl_3$) 5.72, 5.80 μ.

Anal. Calcd for $C_{12}H_9F_3N_2O_2S$: C, 47.68; H, 3.00. Found: C, 47.86; H, 2.84.

Ethyl 3-(3,5-Dimethoxyphenyl)-1,2,4-thiadiazole-5-carboxylate (5c). Use of a similar procedure to that above (92.5-hr reaction time) gave product thiadiazole in 94% yield (isolated) as a white solid, mp 125–126.5° (from dodecane), ir ($CHCl_3$) 5.72, 5.80 μ.

Anal. Calcd for $C_{13}H_{14}N_2O_4S$: C, 53.05; H, 4.79. Found: C, 53.19; H, 4.90.

3-Phenyl-1,2,4-thiadiazole (6). A mixture of 8 g (0.034 mol) of ethyl 3-phenyl-1,2,4-thiadiazole-5-carboxylate, 1.5 g (0.037 mol) of sodium hydroxide, 10 ml of ethanol, and 60 ml of water was heated with stirring on a steam bath for 1 hr. The resultant solution was allowed to cool and was acidified with 3.5 ml (0.042 mol) of concentrated hydrochloric acid. The resultant mixture, containing granular solid carboxylic acid, was heated on a steam bath until decarboxylation was complete. The mixture was cooled and extracted with ether. The ether layer was dried ($MgSO_4$) and concentrated under vacuum to give 5.5 g (99%) of colorless oil. Distillation of this material gave a single fraction, bp 76.5° (0.5 mm) [lit.[9] bp 78–80° (0.3 mm)], nmr ($CDCl_3$) δ 9.90 (s, 1, 5-H), 8.37 (m, 2, ArH), 7.48 (m, 3, ArH).

Anal. Calcd for $C_8H_6N_2S$: C, 59.23; H, 3.74; N, 17.27; S, 19.76. Found: C, 59.03; H, 3.84; N, 17.23; S, 19.91.

Registry No.—**1**, R = Me, 17452-74-3; **1**, R = Ph, 5852-49-3; **3**, R = R′ = Ph, 4115-15-5; **3**, R = Ph, R′ = p-ClC_6H_4, 50483-71-1; **3**, R = *p*-ClC_6H_4, R′ = Ph, 50483-72-2; **3**, R = R′ = *p*-ClC_6H_4, 4115-17-7; **3**, R = Ph, R′ = *p*-MeC_6H_4; 50483-74-4; **3**, R = *p*-MeC_6H_4, R′ = Ph, 50483-75-5; **3**, R = R′ = *p*-MeC_6H_4, 17590-34-0; **3**, R = Me, R′ = Ph, 50483-77-7; **4**, R = *p*-ClC_6H_4, R′ = CH_2CO_2Et, 50483-78-8; **5a**, 50483-79-9; **5b**, 50483-80-2; **5c**, 50483-81-3; **6**, 50483-82-4.

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Hypervalent Sulfur Chemistry. Evidence for Tetracoordinate Sulfur(IV) and Tricoordinate Sulfur(II) Intermediates in the Reaction of *p*-Tolyl Sulfoxide with *p*-Tolyllithium[1a]

Bernard K. Ackerman, Kenneth K. Andersen,* Ivan Karup-Nielsen,[1b] Nihad B. Peynircioglu, and Sandra A. Yeager

Department of Chemistry, University of New Hampshire, Durham, New Hampshire 03824

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p-Tolyl sulfoxide (**1**) reacted with excess *p*-tolyllithium (**2**) to give *p*-tolyl sulfide (**3**, 66%), *p,p′*-bitolyl (**4**, 31%), and *m,p′*-bitolyl (**5**, 26%). The reaction of tri-*p*-tolysulfonium salt with **2**, which gave **3** (87%), **4**, (72%), and **5** (5%), is thought to proceed largely through a tetra-*p*-tolylsulfurane which collapses to product. A mechanism for the reaction of **1** with **2** is proposed which involves 4-toluyne formation from a tetracoodinate S(IV) precursor, tri-*p*-tolyloxysulfurane (**7**). The 4-toluyne adds **2** to give **4** and **5**. *N*-*p*-toluenesulfonyl-*S,S*-di-*p*-tolylsulfimide and **2** gave **3** (80%), **4** (66%), **5** (1–2%), and *p*-toluenesulfonamide (60%), while methoxydi-*p*-tolylsulfonium salt and **2** gave **3**, **4**, and **5** in the ratio of 135:96:1. These two reactions are proposed to proceed largely through tetra-*p*-tolylsulfurane which collapses to **3** and **4**; very little 4-toluyne is involved as an intermediate. Methyl *p*-toluenesulfinate and **2** gave **3** (77%), **4** (37%), and **5** (32%). The reaction is thought to proceed *via* formation of **1** which then reacts *via* **7**. Mesityl sulfoxide and mesityllithium gave 2,4,4′,6,6′pentamethyl-2′-(2,4,6-trimethylphenylmethyl)diphenyl sulfide (16%) but no mesityl sulfide or bimesityl.

Hypervalent sulfur chemistry,[2] the chemistry of nonoctet sulfur compounds such as sulfonium ylides, sulfoxides, and sulfuranes in which the sulfur participates in the reaction, has been of great synthetic utility and theoretical interest and consequently much studied during the past decade. In nucleophilic substitution at tricoordinate sulfur(IV),[3] *e.g.*, sulfinyl sulfur, the presence or absence of tetracoordinate S(IV) intermediates, conveniently named sulfuranes, formed by bonding of the nucleophile to sulfur, has occupied the attention of many workers. In principle, these intermediates can exist, since stable sulfuranes, such as SF_4, are known. In practice, their detection has often proved difficult. Kinetic studies have not unequivocally demonstrated their presence even though efforts have been made to detect them in various reactions (eq 1[4] and 2[5]).

$$ArSOCH_3 + CD_3OH \longrightarrow ArS(=O)OCD_3 + CH_3OH \quad (1)$$

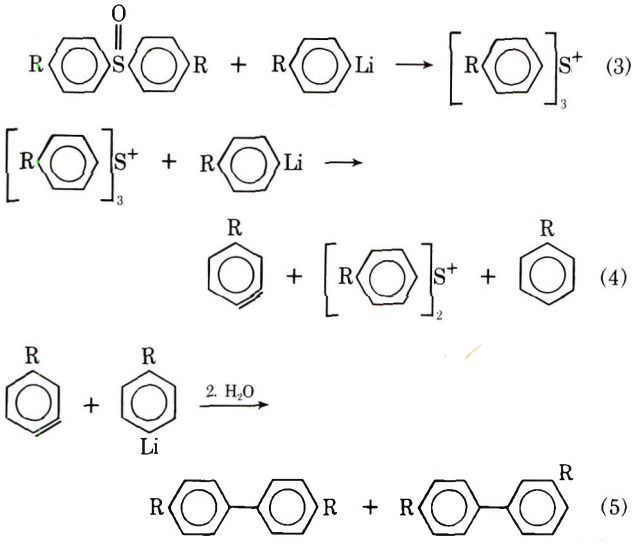
$$ArS(=O)NHAr' + OH^- \longrightarrow ArSO_2^- + Ar'NH_2 \quad (2)$$

Stable sulfuranes usually have four electronegative atoms such as F, Cl, O, or N around sulfur, but recently examples having two carbon atoms as ligands have been synthesized.[6-8] The carbon atoms were shown in one case to be equatorial by X-ray analysis.[6] The two remaining

ligands were still electronegative atoms, in these cases oxygen and fluorine. No sulfurane having four carbon atoms around sulfur has been isolated, but, based on nmr evidence, tetrakis(pentafluorophenyl)sulfurane[9] is said to be stable at temperatures below *ca.* 0°. Apparently, sulfuranes without two electronegative substituents are thermally unstable. Nevertheless, there is often good reason, besides argument by analogy, to believe that they exist as intermediates in various reactions. This paper reports on one of these reactions.

When an ethereal solution of phenyl sulfoxide was treated with phenyllithium, phenyl sulfide (87% yield) and biphenyl (65% yield) were obtained.[10] The analogous reaction of *p*-tolyl sulfoxide (**1**) with *p*-tolyllithium (**2**) yielded *p*-tolyl sulfide (**3**, 66%), *p,p'*-bitolyl (**4**, 31%), and *m,p'*-bitolyl (**5**, 26%).[3]

These reactions were originally assumed to proceed through an initial formation of a triarylsulfonium ion followed by ortho proton abstraction and elimination to give a diaryl sulfide and an aryne. Addition of aryllithium to the aryne followed by protonation of the o-lithiobiaryl upon aqueous work-up of the reaction mixture then would give the biaryls (eq 3-5).



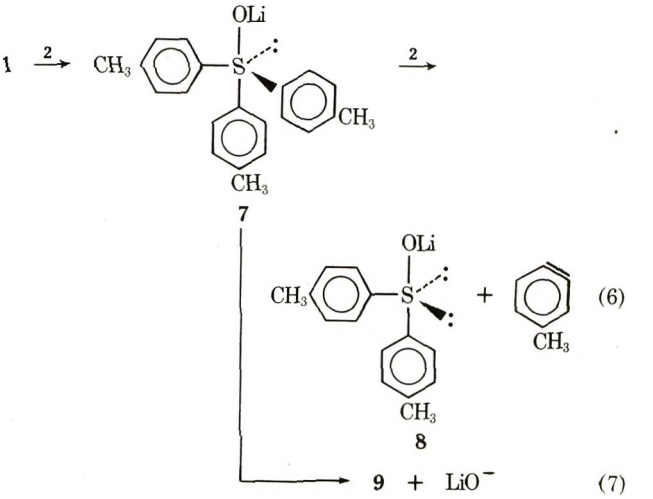
The first reaction is analogous to the formation of triphenylsulfonium ion from phenyl sulfoxide and phenylmagnesium bromide in refluxing benzene.[11] Franzen showed, as Wittig had earlier, that aryl sulfides and biaryls are formed from triarylsulfonium salts upon their reaction with aryllithiums.[12] Thus eq 3-5 seemed like a reasonable pathway to the products.

Franzen suggested, however, that two mechanisms were operative in the reaction of triarylsulfonium salts with aryllithiums. The major process, originally proposed by Wittig,[13] involved formation of a tetraaryl sulfur, a sulfurane, which was thermally unstable and collapsed rapidly to sulfide and a biaryl. The other process involved an aryne (eq 4 and 5) and was believed to be minor based on the low yield of acid formed upon carbonation of the o-lithiobiaryl. Our original note presented evidence for benzyne in the phenyl sulfoxide reaction through trapping by lithium thiophenoxide—the yield of phenyl sulfide increased to greater than 100% based on the triphenylsulfonium salt—and by isolation of o-phenylbenzoic acid formed by the carbonation of o-lithiobiphenyl.[10]

Doubt that a triarylsulfonium cation could be an intermediate arose when Trost and coworkers[14] showed that the reaction of tri-*p*-tolylsulfonium tetrafluoroborate (**6**) with *p*-tolyllithium in tetrahydrofuran at −78° gave only *p*-tolyl sulfide and *p,p'*-bitolyl. No *m,p'*-bitolyl, which would have been formed from 4-toluyne, was detected by ir analysis of the reaction mixture. This aryne is known to form a 50:50 mixture of **4** and **5** upon reaction with *p*-tolyllithium in ether.[15] At about the same time, Oae and Khim[16] reported evidence for aryne formation in the reaction of tri-*p*-tolysulfonium salt with phenyllithium in refluxing ether. Thus, the situation was confused by the appearance of seemingly contradictory results, although differing solvent and temperature conditions may account for this.

When we treated a slurry of tri-*p*-tolylsulfonium bromide with *p*-tolyllithium in ether we obtained *p*-tolyl sulfide (87%), *p,p'*-bitolyl (72%), and *m,p'*-bitolyl (5%) in close agreement with the results of Trost. One might question the origin of the small amount of **5**. In our case, the *p*-tolyllithium was prepared from *n*-butyllithium and *p*-bromotoluene in benzene, a technique which leads to the formation of benzene-insoluble *p*-tolyllithium. Some **4** and **5** were also formed, most of these were removed from the organolithium reagent as it was used in the various reactions, and our results have been corrected for these small amounts. However, the essential point remains that tri-*p*-tolysulfonium salt under our conditions gave very little 4-toluyne; most of the reaction seems to follow another pathway, presumably the one involving a tetratolyl sulfurane for which Trost has presented a good argument.[13] Recently, Jacobus[17] has reinforced the case for a sulfurane.

An explanation for the formation of *m,p'*-bitolyl in the sulfoxide reaction which does not involve a sulfonium salt intermediate must now be forthcoming and a possibility is given by eq 6 and 7.



The initially formed adduct, **7**, is postulated to react in two ways. One (eq 6) is the reaction with p-tolyllithium to give 4-toluyne, which reacts as in eq 5, and the rather novel tricoordinate S(II) species, **8**, which loses lithium oxide to give **3**. The other pathway leads to tri-*p*-tolylsulfonium ion (**9**), which goes on principally to a tetraaryl sulfurane, but which may also have a small 4-toluyne-forming component (eq 7).

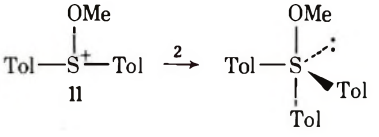
A test for this hypothesis was made by treating *N*-*p*-toluenesulfonyl-*S,S*-di-*p*-tolylsulfimide (**10**) with *p*-tolyllithium. The toluenesulfonamide anion would be expected to be a better leaving group than the oxyanion, assumed to be the leaving group in **7**; so the rate of tritolylsulfonium salt formation should be increased relative to the formation of an intermediate resembling **8**. Thus, the yield of **5** should decrease as a consequence of the decrease in 4-toluyne production, while that of **4** should increase. This was found to be so. The yield of **5** was 1–2% while that of **4** was 66%. *p*-Tolyl sulfide (72–82%) and *p*-toluenesulfonamide (58–65%) were also produced.

Table I
Pmr Parameters of Compounds 14a and 14b[a]

Compd	H_6^1	H_3^2	H_3^3	H_3^4	H_6^5	H_3^6	H_1^7	H_1^8	H_1^9	H_2^{10}	H_2^{11}	H_1^{12}
14[b]	⌊——2.24——⌋				1.99	2.13	⌊—3.98—⌋		6.09	⌊——6.79——⌋		
14b	1.97	2.14	⌊—2.31—⌋		2.50	2.65	4.04	4.15	6.38	⌊——6.99——⌋		
LIS (**14b**)[c]	−1.13	−0.83	−0.55	−0.30	−3.9	−5.0	−3.9	−3.8	−1.57	−0.50	−1.36	−1.63

[a] All measurements were performed on a Jeolco HA-100 instrument in $CDCl_3$ solutions (~0.2 *M*) at ordinary probe temperature. Chemical shifts are given in parts per million downfield from internal tetramethylsilane. [b] Assignments of H^1–H^6 are based on comparison with the $ArCH_3$ groups of mesitylene (δ 2.22), of ditolylmethane (2.27), and of mesityl sulfide [2.17 (ortho) and 2.22 (para)]. [c] Lanthanide-induced chemical shifts were extrapolated to 100 mol % Eu(fod)$_3$ from observed shifts at 0, 14.3, 28.5, 43, and 57 mol % by the method of least squares (correlation coefficients >0.993) and are presented as Δ[Eu(fod)$_3$] values in parts per million: P. V. Demarco, T. K. Elzey, R. B. Lewis, and E. Wenkert, *J. Amer. Chem. Soc.*, **92**, 5734 (1970).

A second variation in leaving group was made by treating methoxydi-*p*-tolylsulfonium fluorosulfonate (**11**) with *p*-tolyllithium (eq 8). Here again, an expected enhance-

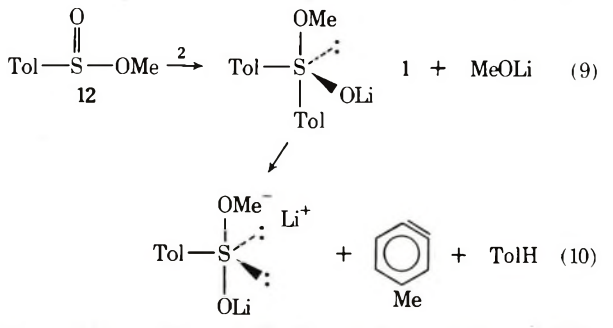


(8)

ment of leaving-group ability should lead to a lowered yield of toluyne-derived product. While the yields of **3**, **4**, and **5** were low, presumably due to reaction of **2** at the methyl group, the ratio of **4** to **5** was 96:1, which again supports the hypothesis of an initially formed sulfurane intermediate reacting in two ways as in eq 6 and 7.

While the presence of 4-toluyne as an intermediate seems well supported, oxyanions rather than **2** may be the bases involved in the aryne-forming elimination reaction. Intramolecular proton abstraction by oxygen in **7** or proton abstraction by lithium oxide (Li_2O or LiO^-) on **7** or the tritolysulfonium salt are conceivable alternatives. However, treatment of triphenylsulfonium bromide with a 28-fold excess of lithium oxide in an ether slurry for 9 days at room temperature gave only a trace of diphenyl sulfide. Apparently, lithium oxide was not a very effective base in catalyzing benzene formation from the sulfonium salt, if indeed that was how the diphenyl sulfide arose. Triarylsulfonium halides have been treated with a variety of nitrogen, sulfur, and oxygen bases in different solvents without any evidence of aryne formation.[18] Although the presence of **8** cannot be demonstrated with certainty and must remain speculative, the arguments supporting **7** and its further reaction along two competing pathways seem strong.

Other experiments are suggested by this hypothesis. One could react a variety of tricoordinate sulfur(IV) species with **2** to form an initial intermediate which might undergo a variety of reactions. For example, the reaction of methyl *p*-toluenesulfinate (**12**) with **2** was performed (eq 9 and 10). Duplicate runs of this reaction gave **5**, **4**,



(9)

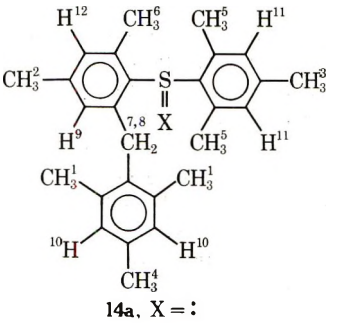
(10)

and **3** in yields of 32 and 25, 37 and 44, and 77 and 69%, respectively. These yields are essentially the same as obtained from **1**, so there seems to be no evidence for a pathway such as shown by eq 10.

Repetition of the various reactions discussed above never gave exactly the same yields on any two occasions. This probably results from the variation in reagent concentrations from one run to the next which is consistent with partitioning of an intermediate in which one step is first order in *p*-tolyllithium and the other zero order. These variations, of course, argue against intramolecular hydride abstraction reactions, which should be independent of the concentration of **2**.

Reaction of mesityl sulfoxide (**13**) with 5 molar equiv of mesityllithium was performed. Although the aryne pathway is ruled out by the presence of ortho methyl substituents, the collapse of a tetracoordinate intermediate to bimesityl and mesityl sulfide is not. However, these two compounds were not detected in the reaction mixture. Column chromatography on alumina of the crude reaction mixture gave mesitylene, a white solid, some unidentified oils, and an emorphous solid.

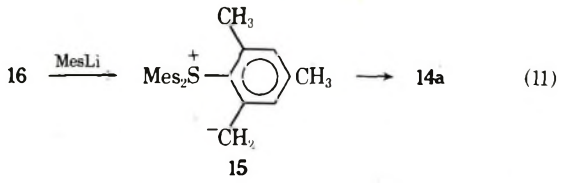
The white solid, $C_{27}H_{32}S$, was assigned the structure **14a** based on the nmr spectrum (Table I) and an osmometrically determined molecular weight of 390 (calcd, 388). Further proof of this structural assignment was gained from the oxidation with hydrogen peroxide, which gave a white, crystalline derivative, $C_{27}H_{32}OS$, assigned as the corresponding sulfoxide (**14b**). The nmr spectrum **14a** showed three different $ArCH_3$ groups and a singlet for the two methylene protons, whereas that of **14b** showed five different $ArCH_3$ groups and an AB quartet for the methylene protons which indicates the presence of a chiral center (sulfur) in **14b**. A lanthanide-induced chemical shift study using tris(7,7-dimethyl-1,1,1,2,2,3,3-heptafluoro-4,6-octanedionato)europium(III) in deuteriochloroform solution (Table I) further resolved the spectrum of **14b** to give six $ArCH_3$ signals and four (ratio 1:2:2:1 H) Ar**H** signals. This allowed an assignment of the protons as shown and therefore confirmed the identification of the reaction product and its derivative as 2,4,4′,6,6′-pentamethyl-2′-(2,4,6-trimethylphenylmethyl)diphenyl sulfide and the corresponding sulfoxide, respectively.



14a, X = :
b, X = O

Several reaction pathways might lead to **14a**. A Smiles rearrangement of the vinylogous ylide **15**, derived from an initially formed sulfonium salt **16**, would give **14a**. Unfor-

tunately, we were unsuccessful in synthesizing **16** from **13** and mesitylene using phosphorus pentoxide as a catalyst or from the reaction of dimesitylethoxysulfonium tetrafluoborate with mesitylmagnesium bromide, and, thus, were unable to test for the possibility of the 1,4-sigmatropic rearrangement represented by eq 11.

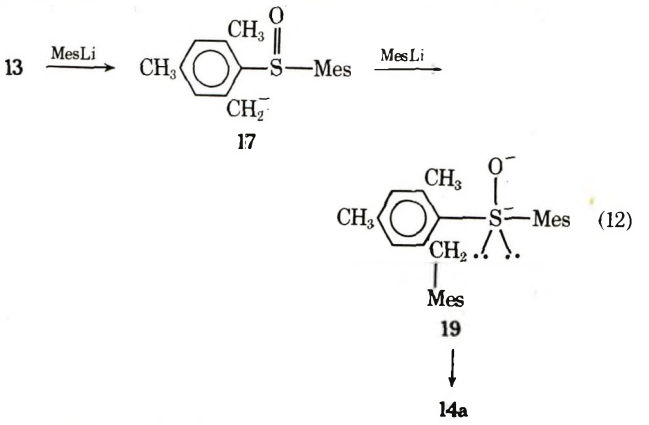


(11)

15

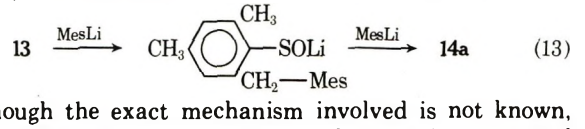
This does not mean that a trimesitylsulfonium salt is incapable of being synthesized nor that it cannot appear as an intermediate during the course of the reaction. Since lithium reagents differ somewhat from Grignard reagents in their reactions, it is possible that such a salt could have been formed and rapidly disappeared to products, thus escaping detection.

Another possible mechanism for the formation of **14a** would involve **13** directly (eq 12). This mechanism implies that the carbanion intermediate **17** is part of a π system involving an orbital on sulfur. When the mesitylllithium adds to **17**, a second electron pair is localized on sulfur, resulting in the formation of a tricoordinate S(II) species **18** analogous to **8**. Loss of lithium oxide yields **14a**.



(12)

A third mechanism is suggested by the rearrangement of mesityl phenyl sulfone to lithium 2-benzyl-4,6-dimethylbenzenesulfinate when treated with *n*-butyllithium.[19] In our case, a sulfenate salt formed from **13** might lead to the product (eq 13). In any event, no products which might arise from a sulfenic acid, presumably too unstable to be isolated, were obtained.



(13)

Although the exact mechanism involved is not known, the essential point remains that no bimesityl nor mesityl sulfide were formed from mesityl sulfoxide reacting with mesitylllithium.

In conclusion, it seems that tricoordinate S(IV) compounds such as aryl sulfoxides, sulfimides, or alkoxysulfonium salts react with aryllithiums to give tetracoordinate S(IV) species, *e.g.*, **7**, which, depending on the nature of the leaving group, partition between two paths (eq 6 and 7). One pathway leads to a triarylsulfonium ion (eq 7) which then reacts further, while the other may (eq 6) involve the formation of a novel tricoordinate S(II) species. Although such a structure may seem unusual, it should be remembered that formally this would be an intermediate present in nucleophilic substitution at dicoordinate S(II) or upon the addition of two electrons in the reduction of sulfoxides to a sulfide. Sekera, Rumpf, and coworkers[20] have written structures similar to **8** as possible intermediates in the reaction of alkyl sulfoxides with organomagnesium halides. While **8** and analogous species may be formulated as transition states rather than as intermediates, our evidence suggests that **7** and similar sulfuranes in which three ligands are carbon and one ligand is oxygen or nitrogen may have sufficiently long lifetimes so that they can react with other substances in the reaction mixture.

Experimental Section

General. *p*-Tolyllithium (**2**) was prepared from *n*-butyllithium and *p*-bromotoluene in hexane–benzene solutions at 60° in nitrogen-flushed, serum-capped centrifuge tubes and washed with benzene seven times, after which it was dissolved in diethyl ether.[21] The ethereal solutions were standardized by titration with benzoic acid according to the procedure of Eppley and Dixon.[22] Gas–liquid chromatographic analyses were carried out using a 20 ft × 0.25 in. column packed with Apiezon L on Chromosorb W (80/100) and a thermal conductivity detector. Biphenyl was the internal standard used to obtain quantitative results.[23]

Reaction of Tolyl Sulfoxide (1) with *p*-Tolyllithium (2).—An ethereal solution of **2** (5.0 ml, 1.44 mmol) was added by syringe to **1** (0.0630 g, 0.274 mmol) dissolved in ether (*ca.* 20 ml) contained in a nitrogen-flushed, serum-capped 200-ml flask. After being stirred magnetically for 20 min, the mixture was hydrolyzed with 5% hydrochloric acid. The organic layer was dried over magnesium sulfate and the ether was removed by distillation through a 25-cm Vigreux column. The residue, analyzed by glc, contained *p*-tolyl sulfide (**3**, 0.0388 g, 0.181 mmol, 66%), *p,p'*-bitolyl (**4**, 0.0157 g, 0.0861 mmol, 31%), and *m,p'*-bitolyl (**5**, 0.0128 g, 0.0702 mmol, 26%). Lower boiling products such as toluene were neglected. Compounds **3**–**5** were identified by retention-time comparisons and by ir comparisons with authentic samples. Sulfide **3** was oxidized to the sulfone, mp 159–160° (lit.[24] mp 159°). Bitolyl (**4**), after recrystallization from methanol, did not depress the melting point of an authentic sample (lit.[25] mp 119–120°). An authentic sample of **4** was available commercially. Bitolyl **5** was synthesized from 3-methylcyclohexanone and *p*-tolylmagnesium bromide according to the method of Ito and Hey.[26] Sulfide **3** was obtained by the acid-catalyzed, iodide ion reduction of commercially available **1**.[27]

Reaction of Tri-*p*-tolylsulfonium Bromide with 2. An ethereal solution of **2** (8.6 ml, 2.47 mmol) was added to a suspension of tri-*p*-tolylsulfonium bromide (0.154 g, 0.400 mmol) in *ca.* 20 ml of ether as described above. Analysis of the hydrolyzed reaction mixture gave **3** (0.0744 g, 0.347 mmol, 87%), **4** (0.0521 g, 0.286 mmol, 72%), and **5** (0.0037 g, 0.0203 mmol, 5%).

Reaction of *N*-*p*-Toluenesulfonyl-*S,S*-di-*p*-tolylsulfimide (10) with 2. An ethereal solution of **2** (14.7 ml, 6.7 mmol) was added to a suspension of **10** (0.382 g, 1.0 mmol) in ether as described above except that the mixture was stirred overnight. Analysis of the hydrolyzed reaction mixture gave **3** (0.153 g, 0.716 mmol, 72%), **4** (0.120 g, 0.656 mmol, 66%) and **5** (0.0022 g, 0.0121 mmol, 1.2%). *p*-Toluenesulfonamide (0.111 g, 65%), mp 135–136.5° (lit.[28] mp 138.5–139.0°), was obtained from the ether layer by extraction with aqueous sodium hydroxide. A second reaction gave **3** (83%), **4** (67%), **5** (2.0%), and *p*-toluenesulfonamide (58%).

Reaction of Methoxydi-*p*-tolylsulfonium Fluorosulfonate with 2. Methyl fluorosulfonate (0.258 g, 2.2 mmol) was added to **1** (0.460 g, 2.0 mmol) in 20 ml of methylene chloride. The solution was stirred for 8 hr, after which 30 ml of ether was added. The solvents were decanted from the resulting oil. Additional ether (10 ml) was used to wash the oil. Ether (30 ml) and **2** (12 ml, 6 mmol) were added and the mixture was stirred for 16 hr. After the usual work-up, the mixture was shown to contain **3** (0.94 g, 0.44 mmol, 22%), **4** (0.057 g, 0.31 mmol, 16%), and **5** (0.00059 g, 0.0032 mmol, 0.16%) as well as a large amount of **1**.

Reaction of Methyl *p*-Toluenesulfinate (12) with 2. An ethereal solution of **2** (0.86 ml, 3.85 mmol) was added to **12** (0.103 g, 0.60 mmol) in ether (30 ml). After 2 hr, the reaction mixture was worked up as above to give **3** (99.2 mg, 46 mmol, 77%), **4** (41.0 mg, 22.5 mmol, 37%), and **5** (34.6 mg, 19.0 mmol, 32%). Repetition of the reaction gave **3** (69%), **4** (44%), and **5** (25%).

Reaction of Mesityl Sulfoxide (13) with Mesityllithium. Mesityl sulfoxide (3.00 g, 0.0105 mol) suspended in ether (100 ml) was added to mesityllithium prepared from mesityl bromide (10.45 g, 0.053 mol) and excess lithium dispersion in *ca.* 70 ml of ether. The bright orange mixture was stirred for 2 hr, hydrolyzed, and then extracted with chloroform, and the dried organic layers were

concentrated to an oil (9 g) which was chromatographed on alumina. The cobalt test for sulfonium salts was negative on both this oil and the aqueous layer.[29] Tlc of the oil showed bimesityl and mesityl sulfide to be absent. The column chromatography gave an initial fraction (5.5 g), shown to be primarily mesitylene by glc. A second fraction gave a white, crystalline, solid **14a**, mp 160–161° (acetone) [0.064 g, 1.7 mmol, 16%; mol wt by osometry in toluene, 390 (calcd, 388)].

Anal. Calcd for $C_{27}H_{32}S$: C, 83,51; H, 8.25; S, 8.25. Found: C, 83.50; H, 8.42; S, 7.98.

The remaining materials obtained from the chromatograph were not identified.

Oxidation of 14a. Compound **14a** (165 mg, 0.425 mmol) was dissolved in 15 ml of acetic acid–chloroform (2:1) and 30% hydrogen peroxide (180 mg, 1.6 mmol) in acetic acid solution (2.8 ml) added in 0.1–0.2-ml portions at room temperature. The reaction mixture was diluted with water and extracted with chloroform. The combined chloroform layers were washed with aqueous sodium carbonate and sodium bicarbonate, dried ($MgSO_4$), and concentrated to give an oil, which crystallized upon standing. Recrystallization gave 112 mg (0.28 mmol, 65%), mp 149–150° (aqueous EtOH). This product (67 mg) was further purified by preparative tlc (silica gel, methylene chloride) to give, after recrystallization, 27 mg of **14b**, mp 167–168° (MeOH).

Anal. Calcd for $C_{27}H_{32}OS$: C, 80.15; H, 7.97. Found: C, 80.21; H, 7.98.

Reaction of Triphenylsulfonium Bromide with Lithium Oxide. A slurry of triphenylsulfonium bromide (119 mg, 0.348 mmol) and lithium oxide (292 mg, 9.7 mmol) in ether was stirred continuously. After 2 days at room temperature, tlc (silica–chloroform) indicated the possible presence of phenyl sulfide. After 9 days, the mixture was hydrolyzed with dilute sulfuric acid and ether extracted. The dried ($MgSO_4$) ether extracts were concentrated to give an oil (51 mg) which was almost totally aliphatic (nmr), although a small aromatic peak (<2%) indicative of phenyl sulfide was present. Glc (5% SP-100 on 80/100 ABS, 6 ft × 2 mm, fid) gave a peak with the same retention time as phenyl sulfide. Chloroform extraction of the water layer, which was shown by the cobalt and bismuth spot tests[27] to contain a sulfonium salt, after the addition of sodium bromide (5 g) gave crude triphenylsulfonium bromide (171 mg).

Registry No.—**1**, 1774-35-2; **2**, 2417-95-0; **10**, 50546-27-5; **12**, 672-78-6; **13**, 3972-22-3; **14a**, 50273-63-7; **14b**, 50458-30-5; tri-*p*-tolylsulfonium bromide, 50273-64-8; methoxydi-*p*-tolylsulfonium fluorosulfonate, 50273-65-9; mesityllithium, 5806-59-7; triphenylsulfonium bromide, 50273-67-1; lithium oxide, 12057-24-8.

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The Mechanism of Hydride Reduction of 1-Alkyn-3-ols

Barbara Grant[1] and Carl Djerassi*

Department of Chemistry, Stanford University, Stanford, California 94305

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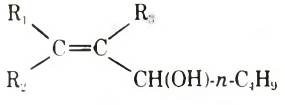
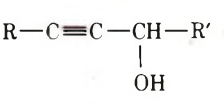
Hydride reduction of 1-alkyn-3-ols (**3**) is shown to proceed *via* site-specific hydride transfer to C-2. A mechanism is proposed which rationalizes the observed reciprocal relationship between solvent basicity and the extent of cis reduction for these systems.

In connection with another problem in this laboratory, it was necessary to synthesize the isotopically labeled allylic alcohols **1a** and **1b**. One convenient route to allylcarbinolic substrates of this type which has been of considerable synthetic use in the past is the lithium aluminum hydride reduction of propargylic alcohols.[2] Mechanistic observations reported on this and related reductions however, suggest that the detailed course of this reaction might be quite structure dependent, thus detracting from its general utility for isotopic labeling.



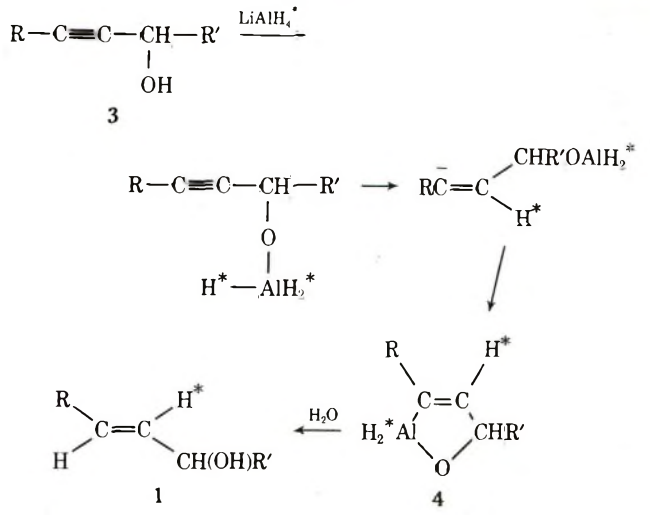


1a, $R_1 = R_2 = H$; $R_3 = D$
b, $R_1 = R_2 = D$; $R_3 = H$
c, $R_1 = R_3 = H$; $R_2 = D$
d, $R_2 = R_3 = H$; $R_1 = D$

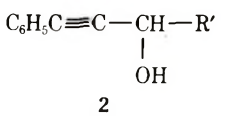
3a, $R = H$; $R' = n\text{-}C_4H_9$
b, $R = D$; $R' = n\text{-}C_4H_9$
c, $R = H$; $R' = CH_3$
d, $R = D$; $R' = CH_3$

Early work[3-5] in this area indicated that the reduction proceeded *via* specific hydride transfer from the aluminum bound to oxygen to the adjacent carbon of the acetylenic linkage, leading after hydrolysis to the olefin resulting from exclusive trans reduction (Scheme I). Corey and coworkers have since demonstrated that for certain substrates (principally 2-alkyn-1-ols) the hydride transfer was not site specific.[6] More recently it was observed that the $LiAlH_4$ reduction of phenyl-substituted propargyl alcohols of type **2** proceeded *via* specific hydride attack[7,8] as

Scheme I



had been proposed earlier,[3-5] but this anomalous specificity was attributed to the powerful directive influence of the phenyl group at C-3.[7]



In light of these indications that the detailed mechanism of the reduction by lithium aluminum hydride of acetylenic alcohols may be quite structure sensitive and faced with the requirement for compounds **1a** and **1b**, a systematic investigation of the mechanism of $LiAlH_4$ reduction of propargylic alcohols of general structure **3** (R = H) was undertaken.

Results and Discussion

Reduction of the acetylenic alcohol **3a** with $LiAlD_4$ in tetrahydrofuran (THF) at room temperature for 3 hr followed by hydrolysis gave a monodeuterated product in 85% yield whose structure was established as **1a** by proton nmr. Correspondingly, $LiAlH_4$ reduction of the deuterated alkynol **3b** followed by D_2O quench yielded the doubly labeled alcohol **1b** (96% d_2). This specificity of hydride attack was observed to be general for alcohols of structure **3**, since similar labeling patterns were observed for the reductions of compounds **3c** and **3d**. In addition, the position of hydride attack was not affected by the addition of trivalent aluminum species ($AlCl_3$) to the reaction medium, contrary to previous observations.[6,9,10] (The rate of reduction was observed to diminish in these cases.[11])

Reduction of alcohol **3a** with $LiAlH_4$ in THF at room temperature for 3 hr followed by D_2O quench yielded exclusively the product of trans reduction, **1c**. However, when the reduction was performed in ether, a second product was obtained which was identified by proton nmr as **1d**, the product resulting from cis reduction of the propargylic alcohol. This result had been obtained previously for the $LiAlH_4$ reduction of 1-*tert*-butyl-3-phenylpropargyl alcohol (**2**, R = *t*-C_4H_9) in ether.[7] Investigation of the effect of solvents on the stereochemistry of the reduction of **3a** with $LiAlH_4$ followed by D_2O quench was undertaken and Table I summarizes the data obtained.

These results indicate a strong inverse correlation between the Lewis basicity of the solvent and the extent of cis reduction such that in the extreme case, isopropyl ether, cis reduction can predominate by a ratio of 3:1.

On the basis of the results obtained in this investigation, the following conclusions can be drawn concerning the mechanism of reduction of propargylic alcohols of general structure **3**. It has been established previously that the function of the aluminum bound to the alcohol oxygen in propargylic systems is to deliver the hydride intramolecularly to the triple bond.[7] This is consistent with the observation that the rate of reduction of **3a** in THF at room temperature is not dependent on the concentration of $LiAlH_4$ above a stoichiometric amount. It is apparent from this study that for propargylic alcohols of general structure **3** (R = H) this hydride transfer occurs exclusively to C-2 in contrast to the results obtained for 2-alkyn-1-ols[6] and in the absence of the powerful directive influence of a phenyl group as proposed by Borden.[7] In addition, the reciprocal relationship between solvent basicity and the extent of cis reduction has been demonstrated. The cis reduction observed in these systems negates the possibility of intramolecular stabilization of the resulting vinylic carbanion by the aluminum bound to oxygen as outlined in Scheme I, since this would impose unlikely geometrical constraints (trans double bond in a five-membered ring) on the resulting oxoaluminum species (assuming that hydrolysis of the C–Al bond occurs with retention of configuration[12]). The stabilization of the vinyl carbanion formed during the cis reduction may therefore best be accomplished by other Lewis acids in the reaction medium. Experiments by Borden[7] on the phenyl-substituted propargylic alcohol **2** (R = *tert*-butyl) suggested that even for trans reduction intramolecular stabilization of the carbanion does not occur initially. Since the extent of cis reduction varies inversely with the ability of the solvent to solvate Lewis acids in the reaction medium, it appears reasonable to assume that these Lewis acids play an important role in the determination of the stereochemistry of the vinyl carbanion. In support of this view recent experiments have indicated that vinyl carbanions exhibit a high degree of stereochemical stability,[13,14] which has been attributed to either sufficiently long lifetimes of the anion in its trigonal configuration or the formation of stereochemically distinct intimate ion pairs with available counterions.[14]

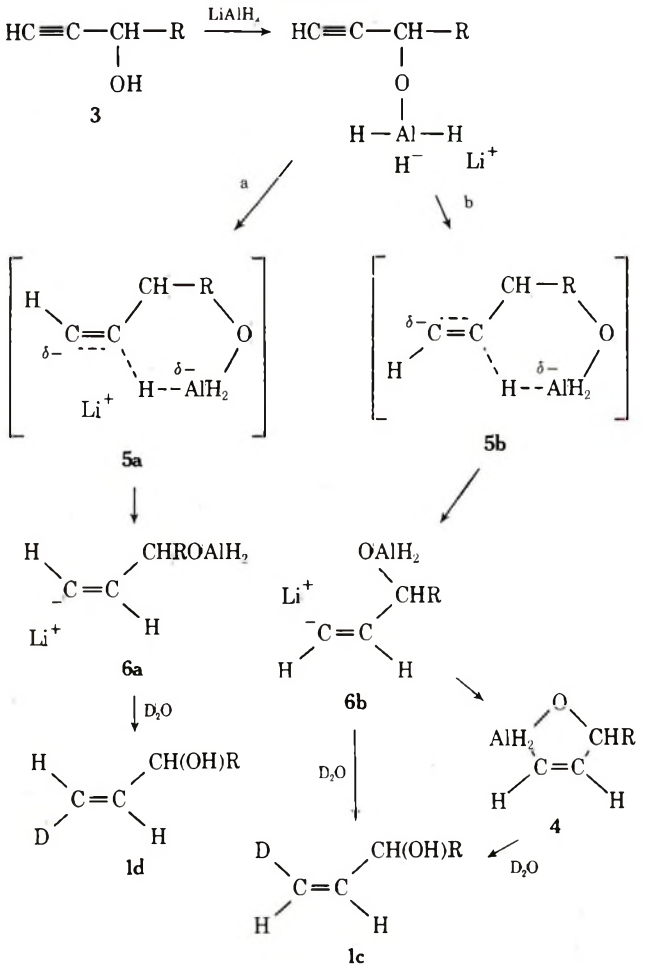
With this information in hand the mechanism outlined in Scheme II is presented, which incorporates all of the available data and provides a rational explanation of the observed results. Logically the first step involves formation of the oxygen–aluminum bond followed by intramolecular hydride transfer to C-2 with concomitant formation of one of two stereochemically stable vinyl carbanions (**6a** or **6b**). In the weaker Lewis base solvents (*e.g.*, ether, 2,5-dimethyltetrahydrofuran) the available counterions (depicted here as Li^+) are less solvated and hence readily available to stabilize existing anionic charges in the transition state (**5a**). This presumably would be best accomplished *via* pathway a. Conversely, in strong Lewis bases (*e.g.*, dioxane, tetrahydrofuran) the highly solvated counterions would not be as available for stabilization of the

Table I
Per Cent Trans and Cis Reduction of 1-Heptyn-3-ol (3a) as a Function of the Solvent

Solvent	% trans reduction[a]	% cis reduction[a]
Dioxane	100	0
Tetrahydrofuran	100	0
Tetrahydrofuran + $AlCl_3$	100	0
2,5-Dimethyltetrahydrofuran	55	45
2,2,5,5-Tetramethyltetrahydrofuran	33	67
Ethyl ether	60	40
Ethyl ether + $AlCl_3$	60	40
n-Propyl ether	50	50
Isopropyl ether	25	75

[a] Values determined using 100-MHz nmr spectrometer.

Scheme II



developing anionic centers and the configuration yielding greatest separation of these sites (**5b**) would be more energetically favorable (pathway b). Hydrolysis of the resulting ion pair **6a** or **6b** with retention of configuration[12] would result in the product of cis (**1d**) or trans (**1c**) reduction, respectively. On the basis of these results a cyclic organoaluminum species (**4**) cannot be ruled out completely and may be involved prior to hydrolysis to the trans-reduction product (**1c**). Finally, the assumption that protonolysis of the carbon–metal bond in the final step proceeds with retention of configuration appears to be quite common in the literature,[3,4,7,12] but definitive experiments on substrates of this particular structure are not yet available. Final experimental proof for this assumption is therefore still lacking.

Two interesting observations have been made which further support the mechanism outlined above (Scheme II). When the reduction of alcohol **3a** was performed in isopropyl ether containing a small amount of the crown ether, dicyclohexyl-18-crown-6, the extent of trans reduction was observed to increase dramatically (approximately 70% trans reduction *vs.* 25% in the absence of the crown ether, Table I).[15] Hence, as the proposed mechanism would predict, the addition of the crown ether, which complexes the lithium counterion[16] rendering it unavailable for stabilization of the developing anionic centers in the transition state, forces the reaction along pathway b. Conversely, from Scheme II it might be expected that lowering the temperature of the reaction would favor pathway a, and this was observed to be the case. Reduction of **3a** at −25° for 6 days in ethyl ether increased the extent of cis reduction by approximately 15%.

Experimental Section

General. The THF used was distilled frum Na and benzophenone under N_2 atmosphere. All other solvents were dried by distillation from $LiAlH_4$. Reductions were run under an atmosphere of purified nitrogen. The alkynols employed were purchased from Farchan Research Laboratories, Willoughby, Ohio. The $LiAlH_4$ was obtained from Alfa Inorganics, Beverly, Mass., and the $LiAlD_4$ from Carl Roth OHG, Karlsruhe, Germany. All products were purified by preparative glpc on an Aerograph gas chromatograph using a 10 ft × 0.25 in. 15% Carbowax M on Chromosorb W column operated at 120°. Isotopic purities were determined using an AEI-MS 9 mass spectrometer. Nmr spectra were recorded on a Varian HA-100 spectrometer.

1-Heptyn-3-ol-*1-d* (2b). Sodium metal (70 mg) was dissolved in 2.5 ml of D_2O and 1-heptyn-3-ol (360 mg) was added. The solution was stirred overnight at room temperature. This procedure was repeated twice, after which the product was purified by microdistillation (97% d_1).

General Procedure for Lithium Aluminum Hydride (or Deuteride) Reduction of the 1-Alkyn-3-ols 2a–d. One millimole of the appropriate alcohol and 1.3 mmol of $LiAlH_4$ (or $LiAlD_4$) was stirred in 3 ml of solvent for 3 hr. Hydrolysis was effected by careful dropwise addition of H_2O (or D_2O). The nmr spectrum ($CDCl_3$) of **1a** had signals at δ 0.95 (m, 3), 1.2–1.4 (m, 6), 3.5 (s, 1), 4.13 (q, 1), 5.05 (m, 2); **1b** at δ 0.95 (m, 3), 1.2–1.4 (m, 6), 3.7 (s, 1), 4.13 (q, 1), 6.0 (m, 1). The per cents of cis and trans reduction that appear in Table I were calculated using the C-1 vinyl signal at δ 6.0 (J_{cis} = 10.5 and J_{trans} = 17.0 Hz).

Acknowledgment. The authors gratefully acknowledge Dr. J. I. Brauman for helpful discussions during the preparation of this manuscript.

Registry No.—**1a**, 50600-35-6; **1b**, 50600-36-7; **1c**, 50600-37-8; **1d**, 50600-38-9; **3a**, 7383-19-9.

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Formation and Reactions of Dihydrophthalic Acids

Steven A. Cerefice* and Ellis K. Fields

Amoco Chemicals Corporation, P. O. Box 400, Naperville, Illinois 60540

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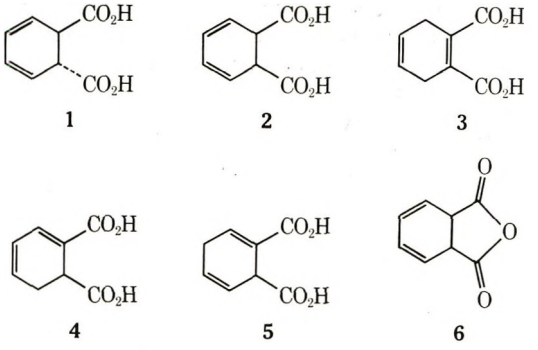
Electrochemical reduction of phthalic acid gave *trans*- and *cis*-1,2-dihydrophthalic acid isomers, ~6:1. Diels–Alder adducts formed from tetracyanoethylene with *cis*-1,2-dihydrophthalic acid, anhydride, and dimethyl ester. 1,2-Dihydrophthalic anhydride dimerized to dicyclohexadiene dianhydride; an isomeric adduct was obtained from 1,2- and 1,4-dihydrophthalic anhydride. A catalyst system of bis(triphenylphosphine)cobalt dibromide plus boron trifluoride etherate inhibited dimerization of 1,2-dihydrophthalic anhydride, isomerized 1,2-dihydrophthalic anhydride to the 1,4 isomer, and catalyzed cycloaddition of 1,2- to 1,4-dihydrophthalic anhydride. Palladium on carbon catalyzed the stereospecific disproportionation of dimethyl dihydro- and tetrahydrophthalates to phthalate and hexahydrophthalates and effected partial decarboxylation of dihydrophthalic acids to benzoic acid. Hydrogen transfer reactions were first order in palladium and zero order in olefin and proceeded mainly by 1,2 addition of hydrogen.

trans-1,2-Dihydrophthalic acid (**1**) was first prepared by Baeyer in 1892 by Na(Hg) reduction of phthalic acid.[1] Baeyer also prepared *cis*-1,2-dihydrophthalic anhydride (**6**), *cis*-1,2-dihydrophthalic acid (**2**), 3,6-dihydrophthalic acid (**3**), 2,3-dihydrophthalic acid (**4**), and 1,4-dihydrophthalic acid (**5**) from **1**. 1,2-Dihydrophthalic acid can now be made in high yields on a large scale by electrochemical reduction of phthalic acid, but the dihydrophthalic acid so produced is an unspecified mixture of isomers.[2-5]



Dihydrophthalic acids are of interest as chemical intermediates, being both dienes and dibasic acids. However, the chemistry of these dienes has hitherto been relatively unexplored. In this work, we have developed methods for analysis and characterization of the electrochemically reduced phthalic acids, prepared several new Diels–Alder adducts, and studied the transition metal catalyzed disproportionation reactions of dihydrophthalic acids and derivatives.

Results and Discussion

Characterization of the Electrochemical Reduction Products of Phthalic Acid. Each of the dihydrophthalic acid isomers has a characteristic nmr spectrum,[6,7] but mixtures of *cis*- and *trans*-1,2-dihydrophthalic acid cannot be analyzed, as their nmr spectra are nearly superimposable, differing only in the shape of the multiplet due to the olefinic protons. The dihydrophthalic acid isomers can be separated and analyzed by esterification gas chromatography (egc).

The major product from electrochemical reduction of phthalic acid was the trans isomer **1** by comparison of the nmr spectrum of its tetracyanoethylene (TCNE) adduct **7** with a reported spectrum of this Diels–Alder adduct.[6]

A minor electrochemical reduction product was identified as the cis isomer **2** by these results: esterification gave a compound with the same egc retention time as the product from esterification of **6**; the TCNE adduct **8** isolated from a mixture enriched (80%) in the dimethyl ester of this isomer was different from **7** and was identical with the adduct obtained from reaction of TCNE with the dimethyl ester prepared by esterification of **6**; and **8** was identical with the esterification product of the TCNE adduct **9**. The compositions of the TCNE Diels–Alder adducts **8** and **9** were shown by their elemental analyses and molecular weights (mass spectra). Both were characterized as cis,endo stereoisomers on the basis of their symmetrical nmr spectra: **9** (acetone-d_6), δ 7.02 (multiplet, 2 H, olefinic), 4.80 (multiplet, 2 H, bridgehead), and 4.18 (singlet, 2 H, exo tertiary); **8** (acetone-d_6), δ 6.70 (multiplet, 2 H olefinic), 4.30 (multiplet, 2 H, bridgehead), 3.74 (singlet, 2 H, exo tertiary), and 3.66 (singlet, 6 H, endo methyl groups). For comparison, the nmr spectra of the trans adduct **7** in acetone-d_6 showed the olefinic protons as two multiplets at δ 6.94 (1 H) and 6.66 (1 H), the bridgehead protons at 4.43 (multiplet, 2 H), two multiplets for

Table I
Electrochemical Reduction Products of Phthalic Acid (PA)

	Electrolysis conditions: Solvent	Temp, °C	Products, %: 1	2	4	5	PA
A	5% H_2SO_4	90	70.2	2.7	1.1	16.2	10.0
B	50% THF/50% 5% H_2SO_4	40	73.6	10.0	0.2	6.4	9.8
C[a]			76.6	4.0	0.3	9.3	9.8

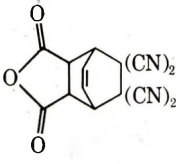
[a] The product distribution in C was obtained by heating the products B in 5% sulfuric acid at 90° for 2 hr.

the tertiary protons at 3.80 (exo, 1 H) and 3.38 (endo, 1 H), and two singlets due to the carbomethoxy groups at 3.83 (exo, 3 H) and 3.76 (endo, 3 H). The single peaks for the methyl groups and the tertiary protons and the similarity of the nmr spectra of 8 and 9 (derived from cis anhydride 6) is evidence that the carbomethoxy groups in 8 are cis. That the substituents are endo is shown by the chemical shifts of the exo tertiary protons in 8 and 9, which are at approximately the same chemical shift as the proton assigned[6] to the exo tertiary position in 7, and are at lower field than the endo proton in 7, shielded by the anisotropy of the adjacent double bond.[8]

1,4-Dihydrophthalic acid (5) was identified by comparison of its nmr and egc spectra with those of an authentic sample prepared by thermal isomerization of 1 in water.[9]

Electrochemical reduction of phthalic acid in an experimental batch cell[4,5,10] at 90° gave dihydrophthalic acids containing 10–20% 5 and 1–5% 2; reduction at 40° gave 2–7% 5 and 10–18% 2. Typical analyses are shown in Table I. When the products from low-temperature electrolysis (B) were heated in 5% sulfuric acid at 90° for 2 hr, 60% of 2 was isomerized to 1 and 5 (C). Therefore, *trans*- and *cis*-1,2-dihydrophthalic acids (1 and 2) are formed in a ratio of about 6:1 by electrochemical reduction of phthalic acid; 4 and 5 are secondary products due to thermal isomerization of 1 and 2 in the solvent system.

Diels–Alder Reactions of 1,2-Dihydrophthalic Acid. Prior to this work, the only known Diels–Alder adduct of 1,2-dihydrophthalic anhydride (6) was its maleic anhydride adduct.[9] *trans*-1,2-Dihydrophthalic acid (1) was reported not to undergo Diels–Alder reactions, although several adducts of the corresponding dimethyl ester have been prepared.[6] Anhydride 6, prepared *in situ* from 1 in acetic anhydride, reacted with TCNE to give an 86% yield of adduct 9, which sublimed and partially decomposed to 6 and TCNE at 300°. Hydrolysis of 9 gave diacid 10, isolated in 70% yield as a tetrahydrate on recrystallization from water. Anhydrous 10 was obtained by recrystallization from acetone and benzene. When 10 was heated at 60° under vacuum a new product was obtained, which was identified as the dihydroxy lactone 11 on the basis of its



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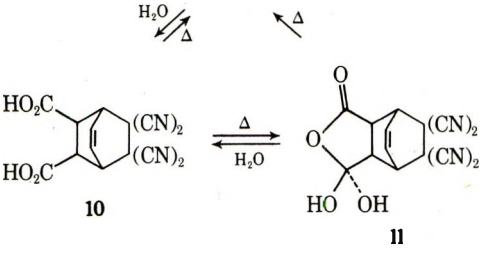


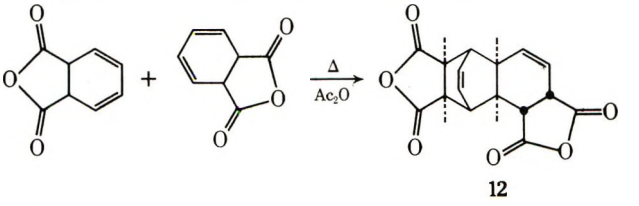
10 11

Table II
Dimerization of Dihydrophthalic Acid in Refluxing Acetic Anhydride

1, mmol	5 mmol	$CoBr_2 \cdot PPh_3$, mmol	$BF_3 \cdot Et_2O$, mmol	Time, hr	Yield, % 12	13
1000.0				15	62	
1000.0				66	70	
11.0		0.27	0.82	15		28
6.0	6.0			15		17
6.0	6.5	0.27	0.82	15		36
7.0	8.4	0.27	0.82	15		22
6.0	6.5	0.33	0.33	15		
6.0	6.0		0.82	15		7
6.0	6.0	0.27		15		
	6.0			16		
	6.0	0.27	0.82	15		

characteristic infrared spectral bands at 3300, 1750, and 1150 cm^{-1} and elemental analysis. Both 10 and 11 gave 9 in acetic anhydride or at 200–220°. In water or acetone 11 was converted to 10.

1 refluxed in acetic anhydride for several minutes was reported to give 84% of anhydride 6.[1,9] We found that refluxing 1 for several hours in acetic anhydride resulted in formation of a Diels–Alder dimer 12 in 70 mol % yield. 12 was also obtained when 6 was heated in acetic anhydride or acetic acid. A mixture of 1 and 5 in acetic anhydride gave an isomeric adduct 13 in 17% yield by [4 + 2] cycloaddition of 6 to the isolated double bond of the anhydride of 5. The proposed endo,endo stereochemistries are assumed based on rules of Diels–Alder additions and the most favorable geometries of the transition states.[11]



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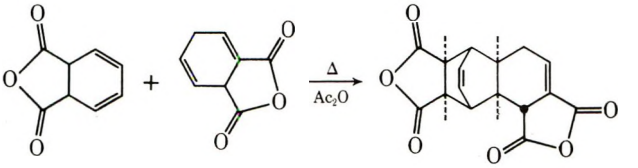

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Transition metal compounds are known to catalyze symmetry-forbidden [2 + 2] and [4 + 4] cycloaddition reactions.[12-15] An attempt to effect dimerization of 1 or 6 using $CoBr_2 \cdot 2PPh_3$ and $BF_3 \cdot Et_2O$, a catalyst system that dimerizes norbornadiene to Binor-S,[14] gave no new products. Instead, we obtained a 30% yield of 13. Dimer 12, obtained in 70% yield in the absence of catalyst, was not observed. The possibility that 12 was the initial product and was catalytically isomerized to 13 was ruled out, as 12 was recovered unchanged when heated under these conditions. 1 and 5 in acetic anhydride with $CoBr_2 \cdot 2PPh_3$ and $BF_3 \cdot Et_2O$ gave the cross dimer 13 in yields twice that of the uncatalyzed reaction. 5 alone gave no dimers in acetic anhydride in the presence or absence of catalyst. The catalyst system inhibited self-dimerization of 1, partially isomerized 1 to 5 (or their anhydrides), and catalyzed the [4 + 2] cycloaddition to 13.

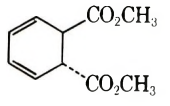
Both $CoBr_2 \cdot 2PPh_3$ and $BF_3 \cdot Et_2O$ were necessary for catalysis; the optimum mole ratio of cobalt to boron was 1:3. No dimers were formed when $BF_3 \cdot Et_2O$ was omitted, and yields of 13, compared to the uncatalyzed system, were lower in the absence of $CoBr_2 \cdot 2PPh_3$, as shown in Table II.

Table III
Palladium-Catalyzed Disproportionation Reactions[a]

Starting material	Pd/C, mol % Pd	Solvent	Time	Yield, % 16	17	18	19 + 21	20
14	2.65	PhH	7 hr	50.5			49.3	0.2
14	4.06	HOAc	2 hr	66.0	29.2	1.0		2.8
19 + 21[b]	2.65	PhH	9 days	66.5	27.0		1.3	5.2
19 + 21[b]	2.65	PhH	12 days	68.2	28.8	1.8	0.7	0.5
15	2.73	PhH	1 hr	52.2	0.9	3.5		43.4
15	4.60	HOAc	2 hr	64.7	0.7	3.3		30.2
20	2.73	PhH	5 days	76.0	3.7	17.7		2.6
20	4.60	HOAc	16 hr	84.4	4.2	11.4		

[a] All reactions were at the boiling points of the solvents indicated. [b] Products **19** and **21** were present in a ratio of 65:35.

Palladium-Catalyzed Reactions of Dihydrophthalic Acids. Palladium compounds are known to dimerize acyclic conjugated dienes such as butadiene,[16] and to effect isomerization and disproportionation of cyclic dienes such as cyclohexadiene.[17] We found that palladium supported on carbon catalyzed the disproportionation of the cyclohexadiene derivatives dimethyl *trans*-1,2-dihydrophthalate (**14**) and 1,4-dihydrophthalate (**15**) to approximately a 2:1 mixture of dimethyl phthalate (**16**) and hexahydrophthalate. The reactions were stereospecific: hexahydrophthalate obtained from **14** was 94% *trans*-hexahydrophthalate (**17**) and 6% *cis*-hexahydrophthalate (**18**); hexahydrophthalate from **15** was 83% **18**, 17% **17**. The reduction products from palladium-catalyzed disproportionation have the same stereochemistry as from palladium-catalyzed hydrogenation: **14** was hydrogenated to give 100% **17**; **15** was hydrogenated to give 97% **18** and 3% **17**. No dimers were obtained. Palladium-catalyzed dimerizations of cyclohexadienes evidently do not compete with hydrogen-transfer reactions leading to disproportionation.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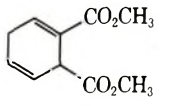
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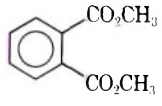
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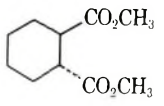
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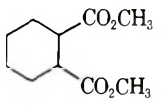
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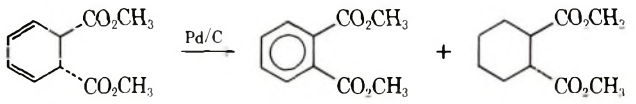
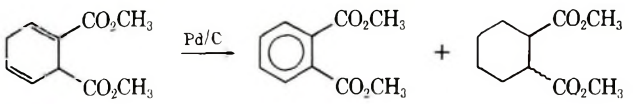
Hydrogen-transfer reactions catalyzed by transition metal compounds proceed *via* metal hydride intermediates.[18-20] The observed ratios of phthalate to hexahydrophthalate, which were higher than the theoretical 2:1 ratio, are attributed to dehydrogenation by formation and loss of hydrogen, in competition with disproportionation by hydrogen transfer from metal hydride intermediates.

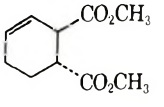


Refluxed in acetic acid	74 %	24 %
benzene	67 %	31 %



Refluxed in acetic acid	84 %	16 %
benzene	73%	22 %

Disproportionations catalyzed by palladium on carbon proceeded stepwise through tetrahydrophthalate intermediates. The rate of disproportionation of dihydrophthalate was about 100 times faster than the disproportionation of tetrahydrophthalate so that the reactions could be stopped easily at the intermediate stage, and 1:1 mixtures of phthalate and tetrahydrophthalates were isolated.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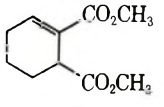
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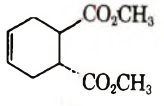
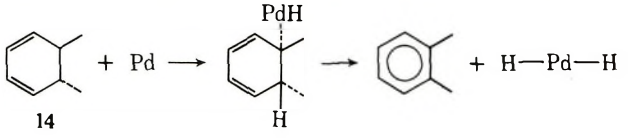
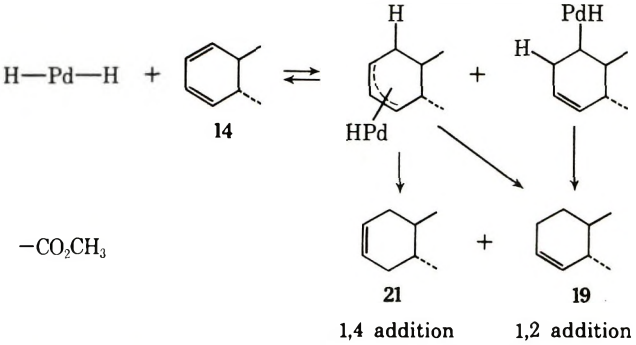

21

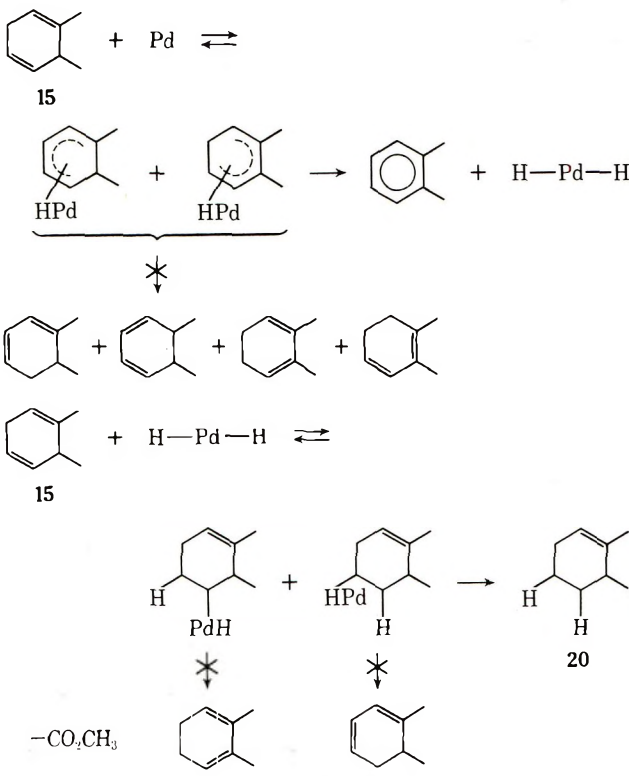
Transition metal compounds are known to catalyze hydrogen transfer reactions of 1,3-cyclohexadienes predominantly by 1,4 addition of hydrogen and to disproportionate 1,4-cyclohexadienes by prior isomerization to the conjugated 1,3 isomers.[19,20] We found that *trans*-1,2-dihydrophthalate (**14**) disproportionated mainly by 1,2 addition of hydrogen. The tetrahydrophthalates consisted of 65% *trans*-1,2,3,4- (**19**, 1,2-addition product) and 35% *trans*-1,2,3,6-tetrahydrophthalate (**21**, 1,4-addition product). Tetrahydrophthalate isomers were identified by their nmr spectra. Their stereochemistries are trans, as continued reaction in the presence of palladium gave *trans*-hexahydrophthalate (**17**), which was 95% isomerically pure.



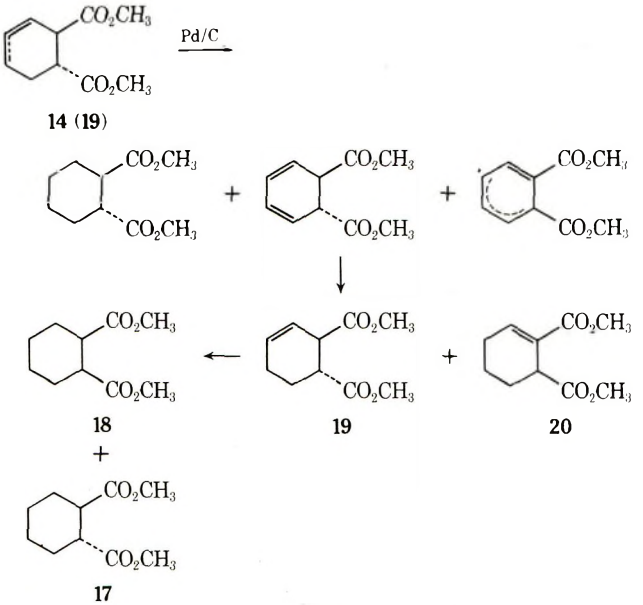


Disproportionation of 1,4-dihydrophthalate (**15**) gave a 1:1 mixture of phthalate and 2,3,4,5-tetrahydrophthalate (**20**) as the only tetrahydro isomer. It formed exclusively by 1,2 addition of hydrogen to the isolated double bond. **15** did not isomerize to a conjugated diene by addition-elimination of palladium or a palladium hydride species, as this would have given dienes and subsequently olefins that were not observed. **15** was not isomerized to a conjugated diene because of its greater thermodynamic stability compared to **14**;[9] the steric interactions in the almost planar **14** are relieved on going to **15** and one of the double bonds becomes conjugated with a carboxy group.

Small amounts of **20** were observed in the disproportionation of **14** and **19**, Table III. We attribute this to the formation of dienes containing a Δ^2 double bond in the conversion of tetrahydrophthalate to phthalate and hexahydrophthalate. Subsequent disproportionation of the isom-



erized olefins may be responsible for the lack of total stereospecificity observed in the formation of hexahydrophthalates. **20** may also be formed by isomerization of **14** to **15**, in competition with disproportionation.



The kinetics of these palladium-catalyzed reactions were studied in an attempt to elucidate the mechanism(s). Each reaction was found to be first order in catalyst and zero order in olefin. Observation of pseudo-zero-order kinetics in heterogeneous catalysis is not uncommon.[21] This indicates that the catalyst is saturated with substrate and the concentration of substrate on the surface of the catalyst is effectively constant over the course of the reaction. Unfortunately, no insight into the molecularity of the hydrogen transfer reactions can be deduced in such cases.

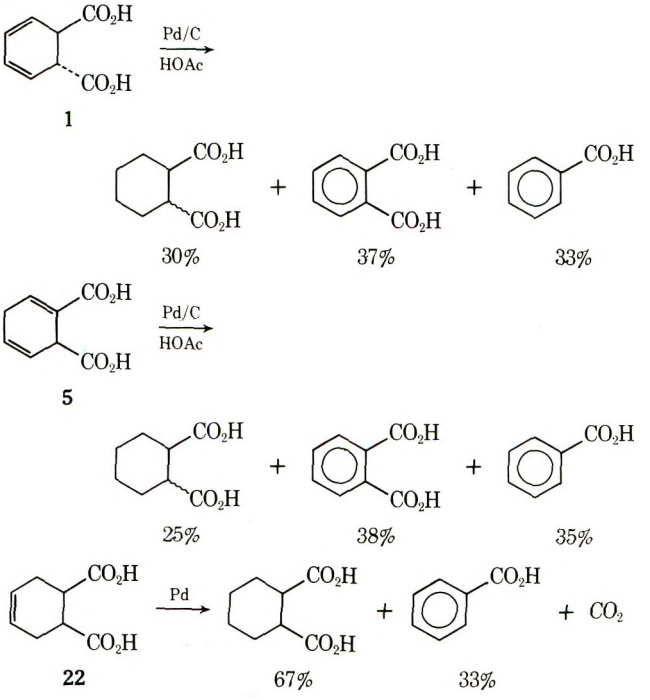
Palladium was the most effective catalyst we found for disproportionations of **14**. The rhodium-catalyzed reaction of **14** stopped at the tetrahydrophthalate stage. A comparison of several transition metal catalyzed reactions of **14** is shown in Table IV.

Table IV
Reactions of Dimethyl *trans*-1,2-Dihydrophthalate (14) Catalyzed by Transition Metals

Catalyst	Mol % catalyst	Product distribution, % 14	16	17	19 + 21	20
10% Pd/C[a]	2.4		66.2	30.9		2.9
5% Rh/C[a]	2.4		51.9		43.5	4.6
5% Ru/C[a]	2.5	72.6	7.8		2.0	6.2
5% Pt/C[a]	1.2	49.9	23.9		17.1	4.6
$Pd(OAc)_2$[b]	5.7		65.0		35.0	

[a] In acetic acid at reflux for 2.0 hr. [b] In acetic acid at room temperature for 4 days; $Pd(OAc)_2$ is rapidly reduced to Pd metal.

In the palladium-catalyzed reactions of dihydrophthalic acids, we found a considerable amount of decarboxylation to benzoic acid in addition to the disproportionation products. When an acetic acid solution of diacid **1** was refluxed in the presence of palladium on carbon for 20 hr, benzoic acid (33%), hexahydrophthalic acid (30%), and phthalic acid (37%) were obtained. Similarly, reaction of diacid **5** gave 35% benzoic acid, 25% hexahydrophthalic acid, and 38% phthalic acid. The palladium-catalyzed reactions gave tetrahydrophthalic acids (19% from **1**, 41% from **5**) together with phthalic acid (35%) and benzoic acid (20%) after 1 hr in refluxing acetic acid. Benzoic acid was formed by loss of carbon dioxide and hydrogen from dihydro- and tetrahydrophthalic acids. Mass spectral analysis of gas samples during the reactions showed carbon dioxide, but no hydrogen. From the relative amounts of phthalic and hexahydrophthalic acids formed, we conclude that the hydrogen produced on formation of benzoic acid was bound to the catalyst and subsequently transferred to olefin parallel to the formation of hexahydrophthalic and benzoic acids by decarboxylation in the palladium-catalyzed reaction of 1,2,3,6-tetrahydrophthalic acid (**22**).[22]



Experimental Section

Nmr spectra were recorded on a Jeol H-100 spectrometer using tetramethylsilane as an internal standard. Infrared spectra were recorded on a Perkin-Elmer 237B spectrophotometer. All new compounds gave satisfactory elemental analyses (±0.3%). Melting points and boiling points are uncorrected.

Egc Analyses. A Hewlett-Packard Model 5750 gas chromatograph attached to a Varian Aerograph Model 477 digital integra-

tor was used for gc analyses. Methyl ester samples were prepared from the corresponding acids with diazomethane in ether or with boron trifluoride etherate in methanol according to standard procedures. Dimethyl esters of phthalic acid and dihydrophthalic acid isomers elute in the following order: on a 15 ft × 0.125 in. column packed with 10% OV 210 (methyl silicone with 50% trifluoropropyl groups) on Chromsorb W (80/100), *cis*- and *trans*-1,2-dihydrophthalate (same retention times), 2,3-dihydrophthalate, 1,4-dihydrophthalate, phthalate; on a 15 ft × 0.125 in. column packed with 10% OV 17 (methyl silicone with 50% phenyl groups) on Chromsorb W (80/100), *trans*-1,2-dihydrophthalate, *cis*-1,2-hydrophthalate, 2,3-dihydrophthalate, phthalate and 1,4-dihydrophthalate (same retention times).

Dimethyl *trans*-1,2-Dihydrophthalate (14). A mixture of 50.0 g of **1** (95%) and phthalic acid (5%) with 500 ml of methanol and 40 ml of $BF_3 \cdot Et_2O$ was refluxed for 24 hr. The reaction mixture was diluted with water and the products were extracted with benzene. The extract was dried, the solvent was removed on a rotary evaporator, and the products were distilled through a Vigreux column to yield a center-cut fraction of 47.5 g (85%), bp 82–85° (1.0 mm), consisting of 95% **14**, 2.5% dimethyl *cis*-1,2-dihydrophthalate, 1.0% **15**, and 1.5% **16**.

Dimethyl 1,4-Dihydrophthalate (15). 1,4-Dihydrophthalic acid (**5**) was prepared by isomerization of **1** in water,[9] mp 226–228°. Esterification of **5** (5.74 g) in 100 ml of methanol with 7 ml of $BF_3 \cdot Et_2O$ as above gave 6.24 g of distillate, bp 83–85° (0.2mm), consisting of 96% **15**, 1.5% **14**, 0.1% **16**, and 2.4% dimethyl 2,3-dihydrophthalate.

Dimethyl 2,2,3,3-Tetracyanobicyclo[2.2.2]oct-5-ene-*trans*-7,8-dicarboxylate (7). Adduct **7** was prepared in 93% yield by heating an equimolar mixture of **14** and TCNE on a steam bath for 20 hr, mp 172–174° (lit.[6] mp 172–173°), identical nmr spectra as reported for **7**.[6]

Dimethyl 2,2,3,3-Tetracyanobicyclo[2.2.2]oct-5-ene-*cis*-*endo*-7,8-dicarboxylate (8). *cis*-1,2-Dihydrophthalic anhydride (**6**), obtained by refluxing **1** in acetic anhydride,[4] was esterified with $BF_3 \cdot Et_2O$ in methanol. The ester was heated with a 50% excess of TCNE under nitrogen on a steam bath for 16 hr to give an 82% yield of **8** after recrystallization from benzene, mp 183–185°, ir (Nujol) 1740 cm^{-1}.

2,2,3,3-Tetracyanobicyclo[2.2.2]oct-5-ene-*endo*-7,8-dicarboxylic Anhydride (9). Ten grams of a mixture of **1** (93.2%, 55.5 mmol) and phthalic acid (6.8%) was refluxed in 25 ml of acetic anhydride for 30 min. TCNE (6.55 g, 51.1 mmol) was added to the cooled solution and the resulting mixture was heated at 50° for 5 days. White crystals precipitated during the course of the reaction. The solid was filtered and washed with benzene: yield 12.43 g (88% based on TCNE); mp 300° dec; ir (Nujol) 1880, 1775 cm^{-1}. The mass spectrum shows no parent ion, but contains a strong M + 1 peak at 279, M − CO_2 at 234.

Anal. Calcd for $C_{14}H_6N_4O_3$: C, 60.4; H, 2.2. Found: C, 60.5; H, 2.3.

Adduct 8 Prepared from Anhydride 9. A solution of **9** (2.00 g) in 25 ml of methanol and 2 ml of $BF_3 \cdot Et_2O$ refluxed for 16 hr produced 2.37 g after recrystallization from benzene. Sublimation at 150° (0.02 mm) and recrystallization from benzene gave 2.04 g (88%) of **8**, mp 181–183°, identical by ir and nmr with the sample prepared above.

Hydrolysis of 9. 9 (3.00 g) was refluxed in 50 ml of water until all solids were in solution (45 min). The solution was cooled to 0° and filtered to give a 70% yield of **10** tetrahydrate, mp 295° dec, ir (Nujol) 3625, 3540, 3360, 1725 cm. When **10** tetrahydrate is heated at 60° *in vacuo* overnight, **11** dihydrate is formed, mp 295° dec, ir (Nujol) 3320, 1750, 1725 (shoulder), 1150 cm^{-1}. Recrystallization of **10** tetrahydrate from acetone–benzene (~1:1) gave an anhydrous sample of **10**, mp 295–300° dec, ir (Nujol) 1735, 1725 cm^{-1}. Heating anhydrous **10** at 60° *in vacuo* overnight gave anhydrous **11**, mp 295° dec, ir (Nujol) 3325, 1750, 1740, 1725 (shoulder), 1150 cm^{-1}. Nmr spectrum of **10** (acetone-d_6): δ 9.92 (singlet, 2 H, acidic protons), 6.80 (multiplet, 2 H, olefinic), 4.32 (multiplet, 2 H, bridgehead), and 3.76 (singlet, 2 H, exo tertiary).

Anal. Calcd for $C_{14}H_8N_4O_4$: C, 56.8; H, 2.7. Found (**10**): C, 56.5; H, 3.1. Found (**11**): C, 56.6; H, 2.7.

Dehydration of 10 and 11 to 9. A sample of **11** was heated at 200–220° *in vacuo* for 30 min. The infrared spectrum of the residue was identical with that of anhydride **9**. When **10** was heated at 200° for 30 min, it was converted to **9** plus small amounts of **11**.

A sclution of **11** (0.30 g) in 20 ml of acetic anhydride at room temperature for 16 hr gave, after removal of solvent, a solid with an infrared spectrum identical with that of **9**. Similarly, **10** in acetic anhydride gave a mixture of **9** and unreached **10**.

Dimerization of 1 to Tricyclo[6.2.2.0^{2,7}]dodeca-3,9-diene-5,6,11,12-tetracarboxylic Dianhydride (12). Dihydrophthalic acid (175 g), containing 96% **1** and 4% phthalic acid, was refluxed in 200 ml of acetic anhydride for 66 hr. White crystals formed. The mixture was cooled to room temperature; the solid was filtered and washed thoroughly with benzene. Yield of **12** was 104 g (70%): mp 238–240° dec; ir (Nujol) 1860, 1775 cm^{-1}; mol wt (mass spectrum) 300; nmr (DMSO-d_6) multiplets centered at δ 6.48 (2 H), 6.00 (2 H), 3.75 (4 H), 3.29 (2 H), and 2.86 (2 H).

Anal. Calcd for $C_{16}H_{12}O_6$: C, 64.0; H, 4.0. Found: C, 64.3; H, 4.0.

Tricyclo[6.2.2.0^{2,7}]dodeca-4,9-diene-5,6-11,12-tetracarboxylic Dianhydride (13) by Reaction of 1 and 5. A mixture of **1** (1.01 g), **5** (0.99 g), and 5 ml of acetic anhydride was refluxed for 15 hr. The solid was filtered and washed with ethanol. The yield of **13** was 0.30 g (17%): mp 268–270° dec; ir (Nujol) 1840, 1780, 1665 cm^{-1}; mol wt (mass spectrum) 300; nmr (DMSO-d_6) multiplets centered at δ 7.28 (1 H), 6.48 (2 H), 3.60 (2 H), 3.45 (2 H), 2.70 (1 H), and 2.20–1.60 ppm (4 H).

Anal. Calcd for $C_{16}H_{12}O_6$: C, 64.0; H, 4.0. Found: C, 63.8; H, 4.2.

13 by Catalyzed Reaction of 1. A mixture of **1** (1.87 g, 11.0 mmol), $CoBr_2 \cdot 2PPh_3$ (0.20 g, 0.27 mmol), $BF_3 \cdot Et_2O$ (10 drops, 0.82 mmol), and 5 ml of acetic anhydride was refluxed for 15 hr; the yield of **13** was 0.46 g (28%), mp 267–269° dec.

13 by Catalyzed Reaction of 1 and 5. A mixture of 1.01 g (6.0 mmol) of **1**, 1.09 g (6.5 mmol) of **5**, 0.20 g (0.27 mmol) of $CoBr_2 \cdot 2PPh_3$, 10 drops (0.82 mmol) of $BF_3 \cdot Et_2O$, and 5 ml of acetic anhydride was refluxed for 15 hr; the yield of **13** was 0.69 g (36%), mp 268–270° dec.

Palladium-Catalyzed Disproportionation of Dimethyl Dihydro- and Tetrahydrophthalates. A mixture of dimethyl dihydrophthalate, palladium on carbon, and solvent was stirred at reflux. Products were analyzed by vpc, after filtration of the catalyst and concentration of the filtrate on a rotary evaporator. For the kinetic studies aliquots of the reaction mixture were analyzed at given intervals. Reaction conditions and product analyses are in Table III. Results of reactions of **14** catalyzed by other transition metal compounds are shown in Table IV.

Tetrahydrophthalates **19**, **20**, and **21** were characterized by their nmr spectra (CCl_4): for **19**, multiplets at δ 5.63 (2 H), 3.40 (1 H), 2.80 (1 H), and 2.4–1.8 (4 H), singlet at 3.63 (6 H); for **20**, multiplets at δ 6.99 (1 H), 3.28 (1 H), 2.10 (2 H), 1.80 (2 H), and 1.52 (2 H), singlets at 3.65 (3 H) and 3.60 (3 H); for **21**, multiplets at δ 5.58 (2 H), 2.70 (2 H), and 2.20 (4 H), singlet at 3.58 (6 H).

Dimethyl *cis*-1,2,3,6-tetrahydrophthalate and 3,4,5,6-tetrahydrophthalate were prepared by esterification of their corresponding anhydrides. Absence of these isomers in the palladium-catalyzed reactions of **14**, **15**, **19**, **20**, or **21** was demonstrated by comparisons of nmr spectra and gas chromatographic retention times.

Palladium-Catalyzed Disproportionation Reactions of 1 and 5. A mixture of 2.0 g (11.8 mmol) of dihydrophthalic acids (91.4% **1**, 2.6% **2**, 0.1% **4**, 2.8% **5**, and 3.1% phthalic acid), 0.50 g (0.38 mmol) of 5% Pd/C, and 15 ml of acetic acid was refluxed for 1 hr under argon. The products were esterified with 20 ml of methanol and 2 ml of $BF_3 \cdot Et_2O$ at reflux for 6 hr. Analysis (mass spectrum) of the gases evolved showed carbon dioxide, in addition to argon and air; analysis of the methyl esters by vpc showed methyl benzoate (17%), **17** (28%), **20** (5%), **19** + **21** (14%), and **16** (36%). When the disproportionation reaction was allowed to proceed for 20 hr at reflux, the product distribution was 33% methyl benzoate, 30% **17** and **18**, and 37% **16**.

A mixture of 1.04 g (6.2 mmol) of dihydrophthalic acids (1.5% **1**, 1.4% **4**, 96.5% **5**, and 0.5% phthalic acid) and 0.25 g (0.19 mmol) of 5% Pd/C was refluxed in 8 ml of acetic acid and the products were esterified. The mass spectrum of a gas sample showed carbon dioxide, argon, and air. Vpc analysis of the methyl esters from a 1-hr reaction showed 20.0% methyl benzoate, 2.7% **17**, 6.0% **19** + **21**, 2.0% **18**, 35.3% **20**, and 34.0% **16**; analysis of products after 20 hr at reflux in acetic acid showed 35% methyl benzoate, 5.3% **17**, 19.7% **18**, 2.0% **20**, and 38% **16**.

Palladium-Catalyzed Hydrogenation of 14 and 15. A mixture of 1.31 g of **14** [93.5% pure, containing the methyl esters of **2** (2.4%), **4** (0.1%), **5** (2.1%), and phthalic acid (1.9%)], 0.26 g of 5% Pd/C, and 100 ml of benzene was hydrogenated in a 300-ml capacity rocking autoclave bomb at 500 psi at room temperature for 1.5 hr. Vpc analysis of the products showed 95.1% **17**, 2.5% **18**, 0.7% **20**, and 1.7% **16**.

Hydrogenation of **15** [90% pure, containing the methyl esters of **1** (0.5%), **4** (7.0%), and phthalic acid (2.5%)] under the same conditions as above gave 1.3% **17**, 34.9% **18**, 60.9% **20**, and 2.9% **16**.

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Registry No.—**1**, 5675-13-8; **5**, 1515-23-7; **6**, 1515-19-1; **8**, 50388-57-3; **9**, 50388-58-4; **10**, 50388-59-5; **11**, 50388-60-8; **12**, 50388-61-9; **13**, 50388-62-0; **14**, 26549-64-4; **15**, 38201-52-4; **19**, 50388-65-3; **20**, 41902-36-7; **21**, 17673-68-6; phthalic acid, 88-99-3.

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Nuclear Magnetic Resonance Studies of the Geometrical Isomers of α,α'-Disubstituted Succinosuccinic Esters

Daniel Y. Chang* and Mou Chuen Chan

Department of Chemistry, The Chinese University of Hong Kong, Hong Kong

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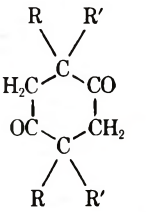
Investigation of the nmr spectra of a series of α,α'-disubstituted succinosuccinic esters, all except one existing as cis and trans isomers, has shown that every pair of these isomers gave nmr spectra which differed from each other in the spacings between the doublets for the four methylene protons in the cyclohexane ring. By association of the nmr spectral data with conformational analysis of the isomeric esters under investigation, it is possible to make plausible assignment of configuration to these isomers. This has found support from nmr spectroscopy of α,α'-dimethylsuccinosuccinic esters at very low temperatures and preliminary results from X-ray analysis of one of the isomers of di-*p*-bromobenzylsuccinosuccinic ester. The difference in the temperature effect on the nmr spectra of the geometrical isomers is discussed. Of the substituted succinosuccinic esters investigated in the present work, those which were previously unknown have been characterized.

While using nmr spectroscopy in the characterization of α,α'-disubstituted succinosuccinic esters, each existing as cis and trans isomers, it was found that, for each pair of such isomers, the nmr spectrum of the one differed from that of the other in the spacing between the doublets for the four methylene protons in the cyclohexane ring. This has led to the attempt at the feasibility of assigning the configurations of these isomers according to their nmr spectra.

The story began when the present authors were reinvestigating the reaction between disodiosuccinosuccinic ester and a benzyl halide, which was first investigated by Nef[1] more than 80 years ago. This latter author regarded the key products that resulted from the reaction as two isomers of diethyl 2,5-dibenzoxy-3,6-dihydroterephthalate, on account of their sluggishness to the action of carbonyl reagents, their resistance to ketonic cleavage by the action of dilute sulfuric acid, and their crystallographic resemblance to the product obtained by reducing diethyl 2,5-dibenzoxyterephthalate.[1] Being curious about the occurrence of the isomerism of the dienolic ethers, Chan[2] repeated Nef's experiment, and isolated exactly the same products as those obtained by Nef. She found, however, that they did react with hydroxylamine to give the corresponding dioximes, showing the presence of two carbonyl groups. Her investigation was not carried any further owing to the failure of the products to undergo ketonic cleavage. Nor did she seem to have obtained pure samples of the dioximes.

Following the discovery of the cleavage of β-keto esters by the action of metal iodides,[3] the present authors again made a study of the reaction between disodiosuccinosuccinic ester and benzyl iodide and of the isomeric products, with a view to elucidating their structure and, should they exist as geometrical isomers, determining their configuration. As those described by Nef, the two crystalline substances that resulted from the reaction melted at 140.5 (Ia) and 148.5° (Ib). Both of them reacted with hydroxylamine, giving the corresponding dioximes, mp 221° dec and 252° dec, respectively. On refluxing for 48 hr with dilute sulfuric acid, Ib was converted into a product of unknown structure, melting at 272°, which had the same percentage



I, R = COOEt; R′ = CH_2Ph
II, R = H; R′ = CH_2Ph
III, R = COOEt; R′ = CH_2COOEt
IV, R = COOEt; R′ = CH_3
V, R = H; R′ = CH_3
VI, R = COOEt; R′ = $CH_2C_6H_4Br$
VII, R = COOEt; R′ = $CHPh_2$

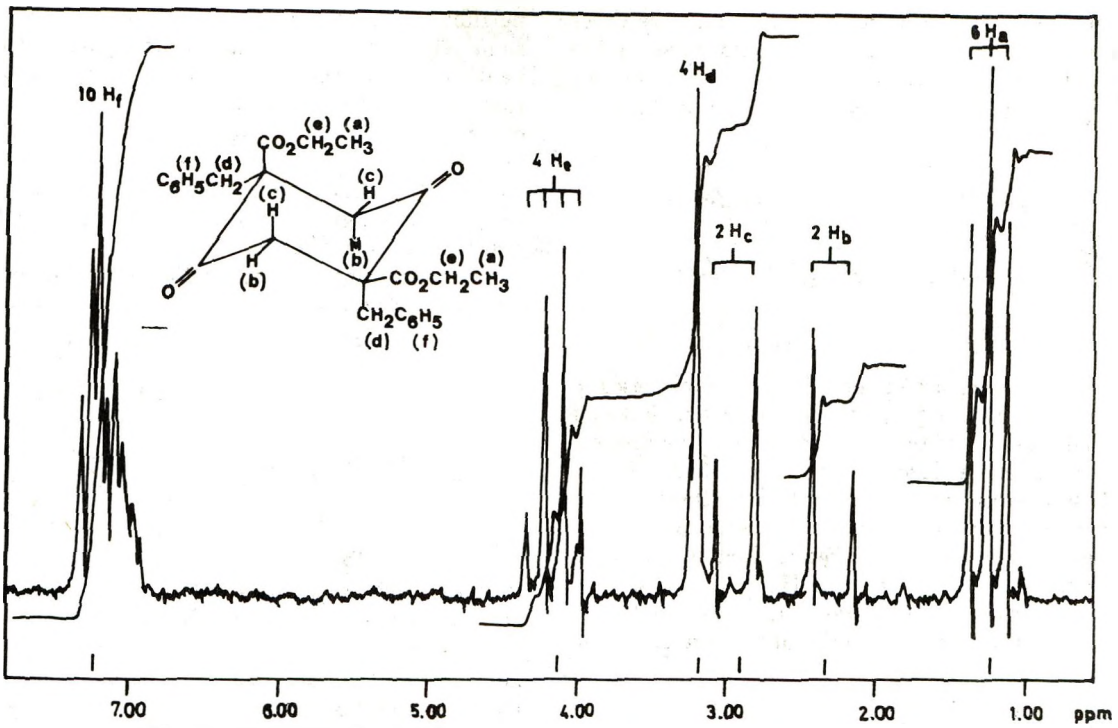


Figure 1. Nmr spectrum of *cis*-2,5-dibenzyl-2,5-dicarbethoxycyclohexane-1,4-dione.

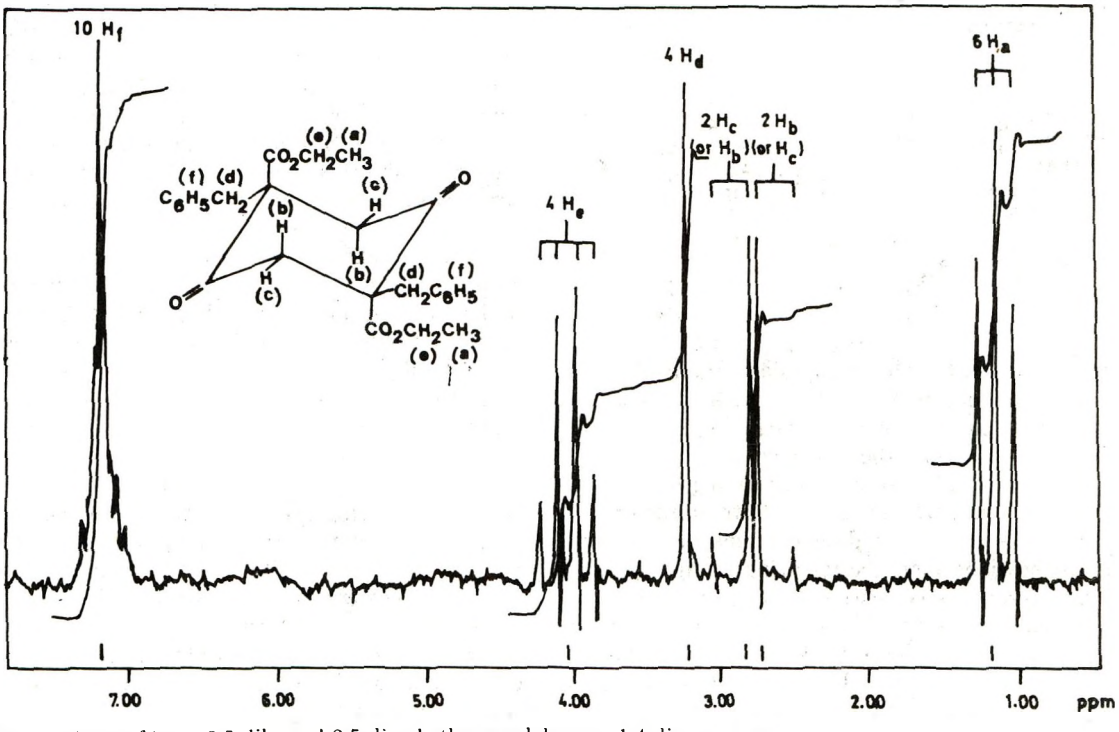


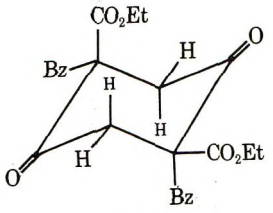
Figure 2. Nmr spectrum of *trans*-2,5-dibenzyl-2,5-dicarbethoxycyclohexane-1,4-dione.

composition as Ib, while Ia remained unchanged. When heated with hydrated calcium iodide, both Ia and Ib were readily decarboxylated, each giving the same pair of isomers, mp 155 (IIa) and 196° (IIb), respectively. These latter products also formed the corresponding dioximes.

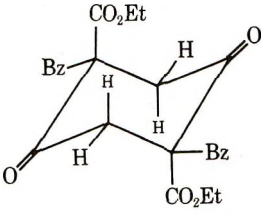
The reactions just outlined clearly indicate that the products Ia and Ib were in all probability geometrical isomers of 2,5-dibenzyl-2,5-dicarbethoxycyclohexane-1,4-dione, and IIa and IIb geometrical isomers of 2,5-dibenzylcyclohexane-1,4-dione. Further information in support of the proposed structures was provided by ir and nmr spectroscopy. It was the nmr spectra of Ia and Ib (Figures 1 and 2) that first attracted our attention to the different features existing in the part of the peaks for the methylene protons in the cyclohexane ring. In both spectra, the absorptions of four ring protons give rise to two doublets with equal coupling constants of 16 Hz. However, the spacings between the chemical shifts are different. In the spectrum of Ia, these chemical shifts lie at 2.33 and 2.90 ppm, while, in the spectrum of Ib, the corresponding shifts lie at 2.70 and 2.83 ppm. In the former case the doublets are separated by a spacing of 0.57 ppm and in the latter case the doublets are separated by a spacing of only 0.13 ppm.

Attempts have been made to correlate the difference in the spacing between the chemical shifts for ring protons with the configuration of the geometrical isomers on the basis of conformational analysis. On the evidence which

will be given in a later section, Ia and Ib and the other disubstituted cyclohexane-1,4-diones should exist in the chair form. Inspection of the cis and trans configurations of I, both in the chair form, would make it clear that the

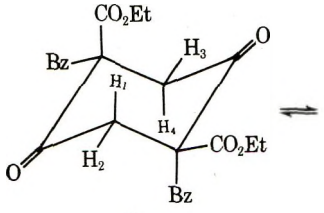


I (cis)

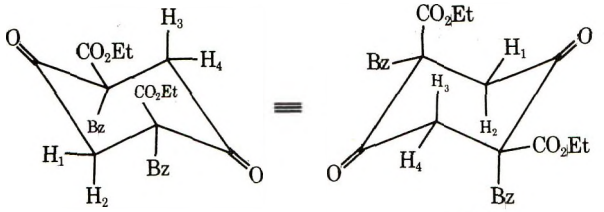


I (trans)

ring methylene protons are of three kinds in both cases. It follows that the absorption of these protons should give three doublets instead of two. To account for this discrepancy we have to take a closer look at these isomers. Let us consider first the cis isomer, Ia, and mark the four ring methylene protons with subscripts. The axial protons H_1 and H_4 lie in environments differing from each other, while the equatorial protons H_2 and H_3 lie in very similar environments. These latter protons may be treated as equivalent. Flipover of Ia gives Ia′, with a perfectly iden-



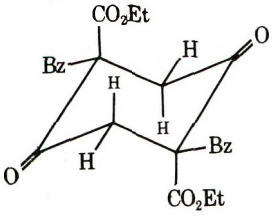
Ia



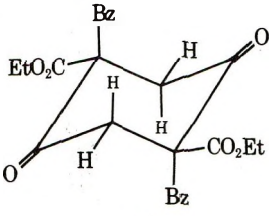
Ia′

tical conformation. After the conversion, H_3 in Ia′ assumes the same environment as H_1 in Ia, and H_4 in Ia′ assumes the same environment as H_2 in Ia. The actual form of the cis isomer may be regarded as consisting of half of Ia and half of Ia′, rapidly transforming one to the other at ordinary temperatures, similar to the interconversion of axial and equatorial hydrogen atoms in cyclohexane. Thus, in the cis isomer, the four ring methylene protons may be regarded as consisting of two kinds, those of the one kind lying in environments intermediate between H_1 and H_3, and those of the other lying in environments intermediate between H_2 and H_4. While proton H_1 is subject to the deshielding effects of the neighboring equatorial carbethoxyl group and the 3-axial carbethoxyl group, proton H_3 is subject to the deshielding effects of the neighboring oxo group and the 3-axial carbethoxyl group, and the shielding effect of the neighboring equatorial benzyl group. As to the protons H_2 and H_4, the former lies in a similar environment to that of H_3, and the latter is subject to the shielding effects of the neighboring equatorial benzyl group and the 3-axial benzyl group. By constructing models it can be shown that the distance between an axial proton and a neighboring equatorial group or a 3-axial group and that between an equatorial proton and a neighboring axial group or equatorial group are approximately equal. We may presume accordingly that the anisotropic effect of an axial substituent group on a neighboring equatorial proton or a 3-axial proton and that of the same group in an equatorial position on a neighboring axial or equatorial proton are nearly the same. On comparing the anisotropic effects of the substituent groups on the ring methylene protons, we see that the pairs of protons H_1–H_3 and H_2–H_4 differ from each other by the shielding effect of one benzyl group and the deshielding effect of one carbethoxyl group. For reasons which will be given in a later section, these two kinds of protons should give rise to two doublets considerably separated from each other.

As to the trans isomer, Ib, there are two conformations possible, as shown by Ib and Ib′. The equatorial protons



Ib



Ib′

in both forms lie in very similar environments and may be treated as equivalent, while the axial protons lie in different environments. However, for reasons given in the foregoing paragraph, the axial protons in Ib and Ib′ may be treated as nearly equivalent. It follows that in the trans isomer there are but two kinds of protons. However, as far as stability is concerned, Ib should be more stable, because strong dipole–dipole repulsion between carbethoxyl groups and oxo groups would cause the former to orient themselves as remote from the latter as possible. We presume that the trans isomer consists entirely of Ib. In this conformer, the ring methylene protons are also of two kinds: the axial protons and the equatorial ones. The former are subject to the deshielding effect of the 3-axial carbethoxyl group and the shielding effect of the neighboring equatorial benzyl group, and the latter are subject to the deshielding effects of the neighboring oxo group the σ electron of a C–C bond,[4] and the neighboring axial carbethoxyl group and the shielding effect of the neighboring equatorial benzyl group. These two kinds of protons differ by the deshielding effects of one oxo group and the σ electron of one C–C bond. As we shall see later, both of these effects are relatively small, and the two pairs of ring protons should give two more closely spaced doublets.

Based on the foregoing discussion, it is plausible to assign the cis configuration to the isomer of melting point 140.5° (Ia) and the trans configuration to the isomer of melting point 148.5° (Ib). Such assignments are in accord with the close constancy of the values of the spacings for the trans isomers of most of the substituted succinosuccinic esters studied, and the wide range of the values for the corresponding cis isomers. This point will be elaborated in the next section.

The nmr studies have been extended to other α,α'-disubstituted succinosuccinic esters including 2,5-dibenzylcyclohexane-1,4-dione (II), dicarbethoxymethylsuccinosuccinic ester (III),[5] dimethylsuccinosuccinic ester (IV),[6] di-*p*-bromobenzylsuccinosuccinic ester (VI), and dibenzhydrylsuccinosuccinic ester (VII). Among these, II, VI, and VII were previously unknown. Each of these esters exists as cis and trans isomers with the exception of VII, of which only one isomer has been found. The formation of II has been mentioned previously. Of the isomers of the dimethylsuccinosuccinic ester, only the crystalline isomer had been known in its pure state, while the liquid isomer was purified in the authors' laboratory by chromatography.

Referring to Table I, it is seen that the pairs of isomers of III, IV, and VI gave nmr spectra with the spacings of

Table I
Assignment of Configuration to the Isomers of I, III, IV, VI, and VII According to the Chemical Shifts for Their Ring Methylene Protons

Isomer	Mp, °C	Chemical shifts, ppm			Configuration	Isomer	Mp, °C	Chemical shifts, ppm			Configuration
		Upfield	Downfield	Spacing				Upfield	Downfield	Spacing	
Ia	140.5	2.33	2.90	0.57	Cis	Ib	148.5	2.70	2.83	0.13	Trans
IIIa	60	2.81	3.30	0.49	Cis	IIIb	106.5	2.97	3.07	0.27	Trans
IVa	Liquid	2.67	3.43	0.76	Cis	IVb	73	2.87	3.13	0.26	Trans
VIa	151–152	2.27	2.87	0.60	Cis	VIb	216–217	3.60	2.91	0.31	Trans
VIIa	216–217	1.97	3.43	1.46	Cis						

the peaks for ring methylene protons differing from each other in much the same way as those in the nmr spectra of Ia and Ib. With the same reasoning as that given for the assignment of configurations of Ia and Ib, we may assign the cis and trans configuration to each of these isomers.

In isomers of II, and those of V, the presence of tertiary protons on α-carbon atoms imposes highly complicated coupling with the neighboring protons, rendering the analysis of the spectrum virtually impossible. The decarboxylation of Ia and Ib by the action of $CaI_2 \cdot 4D_2O$ gave the deuterated counterparts of IIa and IIb, with all the ring methylene protons replaced by deuterons. This will be discussed in the succeeding section. The only isomer of VII isolated is probably the cis isomer, because the peaks for ring methylene protons are widely spaced.

Results of nmr spectroscopy of the dimethylsuccinosuccinic esters (IVa and IVb) at temperatures ranging from 20 to −90° provide strong support to the foregoing accounts for the special features of the nmr spectra of the isomers of α,α'-disubstituted succinosuccinic esters. On the other hand, X-ray analysis of the isomers of di-*p*-bromosuccinosuccinic ester is being carried out, with a view to further justifying the assignment of configuration by nmr spectroscopic data as outlined above. Preliminary results unequivocally establish the configuration of one of the isomers of VI. All these will be discussed in the succeeding section.

Results and Discussion

The nmr spectra of the geometrical isomers of α,α'-disubstituted succinosuccinic esters need to be described in greater detail. As we have seen, the portion of the spectra that is relevant to the determination of configuration of the isomers consists of the peaks for the ring methylene protons. Table I gives the chemical shifts of the doublets for the ring protons in the nmr spectra of the isomers of I, III, IV, VI, and VII, together with the configuration assigned to each of them according to the considerations given in the preceding section.

Let us first focus our attention to the spectral assignments on which the assignment of configuration to the pairs of isomers of I, III, IV, and VI depends. In the compounds I, II, III, VI, and VII, there exists in each of the substituents [$CH_2C_6H_5$, $CH_2C_6H_5$, $CH_2COOC_2H_5$, $CH_2C_6H_4Br$, and $CH(C_6H_5)_2$] a pair of diastereotopic groups. The protons are potentially anisochronous. The best-known examples are the nonequivalence of benzylic protons in some, but not all, *N*-benzyl heterocyclic bases.[7]

Examination of the nmr spectra of the substituted succinosuccinic esters and some of their decarboxylation products investigated in the present study would show that none of the substituent groups mentioned above gave signals that seriously interfered with our spectral assignments. The benzylic protons in Ia and Ib give a singlet. In the deuterated IIa and IIb, in which all the ring protons have been replaced by deuterons (see Experimental Section), the benzylic protons give two doublets with J = 14.0 Hz, differing from the doublets for the ring protons with J = 16.0 Hz. In the spectrum of IIIa, the absorption of the methylene protons of the $CH_2COOC_2H_5$ group gives rise to a singlet at 3.22 ppm, and that of the ring protons to two doublets at 2.81 and 3.30 ppm, with J = 16.0 Hz. As to its isomer, IIIb, the methylene protons of the $CH_2COOC_2H_5$ group give two doublets at 3.13 and 3.32 ppm, with J = 14.4 Hz, differing from the doublets for the ring protons at 2.97 and 3.07 ppm, with J = 16.0 Hz. In the spectra of IVa and IVb, the protons of the methyl groups on α-carbon atoms give their signals quite remote from those of the ring protons. Among the isomers of VI, the cis isomer, VIa, gives a spectrum in which the absorption of the benzylic protons gives rise to two doublets more downfield than those for the ring protons, with J = 14.0 *vs.* 16.0 Hz. In the spectrum of the trans isomer, VIb, the absorption of the benzylic protons gives rise to a singlet. Finally, in the spectrum of VIIa, the doublets for the ring protons are easily characterized by proton counting and finding out the coupling constant. We may conclude that there is scarcely anything ambiguous in the assignments of the doublets to the ring methylene protons in all the pairs of isomers of I, III, IV, VI, and VII.

The interpretation of the spectral data as well as the reasoning on which to base the assignment of the configuration of cis and trans isomers can be provided by considering more specifically the anisotropic effects of the substituent groups on the ring methylene protons. In the spectra of Ia, IIIa, IVa, VIa, and VIIa, to which the cis configurations are assigned, the downfield doublet of the ring protons may be ascribed to the deshielding effect of carbethoxyl group, while the upfield one may be ascribed to the shielding effect of the substituent group $CH_2C_6H_5$, $CH_2COOC_2H_5$, CH_3, $CH_2C_6H_4Br$, or $CH(C_6H_5)_2$. It follows that the magnitudes of the downfield shifts should be close to one another, and those of the upfield shifts may be widely different, and, consequently, the spacings that separate each pair of doublets, or the chemical shift differences, for the doublets in the spectra of these isomers should differ widely. These turned out as expected. Referring to Table I, the downfield shifts lie within the range 2.87–3.43 ppm; the upfield shifts within the range 1.97–2.81 ppm; and the chemical shift differences extend from 0.49 to 1.47 ppm.

It should be noted that for cis isomers the deshielding effect of σ electrons on equatorial protons[4] does not influence the chemical shift differences, since the protons concerned undergo constant axial–equatorial interconversions. Additionally, the substituent groups that ultimately give rise to chemical shifts are capable of taking favorable orientations for exerting their anisotropic effects on neighboring protons.

Far different are the trans isomers in these respects. In the first place, the effect of the σ electrons of C–C bonds should be taken into consideration, although its magnitude may be very small (see below). Secondly, as mentioned earlier, the spacing that separates the chemical shifts for the ring protons depends on the deshielding effects of one oxo group and one C–C bond, and is practically independent of the effects of other substituent groups attached to the α-carbon atoms. Thirdly, the oxo group,

Table II
Effect of Temperature on the Peaks for Ring Methylene Protons in the Nmr Spectra of Isomeric α,α'-Dimethylsuccinosuccinic Esters in Deuteriochloroform

	Cis isomer, liquid, bp 130° (1 mm) (IVa)		Trans isomer, crystalline, mp 73° (IVb)	
Temp, °C	Apparent chemical shifts of ring protons, ppm	Spacing between the apparent shifts, ppm	Apparent chemical shifts of ring protons, ppm	Spacing between the apparent shift, ppm
20	2.67–3.43	0.76	2.87–3.13	0.26
−11	2.75–3.37	0.62	2.90–3.15	0.25
−38	2.83–3.30	0.47	2.87–3.13	0.26
−48	2.87–3.28	0.41	2.88–3.13	0.25
−58	2.93–3.20	0.27	2.88–3.13	0.25

which is held in a rigid system, should exert a rather small deshielding effect on the neighboring equatorial proton, which is barely embraced in its deshielding cone[8] and should give a small chemical shift. So is the deshielding effect of the C–C bond. All these are reflected in the chemical shifts for the ring protons and their differences for the isomers Ib, IIIb, IVb, and VIb, as listed in Table I. The chemical shift differences for the last three isomers lie within the range 0.26–0.31 ppm, and the lowest value, that for Ib, is 0.13 ppm. The close constancy of the chemical shift differences and their relatively small magnitudes are in good agreement with the deductions outlined above. It may also be inferred that, in our present case, neither the deshielding effect of the oxo group nor that of the C–C bond may produce a shift as much as 0.31 ppm.

While the foregoing considerations justify the assignment of configurations to the α,α'-disubstituted succinosuccinic esters, they do not exclude the possibility that these substances might exist in the boat form. It has been known that for certain derivatives of cyclohexanone, the twist-boat form is preferred.[9]

If we assume that the substituted succinosuccinic esters existed in the boat form, the spacings of the doublets for the ring protons could be correlated in a similar way with the anisotropic effects of the substituent groups on these protons, on the assumption that each isomer consisted of two enantiomeric twist forms, which could be represented by the regular boat form as the average state. However, deductions from such correlation would be contradictory to the experimental facts. For example, while the trans configuration (boat form) should be assigned to Ia, IIIa, IVa, and VIa in the same way as the cis configuration (chair form) had been assigned to them, the spacings of the doublets predicted in the way as previously described for the "trans isomers" (Ia, IIIa, IVa, and VIa) would be definitely smaller than the spacings for the corresponding "cis isomers" (Ib, IIIb, IVb, and VIb). Furthermore, if the cis configuration (boat form) should be assigned to Ib, IIIb, IVb, and VIb, the high flexibility of the molecules would obviate the need of taking some preferred conformation. As a result, all the ring protons would be nonequivalent.

Low-temperature nmr spectroscopy of dimethylsuccinosuccinic esters was carried out, with our original aim focused at testing whether some conformational isomers of the cis form of the ester could be "frozen" so that their chemical shifts could be identified and interpreted. The dimethyl derivatives were chosen as the model compounds on account of their ready solubility in most organic solvents. Solutions of the esters in deuteriochloroform at a concentration of approximately 50 mg/0.5 ml were first used. The effect of low temperatures on the absorptions of the ring methylene protons in IVa and IVb is summarized in Table II. It is seen that in the case of the cis isomer, lowering the temperature resulted in the decrease of the spacing between the doublets for the ring methylene protons, with the two chemical shifts apparently drawing nearer to each other from both directions, while, in the case of the trans isomer, practically no change occurred throughout the entire temperature range investigated. The effect of temperature on the peaks for the ring protons is also shown in Figure 3, which indicates that, while the temperature became lower, the peaks for the ring protons grew broader. At −58°, crystallization of the solute took place. In order that the experiment could be carried out at still lower temperatures, deuteriochloroform was replaced by deuteriomethanol as solvent. The concentration of the solution was also approximately 50 mg/0.5 ml. With these solutions, the nmr spectra showed that the chemical shifts of the doublets for the ring protons were generally more closely spaced as compared with those in the spectra using deuteriochloroform as solvent. At temperatures lower than −65°, the broadened peaks for the ring protons in the spectrum of IVa, instead of separating into more peaks as first expected, fused into a single band which grew flatter with decreasing temperature as shown in Figure 4a. For the isomer IVb, its solution in deuterated methanol at the concentration of approximately 50 mg/0.5 ml was used at first. When the temperature was decreased below −40°, crystallization took place, and the experiment could not be carried any further. A more dilute solution (approximately 10 mg/0.5 ml) was then used. At a temperature as low as −66°, when the solution had set to a jelly-like mass, there was still no change in the spacing between the shifts for the ring protons. In order that the spectra of IVa and IVb may be compared on equal bases, the data that resulted from the use of more concentrated solutions only are shown in Figures 4a and 4b.

The temperature effect on the peaks for the ring methylene protons can be satisfactorily interpreted by presuming the flipover of the cyclohexane ring of the cis isomers of the substituted succinosuccinic esters. The assignment of cis and trans configurations to the pairs of these isomeric esters can be made accordingly, as discussed earlier. Let us consider first the cis isomer of an α,α'-disubstituted succinosuccinic ester. Molecules of this isomer can flip over from one conformer to the other, requiring only a small amount of activation energy. At room temperature, the frequency of interconversion is high, and the two chair conformers, being more stable than the intermediate forms, constitute almost the entire population of the molecules. The chemical shifts of the two pairs of ring protons H_1–H_3 and H_2–H_4 (see foregoing part) are virtually the weighted averages of the chemical shifts of H_1 and H_3, and of those of H_2 and H_4, in the two conformers. As the temperature is reduced, the rate of interconversion between the two conformers is slowed down, chiefly owing to decreased thermal agitation and increased viscosity, and the spectrum becomes broader and changes gradually its overall character, until finally the broadened peaks fuse to a flattened band (Figures 3 and 4). On the other hand, since the spectrum of the trans isomer does not show similar temperature effect, we may presume that the trans isomer exists in the form of a *single, more stable* conformer. A precise interpretation of the temperature ef-

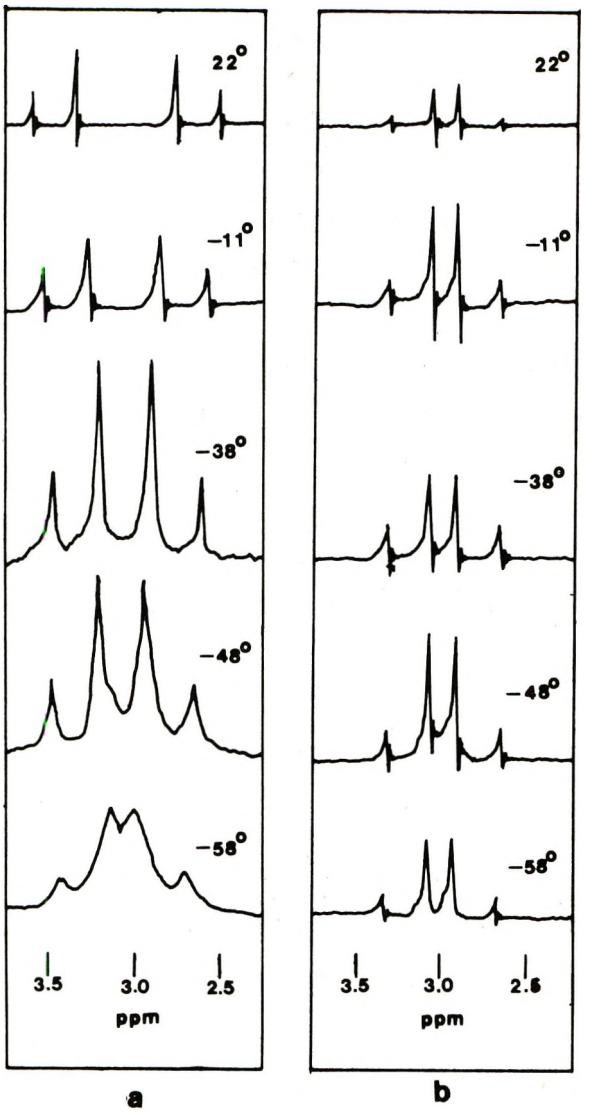


Figure 3. Parts of the nmr spectra of the isomers of dimethylsuccinosuccinic esters (IVa and IVb) embracing only the two doublets for the ring methylene protons, showing the effect of varying temperatures on the spacing that separates the doublets from each other. (a) The doublets for the ring methylene protons in the cis isomer (IVa) approach each other as temperature decreases. (b) Those for the ring methylene protons in the trans isomer (IVb) do not undergo any change in their spacing by decreasing temperature. Solvent used was $CDCl_3$.

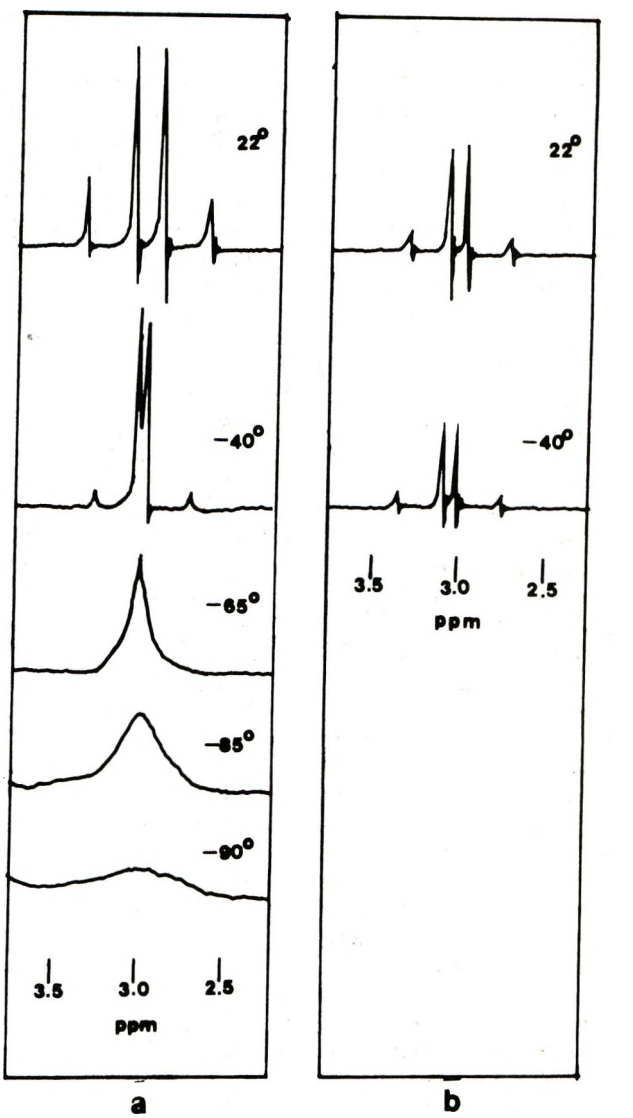


Figure 4. Similar to Figure 3, CD_3OD being used instead of $CDCl_3$ as solvent so as to permit the nmr spectra to be taken at still lower temperatures.

fect on the peaks for the ring protons as described above would call for a total line shape analysis. For our present purpose, it is sufficient to demonstrate that the interconversion of the two conformer of the cis isomer of the dimethylsuccinosuccinic ester by flipping back and forth does take place, while the same thing does not occur in the trans isomer.

The decarboxylation of the substituted succinosuccinic esters to give substituted cyclohexanediones deserves mentioning. As we have seen, the products that resulted from the decarboxylation of Ia or Ib and IVa or IVb gave highly complex nmr signals. Attempts were made to decarboxylate Ia or Ib with $CaI_2 \cdot 4D_2O$, with a view to obtaining IIa and IIb, with their α hydrogen replaced by deuterium. However, these resulted in a failure. The nmr spectra of the deuterated products of IIa and IIb show that all the ring hydrogen atoms have been replaced by deuterium. Unexpectedly, the absorptions for benzylic methylene protons, which give a singlet in the spectra of both Ia and Ib, give two doublets in the spectra of the deuterated counterparts IIa and IIb. The same situation of benzylic methylene protons is also observed in the spectrum of VIa. All these have been mentioned in the earlier part of this section. The question may arise, however, as to whether the ring methylene protons or the benzylic protons are replaced by deuterium when Ia or Ib is decarboxylated with $CaI_2 \cdot 4D_2O$, since it had been found that toluene can undergo deuterium exchange in a strongly alkaline medium, resulting in the replacement of side-chain hydrogen by deuterium.[10] This question is easily settled by referring to the mass spectra of deuterated IIa and IIb (see Experimental Section). In both of them the M^+ peak at m/e 298 reveals that 6 out of 14 hydrogen atoms have been replaced by deuterium, and an intense peak of $C_7H_7^+$ at m/e 91 reveals that ring hydrogen atoms, not the benzylic ones, have been replaced by deuterium. For, if the latter hydrogen atoms were replaced, an intense peak of $C_7H_5D_2^+$ should appear at m/e 93, but this was not the case. In the nmr spectra of deuterated Va and Vb, only the methyl protons appear as a singlet, and the doublet characteristic of C_6 ring protons is absent.

Incidentally, the present investigation firmly establishes the fact that the reaction between disodiosuccinosuccinic ester and benzyl iodide or chloride furnishes the α,α'-dibenzyl derivatives but not the enolic ethers as was regarded by Nef. It also affords examples illustrating the readiness with which β-keto esters, even those known to be re-

sistant to hydrolysis, can be cleaved by the action of hydrated calcium iodide. The formulation of IIa and IIb from either Ia or Ib gives further support to the mechanism suggested by one of the present authors.[3] Equilibration experiments were carried out by the action of ethanolic sodium hydroxide as well as sodium ethoxide on IIa and IIb with a view to further strengthening the establishment of the geometrical isomerism of IIa and IIb. Unexpectedly, the attempt was unsuccessful. Both IIa and IIb were slowly oxidized to deeply colored material when heated in an alkaline medium. Later experiments were conducted in an atmosphere of nitrogen, but the reaction mixture, though only weakly discolored, did not give any crystalline material.

Among the substituted succinosuccinic esters studied in the present work, VIa, VIb, and VII, being previously unknown, were obtained from the reactions of *p*-bromobenzyl bromide and benzhydryl bromide, respectively, on disodiosuccinosuccinic ester. As mentioned earlier, only one isomer of VII, presumably the cis isomer, was isolated. The reason for the failure to obtain the trans isomer is not understood. It is also interesting to note that, while Ib gives a product of much higher melting point but with the same percentage composition on refluxing for a long time with dilute sulfuric acid, the *p*-bromobenzyl analog (VIb) remains unchanged when treated in the same way.

Finally, X-ray analysis of the isomeric di-*p*-bromobenzylsuccinocuccinic esters (VIa and VIb) is being carried out, with the dual purpose of verifying that the substituted succinosuccinic esters exist in the chair, but not in the boat form, and providing justification of the configurations assigned to these esters on the basis of their nmr spectra. Preliminary results from the X-ray analysis of VIb show that the molecule possesses a center of symmetry, indicating that VIb should exist in the chair form, and that it should be the trans isomer. Packing considerations strongly suggest that in this isomer the two bulky *p*-bromobenzyl groups should be in equatorial positions, in agreement with our postulate that in Ib (and IIb, IVb, and VIb) the carbethoxyl groups should take the axial positions for the avoidence of strong dipole–dipole repulsion.

Experimental Section

Reaction between disodiosuccinic Ester and Benzyl Iodide. The disodiosuccinosuccinic ester used was prepared by adding a slight excess of ethanolic sodium hydroxide to a hot ethanolic solution of diethyl succinosuccinate, with vigorous shaking. The magenta-colored disodium enolate was filtered, washed with ethanol, and dried in a vacuum drying oven at 60° until the weight became constant.

Fifteen grams (0.05 mol) of the disodium enolate and 23 g (0.11 mol) of benzyl iodide were placed in a round bottom flask fitted with a reflux condenser, and heated in an oil bath at 140° until the color of the disodium enolate disappeared; 0.5 hr was required. The reaction mixture was extracted with hot benzene and filtered. The filtrate, after removal of benzene, gave pale yellow crystals which on recrystallization from ethanol gave 14.5 g (66%) of colorless needles melting at 128°. This product consisted of a mixture of two components. It was repeatedly recrystallized from ethanol until the less soluble component (Ib) that separated melted at 148.5° (6 g). The combined mother liquor from the recrystallization was evaporated to a small volume. The crystals of the more soluble component (Ia) that separated were recrystallized several times from ethanol. The purified product (5.5 g) melted at 140.5°. On the evidence presented in the foregoing sections, and the the analytical data that follow, the substances Ia and Ib were characterized as *cis*- and *trans*-2,5-dibenzyl-2,5-dicarbethoxycyclohexane-1,4-dione, respectively.

***cis*-2,5-Dibenzyl-2,5-dicarbethoxycyclohexane-1,4-dione (Ia)** was obtained as colorless crystals: mp 140.5°; ir (KBr) 1715 cm^{-1} (ketonic C=O) and absorption maximum characteristic of phenyl group; nmr $CDCl_3$) 7.20 (m, 10, C_6H_5), 4.15 (q, 4, J = 7.0 Hz, CH_2CH_3), 3.20 (s, 4, $CH_2C_6H_5$), 2.90 (d, 2, J = 16.0 Hz, C_6 ring methylene H), 2.33 (d, 2, J = 16.0 Hz, C_6 ring methylene H), and 1.25 ppm (t, 6, J = 7.0 Hz, CH_2CH_3).

Anal. Calcd for $C_{26}H_{28}O_6$: C, 71.48; H, 6.47. Found: C, 71.28, 71.22; H, 6.22, 6.72.

***trans*-2,5-Dibenzyl-2,5-dicarbethoxycyclohexane-1,4-dione (Ib)** was obtained as colorless crystals: mp 148.5°; ir (KBr) 1715 (ketonic C=O), 1745 cm^{-1} (ester C=O), and absorption maximum characteristic of phenyl group; nmr ($CDCl_3$) 7.31 (m, 10, C_6H_5), 4.05 (q, 4, J = 7.0 Hz, CH_2CH_3), 3.23 (s, 4, $CH_2C_6H_5$), 2.83 (d, 1, J = 16.0 Hz, C_6 ring methylene H), 2.70 (d, 2, J = 16.0 Hz, C_6 ring methylene H), and 1.25 ppm (t, 6, J = 7.0 Hz, CH_2CH_3).

Anal. Calcd for $C_{26}H_{28}O_6$: C, 71.48; H, 6.47. Found: C, 71.41, 71.29; H, 6.71, 6.58.

Attempt to Hydrolyze Ia and Ib. A 0.5-g portion of the sample (Ia or Ib) was finely pulverized, dissolved in 2 ml of concentrated sulfuric acid, and then diluted with 20 ml of water. The mixture was refluxed for 48 hr. During the heating, a stream of nitrogen was led through the reaction flask and allowed to pass through a solution of barium hydroxide. No precipitation of barium carbonate was observed. When Ia was used, there was no apparent reaction, and almost all of the starting material was recovered. When Ib was used, a substance of unknown structure was obtained. The latter was purified by recrystallizing from ethanol. Oxidation of this substance with potassium permenganate did not give benzoic acid. The nature of the substance as well as its oxidation product remains to be investigated.

Product of unknown structure was obtained as crystals: mp 272°; ir (KBr) 1690 (ketonic C=O), 1740 cm^{-1} (ester C=O), absorption maximum characteristic of phenyl group absent, broad band at 3390–5590 cm^{-1} probably due to the presence of OH group.

Anal. Calcd for $(C_{26}H_{18}O_6)_n$: C, 71.48; H, 6.47. Found: C, 71.26, 71.27; H, 6.81, 6.57.

Preparation of *cis*- and *trans*-2,5-Dioximino-1,4-dicarbethoxy-1,4-dibenzylcyclohexane. The substances Ia and Ib were converted into the corresponding dioximes by the pyridine method. The crude products were purified by recrystallizing from ethanol.

Dioxime of Ia was obtained as colorless crystals, mp 221° dec.

Anal. Calcd for $C_{26}H_{30}O_6N_2$: C, 67.00; H, 6.44; N, 6.00. Found: C, 66.82, 67.04; H, 6.52, 6.81; N, 6.27. 6.29.

Dioxime of Ib was obtained as colorless crystals, mp 252° dec.

Anal. Calcd for $C_{26}H_{30}O_6N_2$: C, 67.00; H, 6.44; N, 6.00. Found: C, 67.08, 67.08; H, 6.56, 6.58; N, 6.00, 6.02.

Cleavage of Ia and Ib by the Action of Hydrated Calcium Iodide. A mixture of 2.2 g (0.005 mol) of Ia and 8.1 g (0.024 mol) of calcium iodide tetrahydrate was placed in a flat-bottomed flask provided with an outlet tube leading to a downward condenser. The flask was immersed in an oil bath over the hot plate of a magnetic stirrer, and heated with stirring at 170° for 2 hr. The ethyl iodide that distilled over was collected in a strongly cooled receiver, and the carbon dioxide evolved was absorbed in an absorption bottle filled with 40% potassium hydroxide and previously weighed. After the reaction was complete, the reaction mixture was allowed to cool and treated with dilute hydrochloric acid to dissolve unreacted calcium iodide and calcium carbonate formed during the reaction, the carbon dioxide formed being absorbed in a previously weighed absorption bottle. From the weights of carbon dioxide and ethyl iodide produced, it was estimated that at least 78% of the ester was decarboxylated.

The acidified mixture was extracted with chloroform. The chloroform extract on evaporation gave a crystalline material melting at 165°. The latter consisted of two isomers, IIa (mp 155°) and IIb (mp 196°), which were separated by taking advantage of the fact that IIb is less soluble in ether than IIa. The mixture of IIa and IIb was repeatedly crystallized from ether until the less soluble component (IIb) that crystallized melted at 196°. Its homogeneity was confirmed by thin layer chromatography.

The combined mother liquor was evaporated on a hot plate to remove most of the ether. On cooling, IIa crystallized. It was recrystallized several times from ethanol. The melting point of the purified product was 155°. Its homogeneity was also confirmed by thin layer chromatography.

***cis*(?)-2,5-Dibenzylcyclohexane-1,4-dione (IIa)** was obtained as needles, mp 155°, ir (KBr) 1710 cm^{-1} (ketonic C=O) and absorption maximum characteristic of phenyl group.

Anal. Calcd for $C_{20}H_{20}O_2$: C, 82.16; H, 6.89. Found: C, 81.90, 81.96; H, 7.01, 7.02.

***trans*(?)-2,5-Dibenzylcyclohexane-1,4-dione (IIb)** was obtained as long needles, mp 196°, ir (KBr) 1701, 1712 cm^{-1} (C=O),

and absorption maximum characteristic of phenyl group.

Anal. Calcd for $C_{20}H_{20}O_2$: C, 82.16; H, 6.89. Found: C, 81.95, 82.08; H, 7.02, 6.96.

The cleavage of Ib was carried out in exactly the same way as described above for the cleavage of Ia. The same pairs of geometrical isomers IIa and IIb were obtained. The identity of IIa and IIb from the cleavage of Ib with those from the cleavage of Ia was confirmed by thin layer chromatography and ir spectroscopy.

Preparation of *cis*- and *trans*-2,5-Dioximino-1,4-dibenzylcyclohexane. Both IIa and IIb were converted into the corresponding dioximes by the pyridine method. These dioximes were purified by recrystallizing from ethanol.

***cis*(?)-2,5-Dioximino-1,4-dibenzylcyclohexane** was obtained as colorless crystals, mp 220°.

Anal. Calcd for $C_{20}H_{22}O_2N_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.68, 74.12; H, 6.90, 6.92; N, 8.57, 8.64.

***trans*(?)-2,5-Dioximino-1,4-dibenzylcyclohexane** was obtained as colorless crystals, mp 252°.

Anal. Calcd for $C_{20}H_{22}O_2N_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.50, 74.28; H, 6.94, 6.94; N, 8.84, 8.67.

Cleavage of I and II by the Action of Calcium Iodide·4D_2O. In a 150-ml flat-bottomed flask was placed 8.1 g (0.024 mol) of calcium iodide tetrahydrate. The flask was fitted with a cork bearing an inlet tube connected to a hydrogen cylinder, and an outlet tube connected to a downward condenser for distillation. A steady stream of hydrogen was allowed to pass over the surface of the salt, and the flask was strongly heated in a sand bath until no more water passed over. The heat source was removed, the flask was allowed to cool to room temperature, and then the stream of hydrogen was cut off. The cork was replaced by another one carrying a dropping funnel, from which 1.92 g (0.096 mol) of deuterium oxide was added into the flask, with vigorous shaking. To the calcium iodide·4D_2O thus formed was added 2.2 g (0.005 mol) of Ia or Ib. The flask was fitted with a cork carrying an upright condenser with a drying tube on its top, placed in an oil bath, and heated at 170° with stirring on a magnetic stirrer for 2 hr. The reaction mixture was allowed to cool, and then treated with a solution of deuterated acetic acid (CH_3COOD) in deuterium oxide, to dissolve unreacted calcium iodide and calcium carbonate formed during the reaction. The acidified mixture was extracted with chloroform. The chloroform extract on evaporation gave a mixture of IIa′ and IIb′, deuterated counterparts of IIa and IIb, respectively. They were separated by extraction with ether, in which only IIa′ was soluble. The ether extract on evaporation gave crystals of IIa′, which were purified by crystallization from carbon tetrachloride. The residue insoluble in ether was also purified by recrystallization from carbon tetrachloride to give IIb′.

Deuterated cis(?)-2,5-Dibenzylcyclohexane-1,4-dione (IIa′) was obtained as colorless crystals: mp 155°; nmr ($CDCl_3$) 7.22 (m, 10, C_6H_5), 3.19 (d, 2, J = 14.0 Hz, $C_6H_5CH_2$), 2.58 ppm (d, 2, J = 14 Hz, $C_6H_5CH_2$); mass spectrum M^+ at m/e 298 ($C_{20}H_{14}D_6O_2$), intense peak at m/e 91 ($C_7H_7^+$).

Deuterated *trans*(?)-2,5-Dibenzylcyclohexane-1,4-dione (IIb′) was obtained as colorless crystals: mp 196°; nmr ($CDCl_3$) 7.26 (m, 10, C_5H_5), 3.17 (d, 2, J = 14.0 Hz, $C_6H_5CH_2$), 2.68 ppm (d, 2, J = 14.0 Hz, $C_6H_5CH_2$); mass spectrum M^+ at m/e 298 ($C_{20}H_{14}D_6O_2$), intense peak at m/e 91 ($C_7H_7^+$).

Reaction between Disodiosuccinosuccinic Ester and Methyl Iodide. A mixture of 15 g (0.05 mol) of dried disodiosuccinosuccinic ester and 25.5 g (0.2 mol) of methyl iodide was placed in a round-bottom flask and heated on an oil bath under a reflux condenser until the magenta-colored suspended solid changed to dirty gray. During heating, additional amounts of methyl iodide were introduced into the flask to compensate for its loss by evaporation. When the reaction was complete, the contents of the flask was extracted with hot benzene and filtered. The filtrate was cooled when a crystalline product separated, which on recrystallization from ethanol gave crystals melting at 73°. This was the trans isomer of α,α′-dimethylsuccinosuccinic ester (IVb) which was first isolated by von Baeyer. Further cooling of the benzene mother liquor gave a second crop of IVb. The overall yield of the purified product amounted to 2 g. The mother liquor was evaporated to remove most of the benzene, and the residue was distilled under vacuum. Under 1 mm, a light yellow oil boiling at 130° was collected (10 g). Thin layer chromatography of the oil indicated that it consisted of two major components and one minor component. The former included IVb. To separate the components, about 2 g of the oil was dissolved in a small amount of benzene, and the benzene solution was cautiously introduced to a column packed with silica gel consisting of 15% of Camag DFO and 58% of Merck's Kieselguhr (0.2–0.5 mm). The chromatogram was developed by benzene containing 1% of ethanol and was clearly visible when irradiated with a uv lamp, the more strongly adsorbed material being intensely violet while the less strongly adsorbed one was bluish violet. The components in each zone was eluted out by the same solvent. The eluents of the less strongly adsorbed material still consisted of a mixture of unknown composition. The latter part of the eluents of the more strongly adsorbed material was concentrated by evaporation, and the residue was distilled under vacuum, the fraction boiling at 130° (1 mm) being collected. The product thus obtained consisted of a homogeneous substance, as verified by thin layer chromatography. Its nmr data indicated that it should be IVa.

***cis*-2,5-Dimethyl-2,5-dicarbethoxycyclohexane-1,4-dione (IVa)** was obtained as an oily liquid: bp 130° (1 mm); d^{25} 1.1530; $n^{25}D$ 1.4659; ir (CCl_4) 1735 (ketonic C=O), 1720 cm^{-1} (ester C=O); nmr ($CDCl_3$) 4.21 (q, 4, J = 7.0 Hz, CH_2CH_3), 3.41 (d, 2, J = 16.0 Hz, C_6 ring methylene H), 2.67 (d, 2, J = 16.0 Hz, C_6 ring methylene H), 1.38 (s, 6, CH_3), 1.22 ppm (t, 6, J = 7.0 Hz, CH_2CH_3).

Anal. Calcd for $C_{14}H_{20}O_6$: C, 59.15; H, 7.04. Found: C, 59.02, 58.86; H, 7.28, 7.34.

***trans*-2,5-Dimethyl-2,5-dicarbethoxycyclohexane-1,4-dione (IVb)** was obtained as colorless crystals: mp 73°; ir (KBr) 1728 (ketonic C=O) and 1700 cm^{-1} (ester C=O); nmr ($CDCl_3$) 4.18 (q, 4, J = 7.0 Hz, CH_2CH_3), 3.08 (d, 2, J = 16 Hz, C_6 ring methylene H), 2.85 (d, 2, J = 16.0 Hz, C_6 ring methylene H), 1.40 (s, 6, CH_3), 1.20 ppm (t, 6, J = 7.0 Hz, CH_2CH_3).

Decarboxylation of IV by the Action of CaI_2·4D_2O. A 1.4-g portion of IVa or IVb was heated with CaI_2·4D_2O prepared from 8.1 g (0.024 mol) of CaI_2·4H_2O. The reaction was carried out in exactly the same way as that described for the decarboxylation of Ia or Ib by the action of CaI_2·4D_2O. After completion of the reaction, the reaction mixture was acidified with CH_3COOD in D_2O. The solution was saturated with NaCl and extracted with chloroform. The crystalline residue that resulted from the evaporation of the dried chloroform extract was fractionally crystallized from ethanol to get two crystalline substances. The one more soluble in ethanol and melting at 87–88° was probably the cis isomer of the deuterated 2,5-dimethylcyclohexane-1,4-dione (IVa) and the other, less soluble in ethanol and melting at 120–121°, was probably the trans isomer (IVb). In the nmr spectra of these substances the only absorption of the α-methyl protons appears as a singlet around 1.40 ppm.

Decarboxylation of IV with D_2SO_4 in D_2O. A 1.4-g portion of IVa or IVb was refluxed with 20 ml of 6 N D_2SO_4 in D_2O until complete solution occurred. The reaction mixture was cooled and then extracted with chloroform. The chloroform extract after drying was evaporated to dryness. The crystalline mass that resulted was fractionally crystallized from ethanol to give deuterated IVa and IVb as described in the foregoing paragraph. The nmr spectra of these substances also showed that all the ring methylene protons had been replaced by deuterons.

Reaction between Disodiosuccinosuccinic Ester and *p*-Bromobenzyl Bromide. Fifty grams (0.2 mol) of *p*-bromobenzyl bromide and a magnetic stirring bar were placed in a flat-bottomed, 250-ml flask fitted with a reflux condenser, and heated in an oil bath over a magnetic stirrer to 130–140°. Thirty grams (0.1 mol) of carefully dried disodiosuccinosuccinic ester was added, while the stirrer was on, in about ten portions. The addition took about 30 min. The reaction was vigorous. At the end of the reaction, the contents of the flask consisted of a brown, crystalline paste containing small granules of unreacted sodium enolate. Thirty milliliters of dry toluene was added, and the mixture was heated for 30 min longer with stirring and then filtered by suction. The filtrate crystallized readily into a crystalline paste. The solid residue on the filter was extracted first with hot chloroform, then with boiling toluene, and finally the residue, consisting mainly of sodium bromide, was treated with water to isolate small amounts of organic crystalline product. The crystalline paste that constituted the main portion of the product was filtered. The crystals collected amounted to 40 g, which on recrystallization twice from toluene melted at 151–152° (32 g). This product was characterized as *cis*-2,5-di-*p*-bromobenzyl-2,5-dicarbethoxycyclohexane-1,4-dione (VIa). The crystals from the chloroform extract, those from the toluene extract, and those obtained by treating the residue with water consisted of one and the same substance. They were combined and the total amount weighed 10 g. The crude product was recrystallized first from toluene, then from chloroform. The pure product (7 g), melting at 216–217°, was characterized as *trans*-di-*p*-bromobenzylcyclohexane-1,4-dione (VIb). The overall yield of the pure isomeric esters was 67%.

cis-**2,5-Di-*p*-bromobenzyl-2,5-dicarbethoxycyclohexane-1,4-dione (VIa)** was obtained as colorless crystals, very soluble in hot toluene and sparingly soluble in the cold. Single crystals for X-ray diffraction were obtainable by crystallization from chloroform: mp 151–152°; ir (KBr) 1710 cm^{-1} (ketonic and ester C=O); nmr ($CDCl_3$) 7.42 (d, 4, J = 9.0 Hz, C_6H_4Br), 6.93 (d, 4, J = 9.0 Hz, C_6H_4Br), 4.17 (q, 4, J = 7.0 Hz, CH_2CH_3), 3.23 (d, 2, J = 14.0 Hz, $CH_2C_6H_4$), 3.11 (d, 2, J = 14.0 Hz, $CH_2C_6H_4Br$), 2.90 (d, 2, J = 16 Hz, C_6 ring methylene H), 2.26 (d, 2, J = 16.0 Hz, C_6 ring methylene H), 1.28 ppm (t, 6, J = 7.0 Hz, CH_2CH_3) ppm.

Anal. Calcd for $C_{26}H_{26}O_6Br_2$: C, 52.53; H, 4.37; Br, 26.90. Found: C, 52.78, 52.78; H, 5.63, 4.60; Br, 26.92.

trans-**2,5-Di-*p*-bromobenzyl-2,5-dicarbethoxycyclohexane-1,4-dione (VIb)** was obtained as colorless crystals slightly soluble in chloroform and acetone and very sparingly soluble in cold benzene and toluene. Single crystals were obtainable by crystallization from 1:1 acetone–benzene: mp 216–217°; ir (KBr) 1710 cm^{-1} (ketonic and ester C=O); nmr ($CDCl_3$) 7.45 (d, 4, J = 9.0 Hz, C_6H_4Br), 7.03 (d, 4, J = 9.0 Hz, C_6H_4Br), 4.07 (q, 4, J = 7.0 Hz, CH_2CH_3), 3.20 (s, 4, $CH_2C_6H_4Br$), 2.83 (d, 2, J = 16.0 Hz, C_6 ring methylene H), 2.66 (d, 2, J = 16.0 Hz, C_6 ring methylene H), 1.13 ppm (t, 6, J = 7.0 Hz, CH_2CH_3).

Anal. Calcd for $C_{26}H_{26}O_6Br_2$: C, 52.53; H, 4.37; B, 26.92. Found: C, 52.66, 52.55; H, 4.62, 4.64; Br, 26.74.

Reaction between Disodiosuccinosuccinic Ester and Benzhydryl Bromide. A mixture of 30 g (0.1 mol) of carefully dried disodiosuccinosuccinic ester and 54.3 g (0.22 mol) of freshly distilled benzhydryl bromide free from HBr was placed in a round-bottom flask fitted with a reflux condenser. Dry toluene was added into the flask in an amount just sufficient to wet the solid mixture. The flask was heated in an oil bath under reflux for 3 hr. The color of the mixture changed from magenta to dirty green. More dry toluene was added into the flask, and the mixture was boiled for a few minutes and then filtered by suction. The filtrate partially crystallized on standing. On filtration, it gave the first crop of crystals, amounting to 23 g. By cooling the mother liquor, a second crop of crystals (10 g) was obtained which was slightly yellow owing to contamination of succinosuccinic ester. This latter can be removed from the main constituent by recrystallization from ligroin (bp 80–100°). The combined crude product free from succinosuccinic ester was crystallized from benzene. The crystals that separated were recrystallized several times from benzene. The purified product melted at 213–215° and was characterized as 2,5-dibenzhydryl-2,5-dicarbethoxycyclohexane-1,4-dione, probably having the cis configuration (VIIa). The trans isomer, which should have a higher melting point, did not seem to have been formed.

cis-**2,5-Dibenzhydryl-2,5-dicarbethoxycyclohexane-1,4-dione (VIIa)** was obtained as crystals: mp 213–215°; soluble in benzene, sparingly soluble in cold ethanol; ir (KBr) 1730 (ketonic C=O) and 1750 cm^{-1} (ester C=O), and absorption maximum characteristic of phenyl group; nmr ($CDCl_3$) 7.20 (m, 20, C_6H_5), 5.55 (s, 2, CH), 3.85 (q, r, J = 7.0 Hz, CH_2CH_3), 3.43 (d, 2, J = 16.0 Hz, C_6 ring methylene H), 1.97 (d, 2, J = 16.0 Hz, C_6 ring methylene H), 0.83 ppm (t, 6, J = 7.0 Hz, CH_2CH_3).

Anal. Calcd for $C_{38}H_{36}O_6$: C, 77.72; H, 6.11. Found: C, 77.53, 77.81; H, 6.31, 6.15.

Registry No.—Ia, 50378-31-9; Ia dioxime, 50378-32-0; Ib, 50378-33-1; Ib dioxime, 50378-34-2; IIa, 50378-35-3; IIa dioxime, 50378-36-4; IIa′, 50378-37-5; IIb, 50378-38-6; IIb dioxime, 50378-39-7; IIb′, 50378-40-0; IIIa, 50378-41-1; IIIb, 50378-42-2; IVa, 50378-43-3; IVb, 50378-44-4; VIa, 50378-45-5; VIb, 50378-46-6; VIIa, 50378-47-7.

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Nucleophilic Substitution at Phosphorus. Phosphorothioates[1]

William S. Wadsworth, Jr.,* and Yuh-Geng Tsay

Department of Chemistry, South Dakota State University, Brookings, South Dakota 57006

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Cis and trans isomers of 2-substituted 5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinans were used as substrates to determine the stereochemical course of substitution at a thiophosphoryl center. Retention was found to increase with the basicity of the nucleophile while inversion increased with added salts. A mechanism is suggested.

The preparation of an optically active triester of phosphoric acid has not until very recently[2] been accomplished. Thus a definitive study of the stereochemical consequences of nucleophilic substitution at phosphorus in trialkylphosphates has been hindered by the lack of a suitable substrate. This deficiency has, at least to some extent, been overcome by the discovery[3,4] that 2-substituted 5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinans can be prepared in separable cis and trans forms. Fortunately, the geometrical isomers, owing to constraints put on the system by the large preference of groups at phosphorus to be either axial or equatorial, are for all practical purposes conformationally immobile. We have now extended the system to the 2-thio analogs and have studied, as was done previously with their 2-oxo counterparts, the influence of nucleophiles, leaving groups, and salts upon the stereochemistry of nucleophilic substitution at phosphorus.

The stereochemistry of nucleophilic substitutions at thiophosphoryl centers has been the subject of systematic investigations. Most studies which have employed optically active pyrophosphonothioates, phosphonothioic acids, and phosphonochloridothioates have concluded that substitution at thiophosphoryl centers occurs almost exclusively by inversion.[5] Optically active thiophosphates, owing to difficulties in their preparation, have not been investigated.

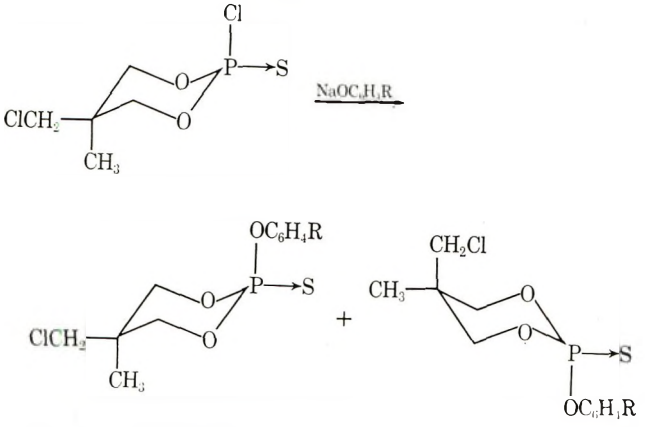
We have been successful in preparing, and in some cases purifying, a number of 2-substituted 5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinans. In all cases only a single conformer of each isomer was detected, which is in accordance with that reported for similar sys-

Table I
Chemical Shifts of 2-Substituted 5-Chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinans[a]

R	Cis, 1		Trans, 2	
	CH_3	CH_2Cl	CH_3	CH_2Cl
Cl	1.01	3.74	1.43	3.37
$OC_6H_4OCH_3$	0.96	3.76	1.17	3.39
$OC_6H_4CH_3$	0.96	3.77	1.18	3.39
OC_6H_5	0.97	3.89	1.20	3.39
OC_6H_4Br	0.98	3.76	1.20	3.40
$OC_6H_4NO_2$	1.01	3.81	1.29	3.47
$OC_6H_3(NO_2)_2$	1.02	3.79	1.38	3.42

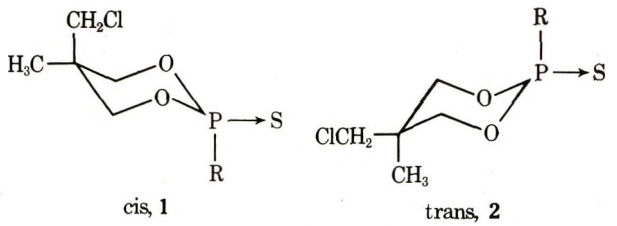
[a] Measured with a Varian A-60A spectrometer at room temperature using $CDCl_3$ as solvent. In parts per million downfield from TMS as an external standard.

Table II
Treatment of *trans*-2-Chloro-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan with Various Nucleophiles in Acetonitrile



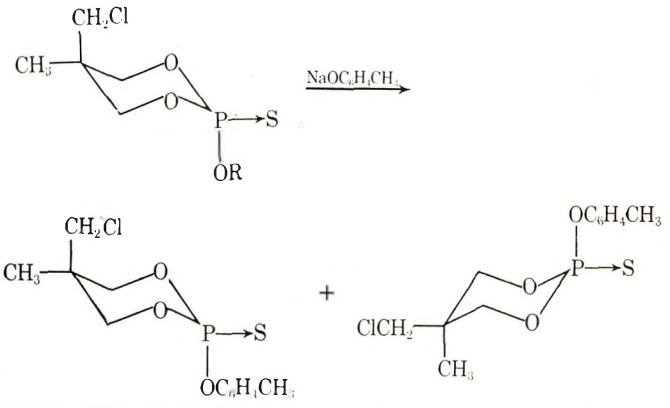
R	% trans (retention)	% cis (inversion)
OCH_3	50.0	50.0
CH_3	40.0	60.0
Br	23.7	76.3
NO_2	5.1	94.9

tems based on ir studies.[6] The lack of conformational mobility persists upon heating samples to over 190°. If indeed mobility does exist to some degree in solution, it has not proved to be a hindrance in the determination of isomer ratios. As with the 2-oxo system, isomer ratios based upon the nmr spectra of isomer mixtures for groups at the 5 position have different chemical shifts dependent upon their being equatorial or axial (Table I). We have previously shown by X-ray analysis that in analogous 2-oxo esters phosphoryl oxygen occupies an equatorial position. We have assumed a similar configuration for the 2-thio esters, phosphoryl sulfur equatorial. Our assumption was validity based on the change in isomer ratios owing to effects discussed in this paper. If effects are to parallel those found in the oxo case, which they do, sulfur must be equatorial. The large preference for sulfur to be equatorial may be a major factor in limiting conformation mobility.



A mixture of the cis and trans isomers, 1 and 2 (R = Cl), of 2-chloro-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan was prepared from thiophosphoryl chloride and 1-chloromethyl-1,1-dihydroxymethylethane. The pure trans isomer (Figure 1)[7] could be isolated by simple recrystallization and proved to be much more hydrolytically stable than the 2-oxo chloridates. It was added under standard conditions to various sodium para-substituted phenoxides, the products were isolated, and isomer ratios were determined by integration of peak heights (Figure 2).[7] In the case of the newly formed esters the pure cis isomers could be purified by fractional crystallization and these were used in further experiments. No attempt was made to isolate pure trans isomers.

Table III
Treatment of Various Cis-2-Substituted 5-Chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinans with Sodium *p*-Methylphenoxide in Acetonitrile

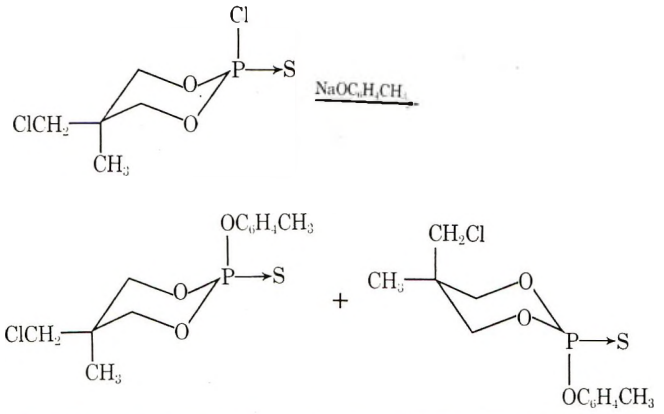


R	% *cis* (retention)	% *trans* (inversion)
C_6H_5	98.5	1.5
C_6H_4Br	97.4	2.6
$C_6H_4NO_2$	95.2	4.8
$C_6H_3(NO_2)_2$		

The stereochemical outcome of substitution depended upon the structure of the attacking nucleophile (Table II). Retention increased with the basicity of the nucleophile, whereas inversion was highly favored by nucleophiles of low basicity.[8] The isomer ratios reflect the mode of substitution and are not the result of prior isomerization of the reactant or isomerization of products following their formation. Thus *trans*-2-chloro-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan gave no indication of isomerization after an acetonitrile solution had stood at room temperature for over 10 days. Also the pure cis isomers, separated from the initially formed products, did not undergo any detectable isomerization when dissolved in acetonitrile and the solutions allowed to stand for a period of weeks. Finally, no change in the product isomer ratios was detected under the reaction conditions and the ratios did not vary during work-up. Yields from the substitutions were consistently above 90%. Thus evidence is provided that substitutions are kinetically controlled.

We have found that the mode of substitution is also dependent upon the stability of the leaving group. Cis 2-substituted 5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinans were added to sodium *p*-methylphenoxide dissolved in acetonitrile and products were isolated. Analysis of nmr spectra indicated that inversion was aided by an increase in stability of leaving groups (Table III). Comparison of Table II with Table III indicates that the trans thio chloridate, 2 (R = Cl), substitutes with a much higher percentage of inversion than do any of the cis esters listed in Table III. Although chloride ion is a better leaving group than the phenoxide ions, which may partially

Table IV
Percentage of Cis and Trans Isomers Obtained by Treating *trans*-2-Chloro-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan with Sodium *p*-Methylphenoxide in Various Solvents



Solvent	% *trans* (retention)	% *cis* (inversion)
CH_3CN + 1 equiv $LiClO_4$	87.5[a]	12.5
CH_3CN	40.0	60.0
CH_3CN + 1 equiv $(CH_3)_4N^+Cl^-$	6.2	93.8
$HCN(CH_3)_2$	5.7	94.3
$HCN(CH_3)_2$ + 1 equiv $(CH_3)_4N^+Cl^-$	5.1	94.9

[a] Isomer ratios (per cent) were obtained by integration of nmr spectra obtained in $CDCl_3$ by means of a Varian A-60A spectrometer using TMS as an external standard.

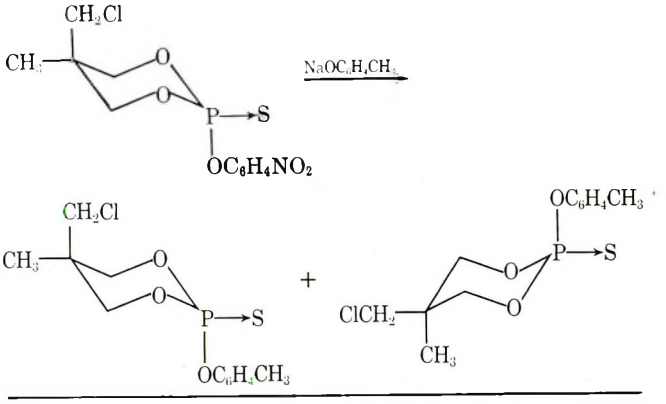
explain the results, the different ratios are also influenced by the fact that different isomers were used. Dipole interactions differ within the two ring conformations and have an effect upon the final isomer ratios. Regardless, the influence of the leaving group upon the final isomer ratio is established.

When the cis 2,4-dinitrophenyl ester 1 [R = $OC_6H_3(NO_2)_2$] was the substrate, substitution at phosphorus did not take place. The water-insoluble product, which was not a phosphate, appeared from its spectra to be an ether which would result from C–O bond cleavage, a situation similar to that found with phosphates.[3]

We have also, as with the 2-oxo system,[4] noted an effect of solvent upon the ratio of isomers obtained upon substitution at a thiophosphoryl center. Thus in the case of the trans 2-thiochloridate, 2 (R = Cl), the amount of inversion increased dramatically upon changing the solvent from acetonitrile to dimethylformamide (Table IV). The result is not due to a simple solvent effect, but is due to the much greater solubility of the by-product, sodium chloride, in dimethylformamide. Indeed, in a single solvent an added cation has a marked effect upon the product ratio by shifting the substitution pathway toward inversion. Sodium chloride, when added to acetonitrile solutions of the nucleophile prior to the addition of the reactant, caused a shift in the ratio, although, owing to its greater solubility, tetramethylammonium chloride had an even more dramatic effect. Owing to its lack of ionic character in organic solvents and ability to reduce the solubility of sodium chloride, lithium perchlorate had an opposite effect.

A similar solvent and salt effect was noted when *cis*-2-*p*-nitrophenyl ester was used as the substrate (Table V).

Table V
Treatment of *cis*-2-(*p*-Nitrophenoxy)-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan with Sodium *p*-Methylphenoxide in Various Solvents



Solvent	% *cis* (retention)	% *trans* (inversion)
CH_3CN	95.2	4.8
CH_3CN + 1 equiv $(CH_3)_4N^+Cl^-$	80.0	20.0
$HCN(CH_3)_2$	87.1	12.9
$HCN(CH_3)_2$ + 1 equiv $(CH_3)_4N^+Cl^-$	76.2	23.8

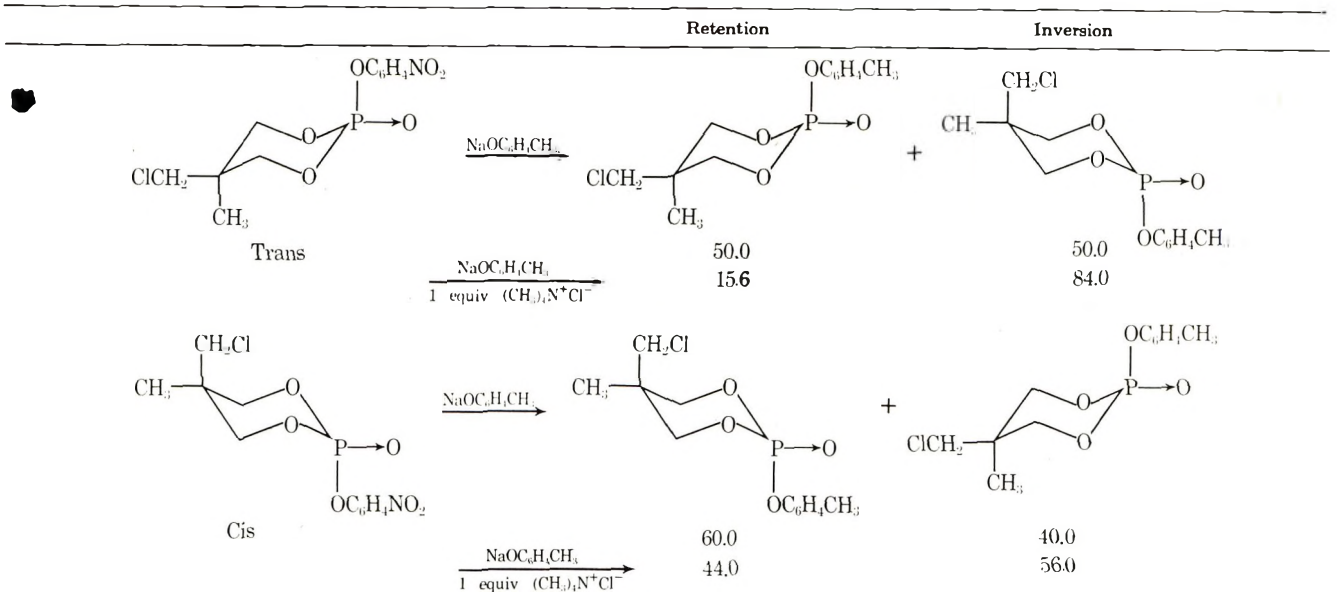
Owing to a difference in ring conformation the results were not as dramatic as in the case of the chloridate. Likewise, when *cis*-2-*p*-bromophenyl ester was added to acetonitrile containing sodium *p*-methylphenoxide, the percentage of inversion rose from 2.6 without added tetramethylammonium chloride to 22.2 in the case where salt was added to the solution prior to addition of the substrate. Thus added cations have a distinct effect.

Discussion

We believe that our results, which correlate with those obtained previously with the 2-oxo system,[4] strengthen our assumption that nucleophilic substitution at phosphoryl centers occurs by two separate mechanisms, one for inversion and one for retention. We assume an equilibrium to be established between thiophosphate and complexed thiophosphate. A charged nucleophile would attack the uncomplexed phosphate from a side opposite the thiophosphoryl center, a position of minimum electron density. The more basic the nucleophile the greater would be its desire to attack from a position as far removed from the electron-rich phosphoryl sulfur as possible. This stereochemical pathway would lead to a pentacovalent intermediate. Since nucleophiles are assumed to enter and leaving groups depart from apical positions,[9] the intermediate would be expected to pseudorotate which would lead to overall retention. On the other hand, complex formation by increasing the positive charge on phosphorus *via* a reduction in backbonding and by reducing charge repulsion by the phosphoryl sulfur leads to a lowering of the energy of activation for direct attack, a situation which would lead to inversion. We believe that inversion does not involve an intermediate but is a direct S_N2 type displacement. Our evidence, although not conclusive, is based primarily upon our experiments with different leaving groups in which we find the percentage of inversion to increase with leaving group stability.

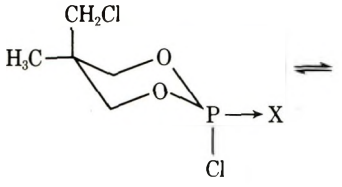
The suggested mechanism is admittedly tentative but does explain our observations, particularly the ability of

Table VI
Effect of Ring Conformation on Isomer Ratios

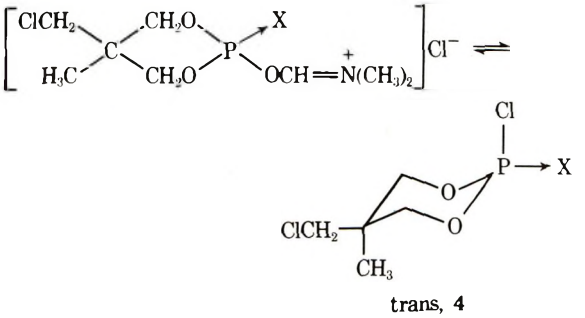


added salts to shift substitutions to the inversion pathway. Complex formation by cations *via* phosphoryl oxygen is well known[10] and it is not unlikely that a similar situation might arise with sulfur.

Although some conclusions can be drawn, with our system it is difficult to make quantitative comparisons between the phosphoryl and thiophosphoryl moieties. It is known from rates of hydrolysis[11] that due to the greater electronegativity of oxygen over sulfur, phosphorus has greater positive character in phosphates than in thiophosphates. In accordance with this conclusion we have observed a variation in the rate of isomerization of comparative compounds. Thus cis phosphorochloridate, **3** (X = O), isomerizes in dimethylformamide to give a final equilibrium ratio (2.5:1) of isomers within 15 min.[3] In contrast trans thiophosphorochloridate, **4** (X = S), under identical



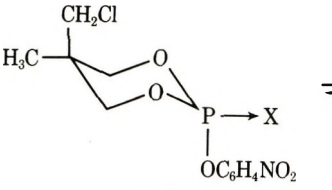
cis, **3**



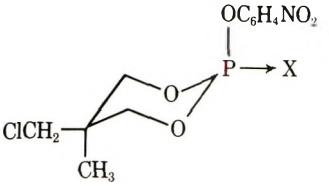
trans, **4**

conditions required 14 days to reach equilibrium (Figure 3).[7] The isomerization in the latter case was complicated by the concurrent formation of what appears from the nmr spectra to be an isomeric mixture of phosphorochloridates,[3] **3** + **4** (X = O). Thus, there is evidence for a transfer between oxygen and sulfur in the Vilsmeier-type intermediate. This phenomenon is being investigated further.

In the case of *p*-nitrophenyl esters added to deuterated acetonitrile saturated with sodium *p*-nitrophenoxide, approximately 5 days was required for the cis thiophosphate ester, **5** (X = S), to reach equilibrium whereas the cis phosphate ester, **5** (X = O), reached equilibrium under



cis, **5**



trans, **6**

identical conditions after 30 hr. From the nmr spectra no side reactions in the case of the thio ester were apparent. Substitution is clearly more facile in the case of the phosphates, where the positive charge on phosphorus is greater. In the absence of added common ion isomerization does not take place with either *p*-nitrophenyl ester regardless of the solvent employed. The *p*-methyl, *p*-methoxy, *p*-bromophenyl, and phenyl esters do not isomerize even in the presence of a common ion.

At equilibrium the ratio of isomers varied. In the case of the *p*-nitrophenyl phosphate the cis/trans isomer ratio at equilibrium was 2.5:1 whereas in the case of the sulfur analog it was 6.0:1. a dipole interaction between axial chloromethyl groups and ring oxygens has been held responsible for the excess of cis over trans at equilibrium.[12] To account for the difference in ratios, the interaction must be greater in the case of the thiophosphate. This is not unreasonable, since the positive charge on phosphorus and thus inductive effect on the ring oxygens would be less than in the phosphate case. Thus a dipole interaction would be greater in the thiophosphate ring system, which would account for the relatively greater amount of cis isomer at equilibrium. The change in dipole interactions in going from the phosphate to thiophosphate system makes a quantitative comparison between the two as regards to salt effects, etc., difficult.

Indeed, by carrying out substitutions on separate isomers of a single phosphate, the effect of a change in ring

dipole interactions upon isomer ratios can be seen. Pure *trans*-*p*-nitrophenyl phosphate when added to an acetonitrile solution of sodium *p*-methylphenoxide underwent substitution with 50.0% retention. The pure cis isomer with the chloromethyl group axial under the same conditions underwent substitution with 60% retention. Thus the position of the chloromethyl group in the starting material and substitution product does influence the retention/inversion ratio. Dipole interactions probably influence the energy of activation for each substitution mechanism. Also, the effect of added cation is more pronounced (Table VI) in the case of the trans *p*-nitrophenyl ester than with the cis. In the case of the trans isomer, the mechanism leading to inversion might be expected to have a lower energy of activation, for the ring undergoes a conformational change during substitution such that dipole interactions would be an asset. Dipole interactions, on the other hand, would be expected to hinder inversion with a cis substrate.

Experimental Section

Analysis were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. 37921.

2-Chloro-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan. Thiophosphoryl chloride, 37 g (0.22 mol), was added dropwise with stirring and cooling to 1-chloromethyl-1,1-dihydroxymethylethane,[13] 30.14 g (0.22 mol), ether (150 ml), and pyridine (34.7 g, 0.44 mol). The solution was stirred for 1 hr and filtered. The filtrate was washed with 5% HCl and H_2O and dried over anhydrous magnesium sulfate. The solvent was removed to give a white solid (36 g, 70% yield) which consisted of cis and trans isomers in a 1:2 ratio. The product was recrystallized four times from a 10:1 hexane–chloroform mixture to give pure trans isomer **2** (R = Cl), mp 64–65°.

Anal. Calcd. for $C_5H_9ClO_2PS$: C, 25.53; H, 3.83; Cl, 30.21; S, 13.62. Found: C, 25.77; H, 3.94; Cl, 30.43; S, 13.77.

***cis*-2-(*p*-Nitrophenoxy)-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan.** To a solution of sodium *p*-nitrophenoxide (8 g, 0.05 mol) and acetonitrile (100 ml) was added the isomeric mixture of 2-chloro-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan, 12.0 g (0.05 mol). The solution was stirred for 2 days, 500 ml of water was added, the solution was filtered, and the precipitate was washed well with water before drying. A pale yellow solid (16.2 g, 95% yield) was obtained. The pure cis isomer was extracted from the isomer mixture by refluxing the product in ether, filtering, and removal of solvent from the filtrate. The residue was recrystallized from carbon tetrachloride to give the pure cis isomer, mp 122–123°.

Anal. Calcd for $C_{11}H_{13}ClNO_3PS$: C, 39.17; H, 3.86; Cl, 10.39; S, 9.50. Found: C, 38.96; H, 3.71; Cl, 10.62; S, 9.62.

The other pure cis esters were obtained in a similar manner.

***cis*-2-(2,4-Dinitrophenoxy)-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan.** The isomer mixture (96.5% yield) was recrystallized twice from carbon tetrachloride–acetonitrile (10:1) to give pure cis isomer, mp 134–135°.

Anal. Calcd for $C_{11}H_{12}ClN_2O_7PS$: C, 34.56; H, 3.14; Cl, 9.16; S, 8.38. Found: C, 34.71; H, 3.20; Cl, 9.36; S, 8.44.

***cis*-2-(*p*-Bromophenoxy)-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan.** The final isomer mixture (97% yield) was recrystallized three times from carbon tetrachloride to give pure cis isomer, mp 145–146°.

Anal. Calcd for $C_{11}H_{13}ClBrO_3PS$: C, 35.58; H, 3.50; Cl, 9.43; S, 8.62. Found: C, 35.34; H, 3.56; Cl, 9.65; S, 8.74.

***cis*-2-(*p*-Methylphenoxy)-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan.** The final isomer mixture (98% yield) was recrystallized twice from hexane–carbon tetrachloride (10:1) to give pure cis isomer, mp 135–136°.

Anal. Calcd for $C_{12}H_{16}ClO_3PS$: C, 47.06; H, 5.32; Cl, 11.44; S, 10.46. Found: C, 47.20; H, 5.34; Cl, 11.60; S, 10.43.

***cis*-2-Phenoxy-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan.** The final isomer mixutre (93% yield) was recrystallized twice from hexane–carbon tetrachloride (10:1) to give pure cis isomer, mp 110–111°.

Anal. Calcd for $C_{11}H_{14}ClO_3PS$: C, 45.20; H, 4.80; Cl, 11.98; S, 10.96. Found: C, 45.16; H, 4.91; Cl, 12.01; S, 10.97.

To determine the effect of the basicity of the nucleophile (Table II), the above were repeated using the pure trans chloridate, **2** (R = Cl).

***cis*- and *trans*-2-(*p*-Methoxyphenoxy)-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan.** To a solution of sodium *p*-methoxyphenoxide (0.29 g, 0.0015 mol) and acetonitrile (15 ml) was added *trans*-2-chloro-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan (0.3 g, 0.0013 mol). The mixture was stirred at room temperature for 1 hr. Substitution was actually instantaneous as indicated by a mild exotherm upon addition of the chloridate. Water (50 ml) was added, and the precipitate was washed thoroughly with water and dried, 0.39 g (96% yield). The product by nmr consisted of both cis and trans isomers in a 1:1 ratio. The above was repeated under identical conditions with sodium salts of other substituted phenoxides.

To determine the effect of leaving groups (Table III), the following standard procedure was followed. To a solution of sodium *p*-methylphenoxide (0.16 g, 0.0012 mol) and acetonitrile (15 ml) was added *cis*-2-(*p*-bromophenoxy)-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan (0.4 g, 0.0011 mol). The mixture was stirred for 2 days and water (50 ml) was added to precipitate the product. The white solid was washed with water and dried (0.3 g, 92% yield). Integration of the nmr spectrum of the product was used to determine isomer ratios.

The following is a typical procedure which was used to determine the effect of salts on isomer ratios (Tables IV–VI). Sodium *p*-methylphenoxide (0.29 g, 0.0015 mol) and tetramethylammonium chloride (0.16 g, 0.0015 mol) were dissolved in acetonitrile (15 ml). To the solution was added *trans*-2-chloro-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan (0.35 g, 0.0015 mol). The mixture was stirred for 1 hr and water (50 ml) was added to precipitate the product. The precipitate was washed with water and dried (0.429 g, 91% yield). Integration of its nmr spectrum provided the isomer ratio (Table IV). The ratios reported in Table V were obtained in a similar manner. *cis*-2-*p*-Nitrophenyl ester **1**, (R = $OC_6H_4NO_2$) was added in place of the trans chloridate. Data for Table VI were obtained similarly using the appropriate substrate.

***cis*-2-(*p*-Nitrophenoxy-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan.** The pure trans isomer, mp 106–107°, was prepared and equilibrated to a mixture of cis and trans isomers as previously described.[3] To separate the cis isomer from the 2.5:1 cis–trans mixture, the product obtained upon equilibration was extracted with boiling chloroform and filtered. The filtrate upon standing slowly deposited crystals of pure cis isomer which could be recrystallized from a small quantity of chloroform, mp 160–161°.

Anal. Calcd for $C_{22}H_{23}ClNO_6P$: C, 41.12; H, 4.05; P, 9.65. Found: C, 41.27; H, 4.14; P, 9.51. Nmr spectra[3] of both isomers confirmed their structures.

Registry No.—**1** (R = Cl), 50378-48-8; **1** (R = OC_6H_4OMe), 50378-49-9; **1** (R = OC_6H_4Me), 50378-50-2; **1** (R = OC_6H_5), 50378-51-3; **1** (R = OC_6H_4Br), 50378-52-4; **1** (R = $OC_6H_4NO_2$), 50378-53-5; **1** [R = $OC_6H_3(NO_2)_2$], 50378-54-6; **2** (R = Cl), 50600-54-9; **2** (R = OC_6H_4OMe), 50378-56-8; **2** (R = OC_6H_4Me), 50378-57-9; **2** (R = OC_6H_5), 50378-58-0; **2** (R = OC_6H_4Br), 50378-59-1; **2** (R = $OC_6H_4NO_2$), 50378-60-4; **2** [R = $OC_6H_3(NO_2)_2$], 50378-61-5; 1-chloromethyl-1,1-dihydroxymethylethane, 21139-44-6; *cis*-2-(*p*-nitrophenoxy)-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan, 36912-38-6; *trans*-2-(*p*-nitrophenoxy)-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan, 36912-37-5.

Supplementary Material Available. Nmr spectra of a mixture of cis and trans isomers, and **2** (R = Cl), the pure cis isomer, **1** (R = Cl), para-substituted phenyl esters, **1** and **2** (R = $OC_6H_7CH_3$), and equilibration of **4** (X = S) will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-984.

References and Notes

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The Synthesis and Properties of Heterofulvenes, Derivatives of 2,6-Dimethyl-γ-pyrone and -γ-thiapyrone and *N*-Butyl-2,6-dimethyl-γ-pyridone

I. Belsky, H. Dodiuk, and Y. Shvo*

Department of Chemistry, Tel-Aviv University, Tel-Aviv, Israel

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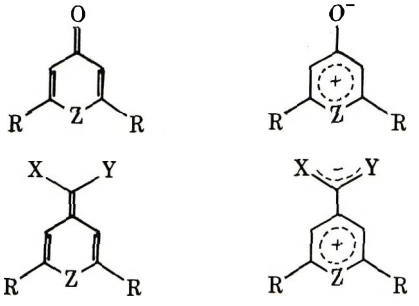
Oxygen-, sulfur-, and nitrogen-containing heterofulvenes, derivatives of 2,6-dimethyl-γ-pyrone (1) and -γ-thiapyrone (2) and *N*-butyl-2,6-dimethyl-γ-pyridone (3), have been prepared, and their properties are reported. The O and S heterocycles were prepared by condensation of 1 and 2, respectively, with active methylene compounds in acetic anhydride. The N heterocycles were obtained from the O heterocycles by reaction with butylamine. Side reactions were observed when butylamine reacted with methyl 2,6-dimethyl-4*H*-pyran-4-ylidenenitroacetate (6) and 2,6-dimethyl-4*H*-pyran-4-ylidenenitroacetone (5). A new convenient route to heterofulvenes which bear a single substituent at the exocyclic double bond was developed. Thus, heterofulvenes substituted by an acetyl group at the exocyclic double bond were found to undergo acetyl cleavage, under very mild acidic conditions, resulting in the formation of monosubstituted heterofulvenes. Deuterium exchange reactions in the systems under consideration were studied. The nmr, uv, and ir data of the disubstituted and monosubstituted heterofulvenes are discussed in terms of the heteroatom and the substituents at the exocyclic double bond.

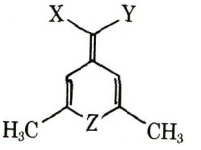
Compounds derived from the formal condensation of γ-pyrones (1), γ-thiapyrones (2), and γ-pyridones (3) with active methylene compounds, having the general structure 4, may be considered as heteroanalogs of heptafulvenes. The literature contains a number of reports on the synthesis and properties of some heterofulvenes and heterofulvalenes derived from γ-pyrones and γ-pyridones.[1] Very little, however, has been published about heterofulvenes derived from γ-thiapyrones (4, Z = S). In this paper we report the synthesis and chemistry of heterofulvenes of type 4; dynamic nmr studies on these compounds will be presented in a later paper.



1, Z = O
2, Z = S
3, Z = N-Bu
4, X, Y = electron-withdrawing groups

Synthesis

The compounds of interest which have been prepared are listed below.



Z = O
5, X = NO_2; Y = $COCH_3$
6, X = NO_2; Y = $COOCH_3$
7, X = NO_2; Y = CN
8, X = $COCH_3$; Y = $COOCH_3$
9, X = $COCH_3$; Y = CN
10, X = $COOCH_3$; Y = CN
11, X = CN; Y = $CONH_2$
12, X = Y = $COCH_3$

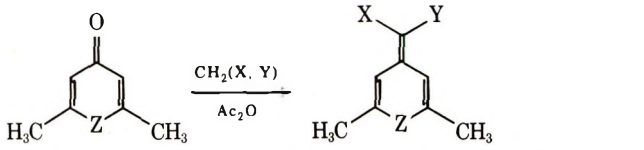
Z = S
13, X = NO_2; Y = $COCH_3$
14, X = NO_2; Y = $COOCH_3$
15, X = NO_2; Y = CN
16, X = $COCH_3$; Y = $COOCH_3$
17, X = $COCH_3$; Y = CN
18, X = $COOCH_3$; Y = CN

Z = *N*-Bu
19, X = NO_2; Y = $COCH_3$
20, X = NO_2; Y = $COOCH_3$
21, X = NO_2; Y = CN
22, X = $COCH_3$; Y = CN
23, X = $COOCH_3$; Y = CN
24, X = CN; Y = $CONH_2$

The oxygen (Z = O) and the sulfur (Z = S) heterocycles were prepared by the condensation of 2,6-dimethyl-γ-pyrone and 2,6-dimethyl-γ-thiapyrone,[3] respectively, with the appropriate active methylene compounds in acetic anhydride (Scheme I). It has previously been reported that the acetic anhydride method is applicable only to those active methylene compounds bearing a nitrile group, but fails with compounds such as acetylacetone and methyl acetoacetate.[4] We have found, however, that this method can be considered to be a general one, inasmuch as, except for 11, all the oxygen and the sulfur analogs could be obtained in this way, although the yields with acetylacetone and methyl acetoacetate were, indeed, very poor. Compound 11 was prepared, as previously reported,[5] by

partial acidic hydrolysis of 2,6-dimethyl-4*H*-pyran-4-ylidenemalononitrile.[6] In the preparation of **7** and **15**, the active methylene compound nitroacetonitrile was generated *in situ*, by dehydration of methazoic acid[7] by the acetic anhydride.

Scheme I

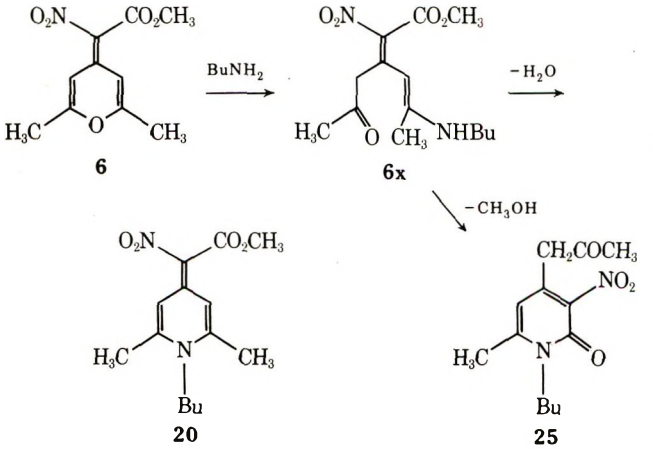


Z = O, S X, Y = electron-withdrawing groups

The nitrogen compounds **19**–**24** were conveniently prepared from the oxygen analogs by N,O exchange accomplished by heating the latter, either in excess, or with equimolar amounts of butylamine in appropriate solvents.[8] The structures of all the new compounds were confirmed by elemental analysis and spectral methods.

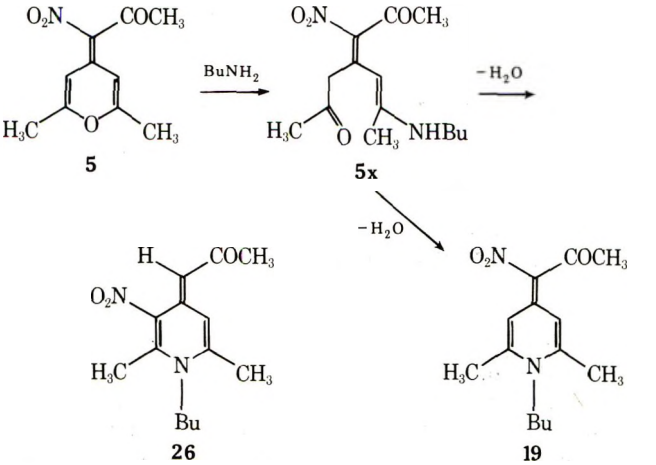
While in most of the cases the reaction with butylamine proceeded satisfactorily, we have encountered two cases in which side reactions took place. When **6** was heated in excess of butylamine at 78°, only one product, mp 127°, was obtained in 34% yield, the physical properties of which were not in accord with structure **20**. This product is considered to be *N*-butyl-3-nitro-4-acetonyl-6-methyl-2-pyridone (**25**), on the basis of spectral data: ir ($CHCl_3$) 1710 (C=O) and 1666 cm^{-1} (CON-Bu); uv λ_{max} (EtOH) 310 nm (ϵ 3300), 370 (3300); nmr ($CDCl_3$) δ 1.03 (3 H, t), 1.60 (4 H, m), 2.26 (3 H, s), 2.44 (3 H, s), 3.66 (2 H, t), 4.02 (2 H, s), 5.94 (1 H, s). The significant features of the nmr spectrum are the two-proton singlet at 4.02 ppm, assigned to $-CH_2COCH_3$, and the presence of only *one* vinylic signal. When the same reaction was carried out in chloroform employing 1 equiv of butylamine, a mixture of **25** and **20**, which could be conveniently separated by crystallization, was obtained. A reaction route that may account for the formation of the two products is presented in Scheme II.

Scheme II



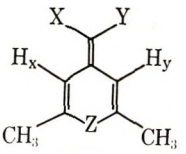
The reaction of **5** in excess butylamine at 78° yielded two structural isomers which were separated by chromatography. One product, obtained in 34% yield, was identified as the corresponding 1,4-dihydropyridine derivative (**19**) on the basis of its elemental analysis and its physical properties. As can be seen (Table I), the chemically nonequivalent protons at positions 3 and 5 of compound **19** exhibit one broad singlet in the nmr spectrum (relative area 2). This observation supports, rather than disproves, structure **19**. The above-mentioned chemical shift equivalency is a consequence of a fast rotation about the exocyclic double bond. This phenomenon was observed in several compounds of type **4** and will be analyzed in a separate publication. The broadening of the vinylic signals was found to be due to allylic type spin coupling with the methyl protons at positions 2 and 6, which was detected in all the compounds of type **4**. The second product, mp 161°, obtained in 30% yield was identified as *N*-butyl-2,6-dimethyl-1,4-dihydropyridine-4-ylideneacetone (**26**). The structural assignment of **26** was based on the following evidence. Elemental analysis was in agreement with the proposed structure; the mass spectrum exhibited a parent peak at *m/e* 264 [mol wt (calcd) 264.33]. The ir spectrum ($CHCl_3$) showed, among others, a conjugated carbonyl band at 1660 cm^{-1}; uv λ_{max} (EtOH) 248 nm (ϵ 6000), 388 (32,700); nmr spectrum ($CDCl_3$) exhibited signals at δ 1.00 (3 H, t), 1.5 (4 H, m), 2.06 (3 H, s), 2.25 (3 H, s), 2.32 (3 H, s), 3.75 (2 H, t), 4.95 (1 H, s, sharp), 8.40 (1 H, s, broad). Although two vinylic-type proton signals are present in the nmr spectrum, this does not support structure **19**, as the signal at δ 4.95, in contrast to the signal at δ 8.40, is very sharp and cannot therefore arise from an allylic coupled proton. The spectrum does, however, support structure **26**, as it is expected that the vinylic proton at the exocyclic double bond would resonate at relatively high field[9] and would not be coupled to the methyl protons. Further information about **26** can be obtained by comparing its nmr data with those of compound **27** (Table I), which was obtained by a different reaction (*vide infra*). Compound **26** is, in fact, a nitro derivative of **27**. This comparison enables us to determine the geometry of **26**. Though **26** can exist in two geometrical isomers, we have isolated only one. On the basis of the similarity in the chemical shifts of the ring proton syn to the acetyl group in **27** (δ 8.27, Table I) and of the ring proton of **26** (δ 8.40), we can safely conclude that structure **26** (Scheme III) correctly describes the geometrical isomer which was isolated. Predomination of this isomer is expected, as this is the thermodynamically more stable one. The reaction pathway which may account for the formation of **19** and **26** from **5** in excess of butylamine is depicted in Scheme III. Initial addition of butylamine and subsequent ring opening lead to the formation of intermediate (**5x**) which possesses two reactive carbonyl groups. Cyclization can therefore take place at either of these carbonyls and thus a mixture of **26** and **19** will result.

Scheme III



The ease with which compounds **5** and **6** tend to participate in competitive modes of cyclization which lead to **26** and **25**, respectively, is attributed to the presence of the strong electron-withdrawing nitro group in the α position

Table I
Nmr Data of Compounds 5–29[a]



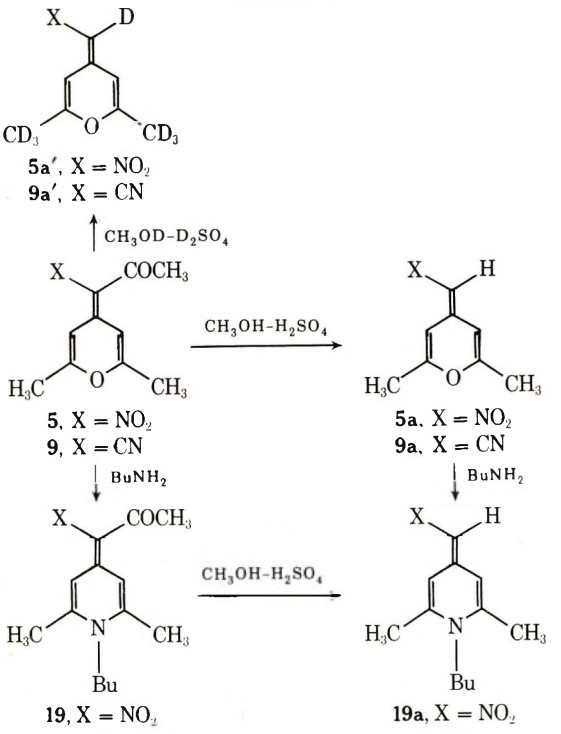
Compd	Yield, %	Mp, °C	Z	X	Y	Chemical shifts in δ ($CDCl_3$) (at ambient temperature) 2,6-Me	H_x	H_y	N-CH_2-	Other groups
5	30	140	O	NO_2	$COCH_3$	2.28	7.10	7.10		$COCH_3$ 2.28
5a	84	105	O	NO_2	H	2.30, 2.32	7.82	5.95		Y = H 6.80
6	34	109	O	NO_2	$COOCH_3$	2.26	7.08	6.60		$COOCH_3$ 3.80
7	8.5	190	O	NO_2	CN	2.48	8.11	6.64		
8	4.5	84	O	$COOCH_3$	$COCH_3$	2.27	6.92	7.32		$COOCH_3$ 3.80, $COCH_3$ 2.20
8a	99	87	O	$COOCH_3$	H	2.10	7.40	5.78		Y = H 4.98, $COOCH_3$ 3.82
9			O	CN	$COCH_3$	2.32	6.58	8.25		$COCH_3$ 2.40
9a	72	94	O	CN	H	2.04, 2.08	6.19	5.77		Y = H 4.19
9a′	81	94	O	CN	D		6.19	5.77		
10	50	178	O	CN	$COOCH_3$	2.29	6.57	7.88		$COOCH_3$ 3.75
11			O	CN	$CONH_2$	2.29	6.62	8.17		$CONH_2$ 5.67
12	1.5	74	O	$COCH_3$	$COCH_3$	2.28	6.95	6.95		$COCH_3$ 2.12
12a	60	85	O	$COCH_3$	H	2.10	7.74	5.76		Y = H 5.35, $COCH_3$ 2.10
13	10	143	S	NO_2	$COCH_3$	2.38	7.71	7.71		$COCH_3$ 2.28
13a	80	83	S	NO_2	H	2.32	8.62	6.54		Y = H 6.94
14	12	116	S	NO_2	$COOCH_3$	2.34	7.50	7.50		$COOCH_3$ 3.79
15	4	216	S	NO_2	CN	2.56	9.04	7.49		
16	0.5	Oil	S	$COOCH_3$	$COCH_3$	2.28	7.52	7.82		$COCH_3$ 2.28, $COOCH_3$ 3.80
17	7	147	S	CN	$COCH_3$	2.44	7.32	9.04		$COCH_3$ 2.44
18	19	185	S	CN	$COOCH_3$	2.42	7.30	8.66		$COOCH_3$ 3.75
19	34	150	*N*-Bu	NO_2	$COCH_3$	2.55	7.94	7.94	4.04	$COCH_3$ 2.49
19a	98	195	*N*-Bu	NO_2	H	2.48	8.30	6.30	3.99	Y = H 6.68
20	32	183	*N*-Bu	NO_2	$COOCH_3$	2.50	7.48	7.48	4.00	$COOCH_3$ 3.83
21	78	263	*N*-Bu	NO_2	CN	2.64	7.50	7.50	4.03	
22	98	178	*N*-Bu	CN	$COCH_3$	2.48	6.80	8.70	3.94	$COCH_3$ 2.34
22a	94	95	*N*-Bu	CN	H	2.30	6.30	5.95	3.68	Y = H 3.75
23	79	135	*N*-Bu	CN	$COOCH_3$	2.43	6.72	8.12	3.90	$COOCH_3$ 3.69
24	62	236	*N*-Bu	CN	$CONH_2$	2.45	6.80	8.47	3.90	$CONH_2$ 5.47
27	70	73	*N*-Bu	$COCH_3$	H	2.32	8.27	6.10	3.75	$COCH_3$ 2.07, Y = H 5.20
28			O	CN	CN	2.34	6.54	6.54		
29			*N*-Bu	CN	CN	2.50	6.70	6.70	3.75	

[a] Satisfactory analytical values (±0.4% for C, H, N, S) for all compounds were reported: Ed.

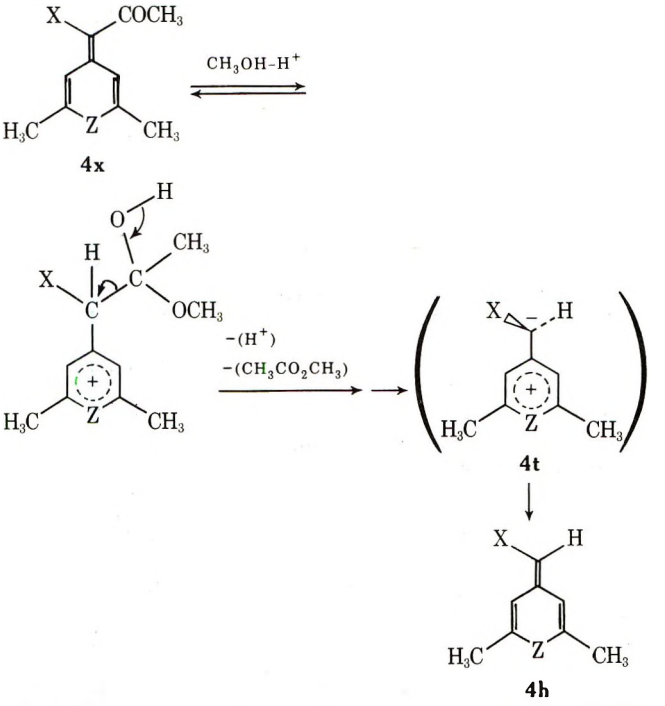
to the acetyl and carbomethoxy groups in these compounds. Thus, the reactivity of these carbonyls toward nucleophilic attack is enhanced, rendering these cyclization routes competitive to the routes leading to **19** and **20**.

Reaction in Acidic Media. The observation that methyl acetoacetate condenses with 2,6-dimethyl-γ-pyrone in poor yield led us to investigate alternative synthetic routes for compound **8**. Specifically, we were interested in finding conditions under which a nitrile group, in this class of compounds, could be transformed into a carbomethoxy group. Thus, heating 2,6-dimethyl-4*H*-pyran-4-ylidenemalononitrile (**28**)[6] in methanol in the presence of 1 equiv of water and a catalytic amount of concentrated sulfuric acid led to the formation of methyl 2,6-dimethyl-4*H*-pyran-4-ylidenecyanoacetate (**10**), identical with the product prepared from methyl cyanoacetate by the acetic anhydride method, as the sole product. When **10** was treated with methanol under the same conditions, no dimethyl 2,6-dimethyl-4*H*-pyran-4-ylidenemalonate was obtained even on prolonged heating, and only starting material was recovered. When 2,6-dimethyl-4*H*-pyran-4-ylidenecyanoacetone (**9**) was subjected to the above reaction conditions, a tlc analysis indicated that the starting material had disappeared completely, and a new spot corresponding to a new product appeared. The isolated product was, however, not the expected **8**, but a new substance to which we have assigned structure **9a** on the basis of the following evidence: the mass spectrum exhibited a parent peak at *m/e* 147 [mol wt (calcd) 147.18]; ir spectrum ($CHCl_3$) showed a conjugated nitrile and double bond stretching bands at 2175 and 1670 cm^{-1}, respectively; the nmr spectrum ($CDCl_3$) showed two methyl signals at δ 2.04 (3 H, s) and 2.08 (3 H, s) and three vinylic signals at 4.19 (1 H, s, sharp), 5.77 (1 H, s, broad), and 6.19 (1 H, s, broad). On repeating the reaction using CH_3OD–D_2O–D_2SO_4, the heptadeuterio derivative (**9a′**) was obtained (Scheme IV), the mass spectrum of which exhibited a parent peak at *m/e* 154, and the ir spectrum ($CHCl_3$) showed additional absorption at 2300 cm^{-1} (C–D). In the nmr spectrum ($CDCl_3$), the methyl signals and the signal at δ 4.19, present in the spectrum of **9a**, were absent. We conclude from these results that under the above reaction conditions the acetyl group at the exocyclic double bond in **9** is cleaved, resulting in the formation of the monosubstituted derivative (**9a**). The sharp high-field vinylic proton signal at δ 4.19 is assigned to the proton at the exocyclic double bond, as was previously argued. The absence of this signal in the deuterio derivative **9a′** supports this assignment.[10] We have found that this "acetyl cleavage" type reaction is common to all acetyl-bearing compounds of type **4** and, in fact, can be carried out under much milder conditions and in the absence of water. Thus, treating a methanolic solution of **5** with catalytic amounts of sulfuric acid at room temperature, resulted in the formation of **5a** (Table I), mp 105°, in 84% yield: mass spectrum *m/e* 167 [mol wt (calcd) 167.17]; ir (KBr) 1670 cm^{-1}; uv λ_{max} (EtOH) 260 nm (ε 5000), 399 (22,200); nmr ($CDCl_3$) δ 2.30 (3 H, s), 2.32 (3 H, s), 5.95 (1 H, s, broad), 6.80 (1 H, s,

Scheme IV



Scheme V



sharp), 7.82 (1 H, s, broad). In CH_3OD-D_2SO_4 the heptadeuterio compound **5a′** was obtained; the mass spectrum exhibited a parent peak at *m/e* 174 and the ir spectrum (KBr) showed additional absorption at 2330 cm^{-1} (C-D). In the nmr spectrum ($CDCl_3$) of **5a′** the signals at δ 2.30, 2.32, and 6.80 were again missing. Further corroborative evidence for the structures of these deacylated derivatives was obtained from the chemical transformations depicted in Scheme IV. The reaction of **5a** with butylamine afforded **19a**, which was identical with the product obtained by the acetyl cleavage of **19** (which is obtained from the reaction of **5** with butylamine). The monosubstituted heterofulvenes which have been prepared are listed in Table I (see Experimental Section).

By following the progress of the acetyl cleavage using tlc, it was found that the rates were dependent on the nature of the other substituent attached to the exocyclic double bond, as well as on the nature of the heteroatom Z. Thus, in compounds **5**, **8**, **9**, and **12** the rates were enhanced by the presence of the other double bond substituent in the order $NO_2 > COCH_3 > COOCH_3 > CN$, which corresponds to the order of the capacity of these groups to stabilize a negative charge. In compounds possessing the same double bond substituents, the dihydropyridines (Z = N-Bu) react faster than the 4*H*-pyrans (Z = O). A tentative mechanism for the deacetylation reaction which accounts for these experimental facts is described in Scheme V.

Assuming that the C-C cleavage step is the rate-determining one, the above qualitative rate orders can now be interpreted in terms of the capacity of X and Z to stabilize the corresponding charges in the transition state leading to **4h**, regardless of whether **4t** describes an intermediate or a transition state.

In view of the mild conditions under which it can be carried out and the excellent yields encountered in most cases, this acetyl cleavage reaction presents an important and facile route to monosubstituted heterofulvenes of type 4 which are not easily accessible by direct routes.[11]

Deuteration. In connection with detailed kinetic nmr studies which are to be carried out on some of the oxygen derivatives, it is necessary to eliminate the allylic coupling between the ring methyl protons and the vinylic protons in positions 3 and 5. To this end, attempts were made to prepare the 2,6-dimethyl-d_6 derivatives of these compounds. Our first approach was to prepare 2,6-dimethyl-d_6-γ-pyrone and condense it with the appropriate active methylene compounds. It has previously been reported that neither the methyl nor the vinylic protons of 2,6-dimethyl-γ-pyrone exchange with deuterium in slightly acidic D_2O solution.[12] In strongly acidic D_2O solutions, exchange occurred mainly at positions 3 and 5 (vinylic protons) and to a lesser extent at the methyls in positions 2 and 6.[13] These results were rationalized in terms of ring opening of the pyrone under strongly acidic conditions, resulting in the formation of a 1,3,5-triketone. Consequently, the more acidic methylene hydrogens exchange faster than the methyl hydrogens. Recyclization, therefore, produces 2,6-dimethyl-γ-pyrone labeled predominantly in the 3 and 5 positions.

In order to minimize the ring opening and thus avoid the exchange of the vinylic protons, we have tried to promote exchange under anhydrous conditions. This was done by treating an anhydrous CH_3OD solution of **1** with D_2SO_4 at room temperature. Under these conditions, however, neither the methyl protons nor the vinylic protons were exchanged with deuterium. Our next approach was to effect the exchange on the heterofulvenes themselves. We have found that the D_2SO_4-CH_3OD method, which failed with 2,6-dimethyl-γ-pyrone, could be successfully applied to some of these compounds. Thus addition of a catalytic amount of D_2SO_4 to a CH_3OD solution of **6**, and maintaining this solution for a few hours at room temperature, resulted in the formation of the corresponding hexadeuterio derivative in a high degree of purity (nmr). Similarly, such exchange could also be performed on the nitrogen analog (**20**). Compound **23**, however, did not exchange deuterium under these conditions. Obviously, such exchange conditions could not be applied to the acetyl-bearing heterofulvenes as they undergo the previously mentioned deacetylation reaction.

Physical Properties

Nmr Spectra. The nmr data of compounds **5-24** are summarized in Table I. Protons H_x and H_y are diastereo-

Table II
Electronic and Infrared Spectral Data of Compounds 5–28

Compd	Uv (95% EtOH) λ_{max}, nm						Ir ($CHCl_3$), γ, cm^{-1}			
							C=C	CN	$COCH_3$	$COOCH_3$
5	260	354	406	5,100	8,600	9,600	1627		1666	
5a	260		399	5,000		22,200	1670[a]			
6	249	330	396	7,000	13,200	11,300	1655			1689
7	260		390	14,350		37,200	1655	2205		
8	247	358		8,300	20,000		1660		1666	1700
8a	231	327		5,000	13,200		1655			1691
9	255	367	381	5,900	24,400	22,600	1622	2177	1666	
9a	227	310		4,900	12,700		1670	2175		
10	248	349	363 sh	6,350	20,200	17,000	1650	2183		1689
12	251	357		7,100	19,300		1630		1655	
12a	244	354		5,900	24,500		1620		1680	
13	270	390 sh	422	6,300	14,300	15,400	1600		1644	
13a							1620			
14	260	363	440	3,600	11,400	9,500	1611			1688
15	274	416 sh	433	13,700	25,800	38,300	1600	2200		
16							1605		1650	1700
17	269	404	423	4,900	28,800	29,600	1600	2180	1649	
18	265	386	405	5,200	37,600	34,400	1605	2177		1683
19	258	330	403	9,900	10,100	16,500	1633		1633	
19a	261		410	2,600		15,200	1635			
20	258		404	10,700		37,400	1627			1711
21	255	277	392	14,400	9,000	43,000	1605	2180		
22	249	374		14,200	39,300		1590	2171	1638	
22a	238	350		1,600	5,400		1640	2160		
23	250 sh	364		4,650	47,000		1611	2161		1656
24		368			40,200		1625	2166		$CONH_2$ 1644
27	250	387		5,000	34,400		1650		1660	
28	255	350		7,200	25,700					

[a] In KBr pellets.

topic and usually give rise to two chemically shifted signals at room temperature which in some compounds are separated by *ca.* 1.5 ppm.[14] The room temperature spectra of **5**, **13**, **14**, **19**, **20**, and **21** exhibit a singlet for $H_x + H_y$. This phenomenon arises from fast thermal isomerization about the exocyclic double bond; at low temperatures, H_x and H_y exhibited chemically shifted singlets. As was previously pointed out, an unambiguous differentiation between the signals of the ring protons (H_x, H_y) and that of the proton at the exocyclic double bond in the monofunctional compounds (**5a**, **8a**, **9a**, **12a**, **13a**, **19a**, **22a**, and **27**; Table I) could be made on the basis of the relative widths of these signals. While the width at half-height of the two signals assigned to the ring protons is in the range of 4–5 Hz, that of the third olefinic signal does not exceed 2 Hz.

A distinction between H_x and H_y could be made on the basis of the following argument. Inspection of the chemical shift data for the N and O series of the *monosubstituted derivatives* reveals that the spectral position of one signal is practically insensitive to the nature of X. This signal was therefore assigned to H_y (Y = H). On the other hand, H_x, being geometrically disposed to the anisotropy effect of X, is shifted by 1.59 (Z = O) and 2.0 ppm (Z = N-Bu) upon changing X from NO_2 to CN. Although H_x and H_y in the *bifunctional* compounds do not resonate at magnetic field values identical with those of H_x in the *monofunctional* compounds, it is assumed that they retain the relative order of the chemical shifts found in the latter group, namely

$$\delta_H(NO_2) \geq \delta_H(COCH_3) > \delta_H(CO_2CH_3) > \delta_H(CN)$$

Such an assumption implies that all factors in a single compound, aside from group anisotropies, affect the chemical shift of H_x and H_y to the same extent. No ambiguities were encountered in our assignments since the differential shifts in all compounds are substantial. Thus, all the assignments in Table I were made on the above basis.

Electronic Spectra. The π–π^* transition maxima of compounds **5**–**27** in ethanol are listed in Table II. A low-wavelength band is present at *ca.* 245–270 nm in the spectra of *all* the compounds in this series (this band is, however, at lower wavelengths in the monosubstituted derivatives). The third band at *ca.* 400 nm in the oxygen and nitrogen heterocycles indicates the presence of a nitro group. Clearly, when comparing compounds with the same X and Y groups the spectra of the S heterocycles are shifted to the red with respect to the O and N analogs. Comparison of the spectra of the latter two groups of compounds indicates that in general the N heterocycles absorb at higher wavelength than the O heterocycles, although some exceptions are noted.

More detailed analysis of the spectra indicated that steric effects play a role in determining the energies and the probabilities of the electronic transitions in some of the compounds. Model examination reveals significant nonbonded interaction between the H atoms at C-3 and C-5 and the X and Y substituents in a planar geometry. Such interaction can be minimized in the monofunctional compounds by adopting the most favorable geometry of the functional group and still keeping this group in the plane of the ring. However, the introduction of a second substituent at the exocyclic double bond restricts the geometrical freedom of the already existing group, since new nonbonded interaction between the two double bond substituents are now generated. This should bring about a larger out-of-plane twist of the two functional groups and should affect the uv spectra. In fact, the above conclusions were reached upon analysis of the relevant spectral data. The longest wavelength high-intensity band should correspond to an electronic transition from the highest occupied MO and is therefore expected to be sensitive to molecular deformation arising from steric interactions. Thus, comparing **12a** with **12** (Table II) reveals a small red shift (3 nm)

of the highest wavelength band, but a 22% *decrease* in the intensity of this band is noted upon the introduction of the second acetyl group. When, however, the highest wavelength bands of **9a** and 2,6-dimethyl-4*H*-pyran-4-ylidenemalononitrile (**28**) (Table II) are compared, it is evident that the introduction of the second cyano group not only produces a pronounced red shift (40 nm) but is also accompanied by an *increase* of over 100% in the intensity of this band. Since the CN group is linear, no steric interactions are generated upon the introduction of the second cyano group and electron delocalization is maximal.

Even more significant is the comparison of the band at the region of 400 nm of compounds **5**, **6**, and **7** with that of **5a**. Thus, upon substituting the exocyclic H of **5a** with acetyl (**5**) and ester group (**6**), the intensity of the above band *diminishes* by 56 and 49%, respectively. However, when a CN group is introduced (**7**), ϵ *increases* by 68%. These results must indicate that while the introduction of the relatively large acetyl and ester groups bring about the said molecular twist, the linear nitrile group does not affect the geometry of the nitro group and allows maximum conjugative interaction of both groups.

Infrared Spectra. The most characteristic ir absorption bands of compounds **5**–**27** are listed in Table II. It can be seen that, with few exceptions, the stretching frequencies of the exocyclic double bond in the oxygen derivatives **5**–**12a** fall in the region of 1650–1660 cm^{-1}, those of the nitrogen derivatives **19**–**27** in the region of 1625–1640 cm^{-1}, and those of the sulfur derivatives in the region of 1600–1610 cm^{-1}. This decrease in the frequency as a function of the heteroatom, which indicates a decrease in the bond strength, or bond order, indicates, in our opinion, that the magnitude of the contribution of a limiting dipolar structure in these series increases in the order of O < N-Bu < S.

Experimental Section

Melting points were determined on a Thomas-Hoover Unimelt apparatus and are uncorrected. Ir spectra were recorded on a Perkin-Elmer grating spectrometer, Model 337. Uv spectra were recorded on a Perkin-Elmer 137UV spectrometer. Nmr spectra were taken on a Varian HA-100 spectrometer and on a Jeol JNM-C-60HL spectrometer. Mass spectra were taken with a Hitachi Perkin-Elmer RMU-6 instrument, electron energy 70 eV. Commercial, redistilled malononitrile, methyl acetoacetate, and methyl cyanoacetate were used. Literature procedures were used in the preparation of nitroacetone,[15] methyl nitroacetate,[16] cyanoacetone,[4] and compounds **9**[4] and **11**.[5]

General Procedure for the Preparation of 5, 6, 8, 10, and 12. A solution of 1 equiv (0.01–0.07 mol) of 2,6-dimethyl-γ-pyrone and 1 equiv of the appropriate active methylene compound in Ac_2O (30–100 ml) was refluxed for 2–5 hr. Removal of the Ac_2O at low pressure left a dark tarry residue which was extracted several times with hot ligroin (**5**) or ether (**6**, **8**, **12**). The combined organic extracts were washed with water and dried over $MgSO_4$. Removal of the solvent left a residue which was subjected to column chromatography on Kieselgel (0.05–0.20 mm) employing EtOAc–petroleum ether as eluent. Pure products were obtained in the 10:90 or 20:80 v/v EtOAc–petroleum ether fractions. Compound **10** was obtained by cooling (Dry Ice–acetone) the Ac_2O solution, filtering, and recrystallizing from MeOH.

2,6-Dimethyl-4*H*-pyran-4-ylidenenitroacetonitrile (7). To a solution of 7.69 g (0.062 mol) of 2,6-dimethyl-γ-pyrone in 70 ml of Ac_2O, 6.65 g (0.064 mol) of methazoic acid was added, and the solution was refluxed for 2 hr. Removal of the Ac_2O left a tarry residue which was extracted several times with 60-ml portions of ether. The combined ether solutions were washed with water and dried over $MgSO_4$. Removal of the ether left the product, which was recrystallized from EtOAc.

General Procedure for the Preparation of 13, 14, 15, 16, and 18. A solution of 1 equiv (3–10 mol) of 2,6-dimethyl-γ-thiapyrone and 2 equiv of the appropriate active methylene compound (methazoic acid in the preparation of **15**) in Ac_2O (15–45 ml) was kept at 80–90° for 2–7 hr. Removal of the Ac_2O at low pressure left a residue which was extracted several times with 50-ml portions of ether. The ethereal solution was washed with 15% $NaHCO_3$ solution, then with water, and dried over $MgSO_4$. Removal of the ether left a solid or an oil which was subjected to column chromatography on Kieselgel (0.05–0.20 mm) employing EtOAc–petroleum ether as eluent. Pure products were obtained from the 5:95 or 10:90 v/v EtOAc–petroleum ether fractions.

2,6-Dimethyl-4*H*-thiapyran-4-ylidenecyanoacetone (17). A solution of 1.0 g (0.01 mol) of cyanoacetone (generated by adding 0.01 mol of glacial AcOH to a suspension of 0.01 mol of sodium cyanoacetone enolate in absolute ether and filtering) in 10 ml of absolute ether was added dropwise to a solution of 0.7 g (5.0 mol) of 2,6-dimethyl-γ-thiapyrone in 20 ml of Ac_2O maintained at 90°. After 3 hr at 90°, the reaction mixture was worked up according to the general procedure given above.

General Procedure for the Reaction of $BuNH_2$ with the O Heterocycles. Preparation of 21, 22, 23, and 24. A solution of the respective oxygen derivatives (3–10 mmol) in $BuNH_2$ (6–25 ml) was refluxed for 1–2 hr. Removal of the excess of $BuNH_2$ at low pressure left a solid which was recrystallized from MeOH (**22**, **23**, **24**) or CH_3CN–EtOAc (**21**), affording pure products.

Reaction of Butylamine with 5. A solution of 0.55 g (2.6 mmol) of **5** in 6 ml of $BuNH_2$ was refluxed for 0.5 hr. On keeping the reaction mixture at 0° overnight, a solid separated, which upon filtering afforded 1-*n*-butyl-2,6-dimethyl-1,4-dihydropyridin-4-ylidenenitroacetonitrile (**19**), mp 150° after recrystallization from EtOAc–ligroin. The above filtrate upon evaporation at low pressure afforded a mixture of **19** and *N*-*n*-butyl-2,6-dimethyl-3-nitro-1,4-dihydropyridin-4-ylideneacetone (**26**), which was chromatgraphed on Kieselgel (0.05–0.20 mm), employing EtOAc–petroleum ether as eluent. The 1:3 v/v EtOAc–petroleum ether fraction afforded 176 mg (30%) of **26**: mp 162° after recrystallization from petroleum ether–EtOAc; mass spectrum (%) 264 (100, M^+). *Anal.* Calcd for $C_{14}H_{20}N_2O_3$: C, 63.62; H, 7.63; N, 10.60. Found: C, 63.46; H, 7.47; N, 10.47.

1-*n*-Butyl-3-nitro-4-acetonyl-6-methyl-2-pyridone (25). A solution of 0.55 g (4 mmol) of **6** in 5 ml of $BuNH_2$ was refluxed for 5 hr. Upon cooling and maintaining the solution for a few hours in an ice bath, a solid separated and was filtered, affording 0.22 g (34%) of **25**: mp 127° after recrystallization from EtOH; mass spectrum (%) 266 (100, M^+). *Anal.* Calcd for $C_{13}H_{18}N_2O_4$: C, 58.63; H, 6.81; N, 10.52. Found: C, 58.82; H, 6.79; N, 10.50.

Methyl 1-*n*-Butyl-2,6-dimethyl-1,4-dihydropyridin-4-ylidenenitroacetate (20). A solution of 1.1 g (8 mmol) of **6** and 1 ml (0.01 mol) of $BuNH_2$ in 60 ml of $CHCl_3$ was refluxed for 50 hr. Upon cooling, crystals separated; they were filtered and recrystallized from $CHCl_3$–EtOAc, affording **20**.

Formation of 10 from 2,6-Dimethyl-4*H*-pyran-4-ylidenemalonitrile. To a solution of 0.51 g (3 mmol) of 2,6-dimethyl-4*H*-pyran-4-ylidenemalononitrile in 10 ml of MeOH, 1 ml of water and 1 ml of concentrated H_2SO_4 were added, and the solution was refluxed for 72 hr. On cooling and addition of 100 ml of water, a solid separated and was filtered, affording 0.24 g (39%) of **10**, mp 178° after recrystallization from EtOH. There was no depression of the mixture melting point of **10** prepared from 2,6-dimethyl-γ-pyrone and methyl cyanoacetate and the compound obtained by the present method.

2,6-Dimethyl-4*H*-pyran-4-ylideneacetonitrile (9a). To a solution of 0.38 g (2 mmol) of **9** in 10 ml of MeOH, 1 ml of water and 1 ml of concentrated H_2SO_4 were added, and the solution was refluxed for 24 hr. Upon cooling and addition of ice-cold water, a solid separated and was collected, affording 0.11 g (42%) of **9a**, mp 85–89°. Chromatography on Kieselgel (0.05–0.20 mm), employing EtOAc–hexane as eluent, afforded a pure sample.

A General Procedure for the Cleavage of the Acetyl Group in Acetyl-Bearing Compounds of General Formula 4. A solution of 5 mmol of the appropriate compound in 5 ml of MeOH was treated with 2 drops of concentrated H_2SO_4 at room temperature. The reaction mixture was kept at room temperature until all starting material disappeared (tlc analysis). This usually took 1 hr for the N-Bu derivatives, and up to 96 hr for the oxygen derivatives. The product was isolated by one of the following methods.

Method A. The reaction mixture was cooled in a Dry Ice–acetone bath, whereupon solid separated and was collected by filtration.

Method B. The MeOH was removed at low pressure and the residue dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with 10% $NaHCO_3$ solution, then with water, and dried over Na_2SO_4. Removal of the $CHCl_3$ left a solid that was recrystallized from ligroin.

1-*n*-Butyl-2,6-dimethyl-1,4-dihydropyridin-4-ylideneacetone (27). A solution of 164 mg (1 mmol) of **12a** in 5 ml of $BuNH_2$ was refluxed for 8 hr. The excess of $BuNH_2$ was removed at low pressure and the residue was dissolved in petroleum ether–EtOAc. On cooling (Dry Ice–acetone), 153 mg (70%) of **27** precipitated and as collected by filtration.

Methyl 2,6-Hexadeuteriodimethyl-4*H*-pyran-4-ylidenenitroacetate. To a solution of 215 mg (1 mmol) of **6** in 8 ml MeOD, 4 drops of D_2SO_4 was added, and the solution was kept at 50° for 72 hr. On cooling (Dry Ice–acetone), 200 mg (90%) of product separated and was collected by filtration. The nmr spectrum of the product indicated exchange of about 50% of the methyls' hydrogens by deuterium. The product was redissolved in 8 ml of MeOD containing 4 drops of D_2SO_4, and the reaction mixture was maintained at 50° for an additional 100 hr. Upon cooling, 180 mg (70%) of product was obtained, mp 109°, which was more than 95% hexadeuterated (nmr).

Registry No.—**1**, 1004-36-0; **2**, 1073-80-9; **5**, 49810-66-4; **5a**, 49810-67-5; **6**, 49810-68-6; **7**, 49810-69-7; **8**, 49810-70-0; **8a**, 39588-78-8; **9**, 3280-35-1; **9a**, 49775-27-1; **9a'**, 49810-73-3; **10**, 49810-74-4; **11**, 49810-75-5; **12**, 49810-76-6; **12a**, 39588-76-6; **13**, 49810-78-8; **13a**, 49775-28-2; **14**, 49810-79-9; **15**, 49810-80-2; **16**, 49810-81-3; **17**, 49810-82-4; **18**, 49810-83-5; **19**, 49810-84-6; **19a**, 49810-85-7; **20**, 49775-29-3; **21**, 49810-86-8; **22**, 49810-87-9; **22a**, 49810-88-0; **23**, 49810-89-1; **24**, 49810-90-4; **25**, 49810-91-5; **26**, 49810-92-6; **27**, 49810-93-7; **28**, 28286-88-6; **29**, 49810-95-9; 1-nitro-2-propanone, 10230-68-9; nitromethane, 75-52-5; methyl nitroacetate, 2483-57-0; nitroacetonitrile, 13218-13-8; methyl-3-oxobutyric acid, 105-45-3; methyl acetate, 79-20-9; 3-oxobutyronitrile, 2469-99-0; acetonitrile, 75-05-8; acetonitrile-*d*, 26456-53-1; methylcyanoacetic acid, 105-34-0; 2-cyanoacetamide, 107-91-5; 2,4-pentanedione, 123-54-6; acetone, 67-64-1; malononitrile, 109-77-3; butylamine, 109-73-9; methyl 2,6-hexadeuteriodimethyl-4*H*-pyran-4-ylidenenitroacetate, 49810-96-0.

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Intramolecular Friedel–Crafts Acylation Reaction of 4-Cycloocten-1-yl Acetyl Chloride. A Competitive $[\pi 2_s + \pi 2_a]$ Cycloaddition

Sung Moon* and Thomas F. Kolesar

Department of Chemistry, Adelphi University, Garden City, New York 11530

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The stannic chloride catalyzed intramolecular reaction of 4-cycloocten-1-yl acetyl chloride (**2**) yields the expected Friedel–Crafts type product, *endo*-2-chlorobicyclo[4.2.2]decan-8-one (**5**). The uncatalyzed reaction yields tricyclo[5.3.0.$0^{3,10}$]decan-2-one (**3**) and tricyclo[4.4.0.$0^{3,10}$]decan-2-one (**4**) through a $[\pi 2_s + \pi 2_a]$ process.

The fact that a double bond can participate in an intramolecular reaction with a suitably placed cationic center has been known for a long time.[1] The first example of a solvolytic intramolecular cyclization of a simple substituted cycloalkene was reported by LeNy in 1960.[2] Since this report, many papers dealing with intramolecular participation of double bonds in cyclic systems have been published. These papers reported studies on the factors which influence ring closures,[1,3-5] aspects of the π route[6] to classical–nonclassical systems,[7,8] and synthetic routes to otherwise difficultly accessible bicyclic compounds.

The work of Erman and Kretschmar[9] extended the study of ring closures to cases where the cationic center was derived from an acyl chloride group. A number of similar papers have appeared recently[10a,11,12] in which the Friedel–Crafts intramolecular cyclization has led to formation of bicyclic products. The Friedel–Crafts closures to give bicyclic products are of interest for two reasons. First, ring closure affords bifunctional bicyclic products having a ketone and either a halo or olefinic group, while solvolytic ring closures of sulfonate esters, etc., yield monofunctional derivatives. Second, solvolysis of esters derived from alcohols related to the acyl halide may have different selectivities. Thus, 3-(3-cyclohexen-1-yl)-propionyl chloride undergoes an intramolecular ring closure,[10a] but buffered acetolysis of the tosylate of 3-(3-cyclohexen-1-yl)propyl alcohol fails to give cyclization products.[10b]

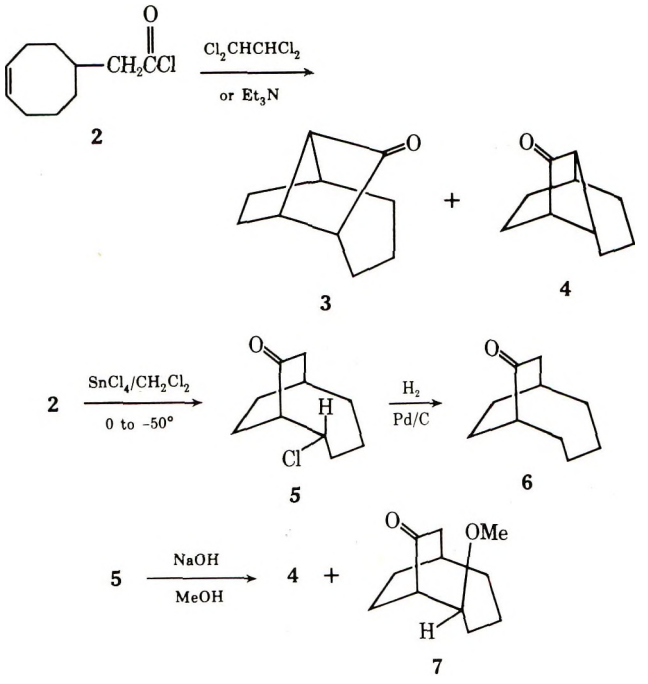
As part of a study on cationic ring closures of cyclooctenyl derivatives, we investigated the Friedel–Crafts intramolecular acylation reactions of 4-cycloocten-1-yl acetyl chloride (**2**). The stannic chloride catalyzed reaction of **2** gave products expected of a Friedel–Crafts reaction. The uncatalyzed reaction of **2** gave products which arise through the intermediacy of a ketene rather than a cationic intermediate.

Results

4-cycloocten-1-yl acetic acid (**1**) was prepared from 5-bromocyclooctene[13] by malonic ester synthesis. The acid **1** in carbon tetrachloride was converted to the acyl halide **2** with thionyl chloride. Glpc analysis of the product mixture obtained when **2** was heated at reflux in CCl_4 for 7 days showed two compounds (Scheme I) in addition to unchanged starting material. The infrared spectrum of the first unknown compound eluted, **3** (1%), showed no ab-

sorptions due to unsaturation. The carbonyl stretching frequency was unexpectedly high at 1770 cm^{-1}, indicative of a cyclobutanone ring.[14] The second unknown compound, 4 (10%), like the first, had no absorptions in the infrared spectrum which could be ascribed to an olefinic group, and also had a high carbonyl stretching frequency at 1774 cm^{-1}. The fingerprint region of both 3 and 4 showed many very sharp, moderately intense absorptions. These fingerprint absorptions suggested that the two compounds were strained.[15] The nmr spectra of both compounds confirmed the lack of an olefinic group. Finally, elemental analysis and mass spectra showed the chemical composition of 3 and 4 to be $C_{10}H_{14}O$.

Scheme I



Heating, at reflux, a solution of 2 in 1,1,2,2-tetrachloroethane for 7 days gave a higher yield of compounds 3 and 4 in the ratio of 1:10, respectively.

Structures for the $C_{10}H_{14}O$ compounds were tentatively assigned as tricyclo[5.3.0.$0^{3,10}$]decan-2-one (3) and tricyclo[4.4.0.$0^{3,10}$]decan-2-one (4). The actual assignment of structure to major and minor product depended on the chemical evidence outlined below. The two tricyclic compounds could arise by means of an intramolecular ketene cycloaddition.

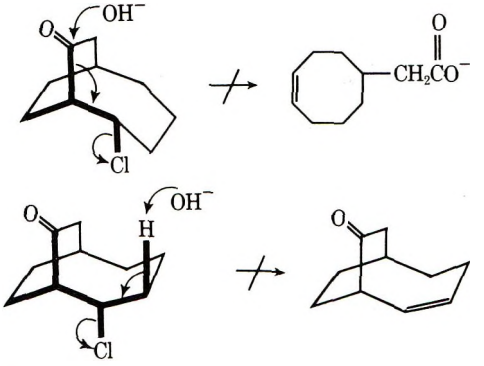
Treatment of the acyl chloride 2 with triethylamine, a standard method for the generation of ketenes,[16] produced the two tricyclodecanones in the same ratio as formed from the uncatalyzed reaction in refluxing 1,1,2,2-tetrachloroethane. The formation of the two tricyclodecanones was accompanied by the formation of dimeric products. The fact that tertiary amines catalyze the processes by which dimers and higher oligomers are formed is well known.[16]

The stannic chloride catalyzed reaction of 2 in dichloromethane at −50 to 0° gave a major product (~95%), in addition to unchanged 2 and several other unidentified products. The major component was identified as a chloro ketone 5 on the basis of its ir and nmr spectra and elemental analysis ($C_{10}H_{15}ClO$). Further, the following evidence supported the structure of the chloro ketone as *endo*-2-chlorobicyclo[4.2.2]decan-8-one (5). Hydrogenolysis[17] of the chloro ketone 5 gave bicyclo[4.2.2]decan-7-one (6)[18] as principal product (58%). In addition, the tricyclodecanone 4 (23%) and the methyl ether 7 (18%) were produced. The formation of the latter two products under the basic condition of the reaction, sodium hydroxide in methanol, is consistent with the observation below.

Since the most probable conformation of the bicyclo[4.2.2] system is not known, nmr data could not be used to assign the configuration of the chloro group. Degradation of the chloro ketone 5 with base was carried out to determine the configuration of the chlorine atom.[9,12]

Treatment of 5 with methanolic sodium hydroxide at reflux for 24 hr gave two products. The first product was identical with 4 and the second product was a methyl ether 7. The nmr spectrum of 7 is similar to that of the starting chloro ketone in the methylene envelope region, indicating that no rearrangement of the bicyclic skeleton had taken place.[19] Examination of molecular models of the bicyclo[4.2.2]decane system shows that conformations with a trans diaxial array involving the endo C-2 chlorine atom which would lead to elimination or cleavage would not be highly populated because severe transannular and 1-3 interactions were present.

It has been noted that the bicyclo[4.2.1]non-2-yl system or the carbonium ion does not readily eliminate, as compared to the isomeric bicyclo[3.3.1]non-2-yl system or its carbonium ion.[20] No explanation has been offered for this difference, but examination of models of the bicyclo[4.2.1]nonane system indicates that nonbonded interactions are important. This is shown in the dissociation constants of the cyanohydrins of the various bicyclo[4.2.1]nonanones.[21] The cyanohydrins are destabilized relative to the ketones because of severe nonbonded interactions.



The structure of the chloro ketone 5 was assigned as *endo*-2-chlorobicyclo[4.2.2]decan-8-one on the basis of the fact that the tricyclodecanone 4 must arise by an SN2 displacement of the chloro group by the enolate of the ketone, generated under the basic conditions of the reaction. There are similar examples of such transannular displacements in the literature.[22] Treatment of 1-acetyl-4-chlorocyclooctane with a variety of bases in different solvent systems affords good yields of 1-acetylbicyclo[4.2.0]octane.[22a]

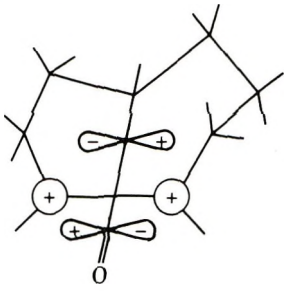
To determine if the Friedel-Crafts pathway might be competitive with the ketene intramolecular cycloaddition pathway in the uncatalyzed reaction, a study was performed to determine the stability of 5 to the uncatalyzed conditions. The chloro ketone 5 was heated in 1,1,2,2-tetrachloroethane at reflux. Periodically samples were withdrawn and subjected to glpc analysis. After 48 hr, 89% of 5 remained and the tricyclodecanone 4 had been formed. Formation of 4 probably arises through the reaction of the enol or enolate of 5. Because the half-life of 5 under the reaction conditions is approximately 11.5 days and no 5 is detected in the uncatalyzed reaction, one can conclude that the Friedel-Crafts pathway is not competitive to the ketene intramolecular cycloaddition.

Discussion

For ring closure or double-bond participation to be important in cationic reactions of the type studied here, two criteria must be met. First, the energy required to effect ring closure or double-bond participation must not be much greater than the energy required for any other processes by which starting material can be transformed into product(s). Second, the energy required to effect ring closure or double-bond participation must be such that the energy level is reasonably populated under the reaction conditions.

Inspection of molecular models of 2 shows that, in the conformation of closest approach, the distance between the potential cationic center and the midpoint of the double bond is 1.1 Å. The chloro group is thrust down toward the double bond, causing a serious nonbonded interaction. In uncatalyzed Friedel–Crafts reactions the reacting species is considered to be a tight ion pair;[9] so the molecular model should give a close approximation to the reacting species. In addition, a 1,5-nonbonded interaction involving the cis C-2 and C-6 hydrogen atoms is present in this conformation. Estimates of the energy involved can be obtained by reference to nonbonded interaction curves.[23] The normally expected Friedel–Crafts reaction is thus sterically disfavored.

On the other hand, studies of molecular models of 2 and the ketene 8 derived from it show that a slightly distorted orthogonal array involving the carbon–carbon double bond and ketene moieties is readily achieved. According to the Woodward and Hoffmann conservation of orbital symmetry rules, thermal [2 + 2] cycloaddition reactions are symmetry allowed if the mode of addition is [$_{\pi}2_s$ + $_{\pi}2_a$].[24] To achieve this mode of addition an othogonal array of the reacting species is necessary. The regioselectivity observed in the formation of 3 and 4 is due to the fact that rotation of the ketene moiety to form 4 is less hindered than that required to form 3. As the ketene moiety moves toward carbon 1, which would yield 3, a severe interaction of the hydrogen atoms at C-3 and C-7 trans to the ketene moiety occurs. On the other hand, movement toward carbon 2, which would yield 4, results in a conformation which is staggered for the most part.



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While one would not expect reaction through a ketene or ketene-like intermediate to compete favorably with the normally expected Friedel–Crafts mode of reaction, the formation of ketenes when acyl halides are heated is well documented.[25] Although Erman and Kretschmar did not observe the formation of products arising through the intermediacy of a ketene, they suggested the possible formation of a ketene to account for rearrangements which occur in the uncatalyzed reaction of 4-cycloocten-1-yl carbonyl chloride.[9] The chemistry of ketenes, protonated ketenes, and "ketene-like" species has been the subject of recent experimental and theoretical studies.[26]

In contrast to the uncatalyzed reaction of 2, the stannic chloride catalyzed reaction proceeded through the expected Friedel–Crafts reaction. Inspection of molecular models shows that closure to bicyclo[4.2.2]decane products is favored over closure to bicyclo[3.3.2]decane products because of steric hindrance. The reason(s) for the stereospecificity observed in the formation of the endo isomer of 5 is difficult to define. It is known that the products obtained are dependent on the structure of the reactant(s), polarity of the solvent, catalyst, and temperature.[9] Thus, when freshly sublimed aluminum chloride is used as catalyst in the reaction of *cis*-cyclooctene and acetyl chloride the predominant product is 4-acetyl-1-ethylcyclohexene. However, if the sublimed catalyst is deactivated by exposure to the atmosphere, 1-acetyl-4-chlorocyclooctane is the main product.[22a] The catalyst exerts its effect in two ways. First, the size of the catalyst–substrate complex will affect the cis–trans product ratio. Second, a more active catalyst will increase the lifetime of the carbonium ions formed and promote rearrangements.[9] Molecular models of bicyclo[4.2.2]decan-7-one indicate that both the exo and endo sides of the system at the 2 carbon are amenable to nucleophilic attack. The presence of a fairly large complex as would be formed with stannic chloride and the carbonyl function may present enough hindrance to cis attack giving the exo product and thus the trans endo product 5 is formed. Fickes and Kemp also observed the intramolecular stereospecific trans addition of cyclohept-4-ene-1-carbonyl chloride in the presence of aluminum chloride and suggested the possible intervention of a nonclassical intermediate.[12]

Experimental Section

Nmr spectra were determined on a Varian A-60 spectrophotometer, using tetramethylsilane as an internal standard. Ir spectra were determined on a Perkin-Elmer 257 grating infrared spectrophotometer using polystyrene film as the calibration standard. Solution ir spectra were recorded at concentrations of 5–10%. Boiling points and melting points are uncorrected. Melting points were determined on a Thomas-Hoover 6406-H apparatus. Glpc separations were performed on an F & M Scientific 720 dual column programmed temperature gas chromatograph. A 2 ft × 0.25 in. column packed with 20% neopentyl glycol succinate on 60/80 mesh Chromosorb W acid washed and treated with hexamethyldisilane was used.

4-Cycloocten-1-ylacetic Acid (1). A 1-l. flask equipped with a dropping funnel and a water condenser protected with a calcium chloride drying tube was charged with 12.5 g (0.500 g-atom) of sodium in small pieces. Anhydrous ethanol (200 ml) was added, and the mixture was stirred by means of a magnetic stirrer. When the initial reaction had subsided, an additional 300 ml of anhydrous ethanol was added over 0.5 hr.The mixture was heated on the steam bath at reflux until all the sodium had reacted. The solution was allowed to cool to approximately 40° and 80.0 g (0.500 mol) of diethyl malonate was added over 15 min. To the stirred solution was added 94.6 g (0.500 mol) of 4-cycloocten-1-yl bromide. The mixture was heated at reflux for 72 hr. The condenser was replaced with a simple distilling head and the mixture was heated on the steam bath until no more alcohol distilled. To the concentrate was added 40 g (1.0 mol) of sodium hydroxide dissolved in 150 ml of water. The mixture was heated at reflux for 18 hr. The solution was allowed to cool to room temperature and acidified with HCl. The solution was filtered and the crude 4-cycloocten-1-ylmalonic acid was air dried. The crude malonic acid (65 g, 61%) was placed in a 250-ml round-bottomed flask and distilled with decarboxylation. The acid 1 was collected as a viscous oil (46 g, 55% overall). Portions of the oil were crystallized from a hexane solution at Dry Ice–acetone temperature. The first crop of crystals was recrystallized twice to give the analytical sample, mp 34.2–35.5°. The acid had the following properties: ir (CCl_4) 3400–3050 (COOH), 3010 (C=CH), 1700 cm^{-1} (C=O); nmr (CCl_4) τ ~0.10 (s, 1, COOH), 4.44 (m, 2, C=CH), 7.2–9.2 (complex with major absorptions at 7.82 and 8.49, 13, other hydrogens).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.28; H, 9.77.

Uncatalyzed Reaction of Acyl Chloride 2. A. In Carbon Tetrachloride. To a solution of 12.2 g (73.0 mmol) of 1 in 30 ml of

carbon tetrachloride was added 8.7 g (73 mmol) of thionyl chloride. The solution was heated at reflux for 1 hr and concentrated and an ir spectrum (film) was taken, C=O 1800 cm^{-1}. A solution of 5.0 g of the acyl chloride **2** in 50 ml of carbon tetrachloride was heated at reflux for 7 days. To the refluxing solution was added 20 ml of water and the mixture was heated at reflux for 1 hr. The organic layer was separated and the aqueous layer was extracted with carbon tetrachloride. The combined extracts were dried and glpc analysis was performed at 160°. The product composition by area was **3**, 1%; **4**, 10%; and **2**, 89%. The products had the following properties.

3 had mp 40–42°, as collected from glpc; ir (CS_2) 2920, 2870, 2840, 1770, 1355, 1308, 1298, 1242, 1216, 1156, 1132, 1028, 992, 936, and 896 cm^{-1}, the bands in the fingerprint region were moderately intense and sharp, characteristic of small strained rings; nmr (CCl_4) τ 6.54, (m, 1, bridgehead α to carbonyl), 6,74 (m, 1, bridgehead α to carbonyl), 7.0–9.0 (complex with major absorptions at 7.10, 7.24, 7.34, 7.50, 7.90, 8.34, 8.44, 8.54, and 8.60, 12 H); mass spectrum (75 eV) *m/e* 150, 122 (−CO).

Anal. Calcd for $C_{10}H_{14}O$: C, 79.96; H, 9.39. Found: C, 79.81; H, 9.14.

4 had mp 152–156° (sealed tube), after collection from glpc and sublimation at 135° (15 mm); ir (CS_2) 2932, 2874, 2850, 1774, 1375, 1340, 1308, 1282, 1274, 1250, 1232, 1188, 1158, 1131, 1108, 1054, 1028, 986, 958, 932, 901, and 862 cm^{-1}, the bands in the fingerprint region were moderate to weak in intensity and sharp, characteristic of small strained rings; nmr (CCl_4) τ 6.42 (m, 1, bridgehead α to carbonyl), 7.0–9.0 (complex with major absorptions at 7.08, 7.17, 7.28, 7.35, 7.50, 7.56, 8.03, and 8.28, 13 H); mass spectrum (75 eV) *m/e* 150, 122 (−CO).

Anal. Calcd for $C_{10}H_{14}O$: C 79.96; H 9.39. Found: C, 79.85; H, 9.20.

B. In 1,1,2,2-Tetrachloroethane. The acyl chloride **2** prepared from 1.68 g of **1**, as above, was dissolved in 10 ml of tetrachloroethane and the solution was heated at reflux for 7 days. A crystalline product had formed on the condenser. The solution was concentrated on a rotary evaporator and the residue was sublimed at 130° and water aspirator pressure. An off-white solid, 750 mg, was collected. The solid consisted of **3** and **4** in a ratio of 1:10, respectively (glpc analysis). The residue consisted of unchanged **2** and some **3** and **4**.

Stannic Chloride Catalyzed Reaction of 2. The acyl chloride **2** prepared from 1.68 g of **1** as above was dissolved in 30 ml of dichloromethane. The solution was cooled to −50° in a Dry Ice–acetone bath and 2.60 g (10.0 mmol) of stannic chloride (1:1 reactant/catalyst mole ratio) was added over 5 min. The solution was kept at −50° for 0.5 hr and then removed from the bath. When the temperature of the solution reached 0°, a mixture of ice and water was added to quench the reaction. The dichloromethane layer was drawn off and the aqueous layer was extracted with one 10-ml portion of dichloromethane. The combined dichloromethane solutions were dried ($MgSO_4$) and concentrated. Analysis by glpc (area integration) at 160° showed **2**, 3%; **5**, 95%; and two unidentified peaks, 2%. The chloro ketone **5** had the following properties: mp 48–52°, as collected from glpc; ir (CS_2) 2920, 2880, 1705, 1335, 1325, 1290, 1235, 1160, 1115, 1035, 964, 935, 830, and 785 cm^{-1}; nmr (CCl_4) τ 5.5–5.9 (m, 1, ClCH), 7.2–9.3 (complex with major absorptions at 7.35, 7.58, 7.65, 7.86, 8.03, 8.05, and 8.27, 14, other hydrogens).

Anal. Calcd for $C_{10}H_{15}ClO$: C, 64.34; H, 8.10. Found: C, 64.60; H, 8.17.

Hydrogenolysis of 5. To 10 ml of methanol was added 107 mg of **5**, 90 mg of 5% palladium on carbon, and 120 mg of potassium hydroxide. The mixture was hydrogenated at 30 psi for 4.5 hr in a Parr low-pressure hydrogenation apparatus. The solution was filtered and allowed to concentrate overnight by evaporation. The solution was further concentrated on a rotary evaporator to give a mixture of inorganic and organic products. The mixture was extracted with petroleum ether (bp 30–60°) and glpc analysis and separations were performed. The following temperature program was used: isothermal at 135° until **6** eluted and then at 5°/min to 160°. The ir spectrum of the major product **6** was identical with that of an ir spectrum of an authentic sample[17] of bicyclo[4.2.2]decan-7-one (**6**). The two other products identified were **4** (23%) and **7** (18%). A fourth compound (1%) was unidentified.

Treatment of 5 with 10% Methanolic Sodium Hydroxide Solution. To 30 ml of a 10% methanolic sodium hydroxide solution was added 252 mg of **5**. The solution was heated at reflux for 24 hr and cooled. The solution was diluted with 50 ml of water and extracted with three 25-ml portions of ether. The combined extract was washed with three 10-ml portions of water and dried ($MgSO_4$), and glpc analysis was performed at 160°. Two compounds eluted. The minor component (16%, area integration) was identical with **4** (ir and nmr spectra). The major product (84%) was the methyl ether **7**: ir (CS_2) 2975, 2930, 2910, 2872, 2820, 1700, 1407, 1337, 1285, 1238, 1185, 1146, 1095, 1038, 929 cm^{-1}; nmr (CCl_4) τ 6.70 (s, 3, CH_3O), this peak is superimposed over an absorption at 6.5–6.7 (m, OCH), other absorptions at 7.28, 7.40, 7.65, 7.98, 8.15, 8.22, 8.40, and 8.60 (14, other hydrogens).

Anal. Calcd for $C_{11}H_{18}O$: C, 72.51; H, 9.95. Found: C, 72.47; H, 9.84.

Stability of 5 under Uncatalyzed Conditions. A solution of 20 mg of **5** in 10 ml of 1,1,2,2-tetrachloroethane was heated at reflux. After 24 hr at reflux a sample was withdrawn and analyzed by glpc. The relative areas found were 95% **5** and 5% **4**. After 48 hr at reflux the ratios were 89% **5** and 11% **4**.

Treatment of Acyl Halide 2 with Triethylamine. To a solution of 1.86 g of **2** in 25 ml of ether cooled in an ice–water bath was added dropwise 1.01 g (10 mmol) of triethylamine. The solution was swirled after each addition; a white precipitate formed immediately. The mixture was allowed to warm to room temperature, extracted with dilute HCl, dried ($MgSO_4$), and analyzed by glpc. The chromatogram showed the tricyclodecanones **3** and **4** in the ratio of 1:10, respectively, identified by ir. In addition a number of dimeric products at longer retention times were observed. From total area integration the yield of monomeric products was calculated as 45%.

Registry No.—**1**, 50585-13-2; **2**, 50585-14-3; **3**, 50585-15-4; **4**, 50585-16-5; **5**, 50585-25-6; **7**, 50585-26-7; diethyl malonate, 105-53-3; 4-cycloocten-1-yl bromide, 4103-12-2; $SnCl_4$, 7646-78-8.

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Acid-Catalyzed Rearrangement of Two Cyclohexadienone Monoepoxides

Harold Hart,* Irene Huang, and Paul Lavrik

Department of Chemistry, Michigan State University, East Lansing, Michigan 48824

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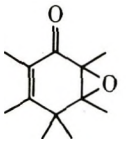
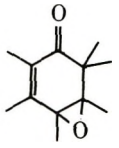
Rearrangement of 2,3-epoxy-2,3,4,4,5,6-hexamethyl-5-cyclohexenone (**1**) in trifluoroacetic acid (TFA) at room temperature gave 5-acetyl-2,3,4,4,5-pentamethyl-2-cyclopentenone (**3**, 50%), 2-acetyl-2,3,4,5,5-pentamethyl-3-cyclopentenone (**4**, 35%), and 6-hydroxy-4-methylene-2,3,5,5,6-pentamethyl-2-cyclohexenone (**5**, 10%). Independent treatment of **5** with TFA gave **4**, but at a much slower rate than the formation of **4** from **1**. Deuterium-labeling experiments support the mechanisms in Schemes I and II for the rearrangement of **1**, all products arising from opening the epoxy ketone to a cation (B) in which the positive charge is not adjacent to the carbonyl group. 4,5-Epoxy-2,3,4,5,6,6-hexamethyl-2-cyclohexenone (**2**), prepared from the corresponding dienone and *m*-chloroperbenzoic acid, rearranged quantitatively in aqueous acid to 5-hydroxy-4-methylene-2,3,5,6,6-pentamethyl-2-cyclohexenone (**12**). In neat TFA, **12** rearranged to 5-isopropenyl-4-methylene-2,3,5-trimethyl-2-cyclopentenone (**15**) which, on longer treatment with TFA, was dealkylated to 4-methylene-2,3,5-trimethyl-2-cyclopentenone (**16**) and acetone. When **2** was treated directly with neat TFA, there was formed, in addition to **15** and **16**, a small yield of **4** and a larger amount of 4-acetyl-2,3,4,5,5-pentamethyl-2-cyclopentenone (**14**). Deuterium-labeling experiments support the mechanism in Scheme IV for the formation of **12** from **2**, and the mechanisms in Schemes VI and VII for the rearrangement of **2** in neat TFA. The formation of **4** from **1** and from **2** is unexpected, and that mechanism, in each case, is of more than usual interest.

The acid-catalyzed rearrangement of epoxy ketones can take several paths which may be synthetically useful, provided that one can predict in any particular case what the major products will be.[1] Little is known regarding the acid-catalyzed rearrangement of cyclohexadienone monoepoxides. As examples of cross- and fully conjugated cyclohexadienone epoxides, we prepared the hexamethyl derivatives **1** and **2**, and describe here their rearrangement in trifluoracetic acid (TFA). Each epoxide was prepared in good yield by oxidizing the corresponding dienone with *m*-chloroperbenzoic acid (*m*-CPBA).



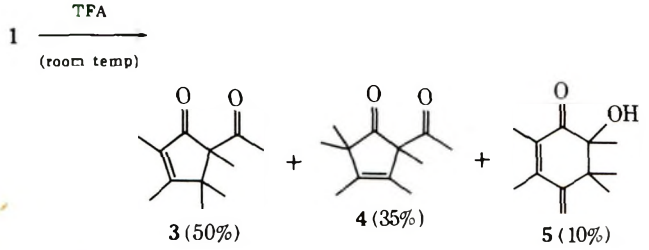
1



2

Results

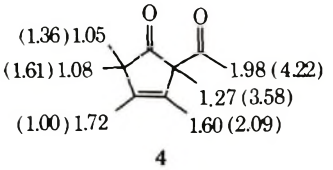
Rearrangement of 1. Treatment of **1** with TFA at room temperature for 3 hr afforded a high yield of three isomers, two diketones and a hydroxy ketone, to which we assign the structures **3**–**5**.



3 (50%) **4** (35%) **5** (10%)

Compound **3** was identical with the sole photoisomer of **1**; evidence for its structure has already been presented.[2]

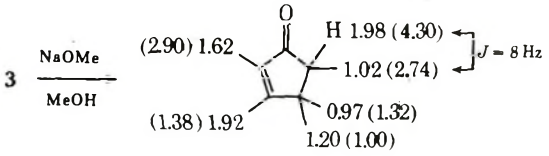
The structure of **4** is based on its spectra and cleavage with base. The compound showed two carbonyl absorp-



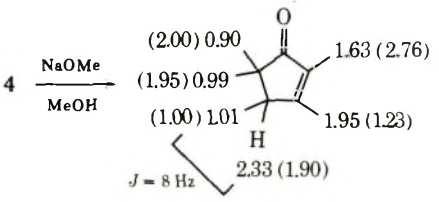
4

tions,[3] at 1740 and 1710 cm^{-1}, and only weak uv absorption, indicating that neither carbonyl group was conjugated with the double bond. The nmr spectrum with europium shift data[4] is consistent with the structure.[5]

Cleavage of **3** and **4** with sodium methoxide in methanol afforded two different conjugated cyclopentenones ($\nu_{C=O}$ 1700 cm^{-1}, $\nu_{C=C}$ 1650 cm^{-1}), assigned structures **6** and **7**, respectively.



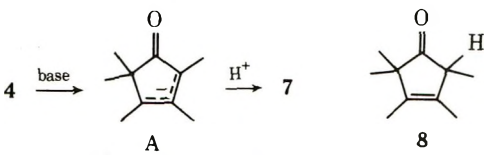
6



7

Structure **6** is the only plausible one which can be obtained from **3**, and the nmr data support the assignment. The two allylic methyls were distinguished on the basis of chemical and europium shifts, and the *gem*-dimethyl was located as remote from the carbonyl group by comparing the europium shifts of **6** and **7**.

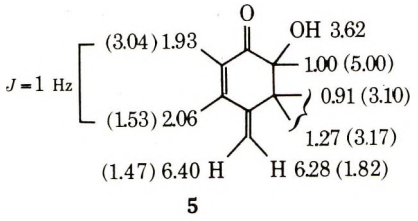
Cleavage of **4** should give the allylic anion A, which is protonated in the γ position to give **7**. Structure **8**, which could be formed by α protonation, is eliminated by the ir and uv data. Consistent with these structural assignments is the observation that **4**, which gives an allylic enolate anion, was cleaved by base much more rapidly than was **3**.



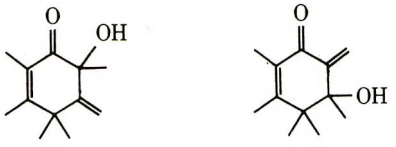
A **8**

The structure of the minor product **5** is based on its spectra. The $\nu_{C=O}$ at 1660 cm^{-1} was consistent with a conjugated carbonyl in a six-membered ring; the presence of a hydroxyl group was clear from the ν_{OH} at 3600 cm^{-1} and from the presence of a broad one-proton peak in the

nmr at δ 3.62 which was removed on D_2O exchange. The nmr spectrum showed two vinyl protons (δ 6.28, 6.40). The ir spectrum indicated that these were on a terminal methylene group (935 cm^{-1}) and the uv maximum at 281 nm (ε 7500) suggested that both double bonds were conjugated with the carbonyl group. The remainder of the nmr spectrum was consistent with the structure, with two mutually coupled vinyl methyl groups and three sharp aliphatic methyl singlets. Alternate structures for the hydroxy ketone, such as **9** or **10**, which can be envisioned as arising from **1**, do not fit the spectral data as well as **5**, and were eliminated conclusively by deuterium-labeling experiments to be described below.



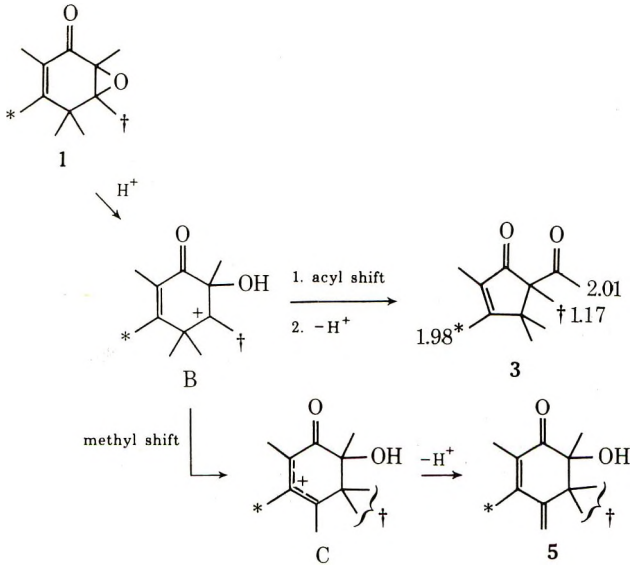
5



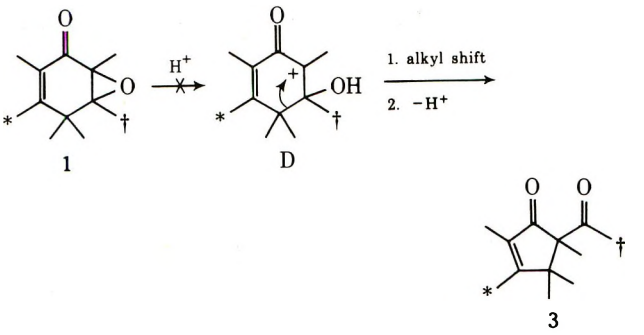
9 **10**

Mechanisms. The mechanisms leading from **1** to **3** and **5** are quite obvious, as shown in Scheme I. The epoxide ring opens to give B, in which the positive charge is remote from the carbonyl group. An acyl shift or a methyl shift, followed by proton loss, leads to **3** and **5**, respectively.

Scheme I



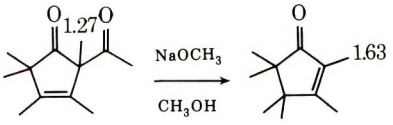
A less likely route to **3** might involve opening the epoxide ring in the opposite sense, to give D, followed by an alkyl shift and proton loss. To distinguish between these alternatives, **1** labeled with CD_3 groups in the positions marked * and † (called **1***,†) was rearranged. The nmr spectrum of the resulting **3** lacked the methyl singlet at δ 1.17 and the allylic signal at δ 1.98, but contained the sharp acetyl methyl singlet at δ 2.01. When **1** labeled with a CD_3 group only at the position marked * (called **1***) was rearranged, the resulting **3** lacked only the signal at δ 1.98. These results show that **3** is formed by the acyl shift mechanism shown in Scheme I (and not *via* D).



The minor product **5**, which was isolated from these labeling experiments when **1*** was the reactant, lacked the signal at δ 2.06 (and that at δ 1.93 became a sharp singlet). Starting with **1***,†, the resulting **5** lacked the δ 2.06 signal and the singlets at δ 1.27 and 0.91 integrated for only 1.5 instead of 3 protons each. This result shows that the methyl shift (B → C) is not stereospecific.[6]

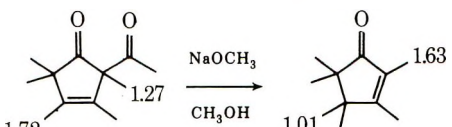
The mechanistic route from **1** to **4** is less obvious. Treatment of **3** with TFA at room temperature for several hours showed that it is stable and does not rearrange to **4**. Treatment of **5** with TFA under similar conditions did give **4**, but much more slowly than the rate at which it is formed from **1**, requiring the existence of a more direct route from **1** to **4**.[7] The labeling results which must be accommodated by such a mechanism are as follows. Starting with **1***, the resulting **4** lacked the allylic methyl signal at δ 1.60 (and the other allylic signal at δ 1.72 sharpened to a singlet). Starting with **1***,†, the product **4** lacked no signals except that at δ 1.60, but the combined areas of the methyl singlets at δ 1.05 and 1.08 was reduced to only three protons.

In order to ascribe meaning to these results it was necessary to establish unequivocally the nmr assignments of **4**. Although the europium shift data support the assignment shown in the structure, they are open to some uncertainty because the molecule contains two functional groups with which coordination of the europium can occur. Consequently, an absolute, though somewhat indirect, route was used. Compound **4** labeled with a CD_3 group at δ 1.27 was obtained from CD_3-labeled **2** (*vide infra*). When this material was cleaved with base, the resulting **7** lacked the allylic methyl signal at δ 1.63 (whose location is unambiguous from both chemical and europium-shift data). Consequently, the methyl in **4** corresponding to the signal at δ 1.27 must be the methyl between the two carbonyl groups. The signals at δ 1.05 and 1.08 in **4** must therefore correspond to the *gem*-dimethyl group.



4 **7**

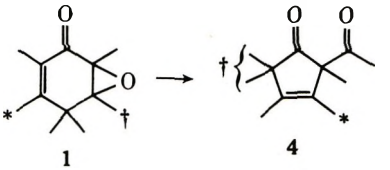
The assignment of the allylic methyl signals was made from yet a differently labeled **4**. Treatment of a particular 2-d_6 with acid (*vide infra*) gave a sample of **4** lacking the methyl signals at δ 1.27 and 1.72. Cleavage of this labeled **4** with base gave **7** lacking the allylic methyl signal at δ



4 **7**

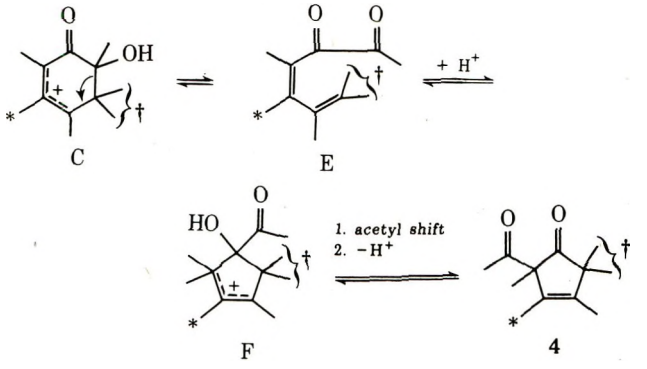
1.63 and the doublet (J = 8 Hz) at δ 1.01. This result establishes unequivocally that the allylic methyl furthest from the acetyl group is at 1.72, and that all the other assignments for 4 are correct as shown in the first structure.

The label result which must be accommodated, in the conversion of 1 → 4, is therefore as shown. One possible



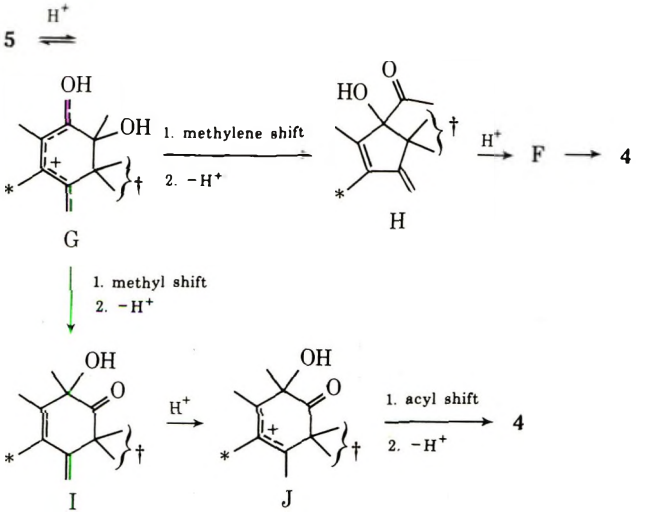
mechanism is shown in Scheme II.[8] Intermediate C (from Scheme I) may either lose a proton to give 5 or may suffer carbon–carbon bond cleavage and proton loss to give the intermediate diketone E. This cleavage of a bond between a tertiary alcohol function and a quaternary carbon might be expected to be facile. Reprotonation of E at the unsaturated carbonyl group should be favored, and recyclization can afford the allylic cation F. Acetyl migration and proton loss completes the reaction.

Scheme II



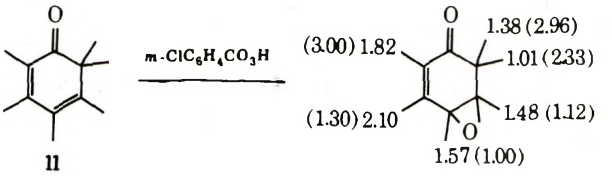
To rationalize the much slower formation of 4 from 5, we suggest (Scheme III) that 5 is protonated preferentially on oxygen to give G, which may rearrange to 4 by either of two routes, the first of which (*via* H) seems the more probable.

Scheme III

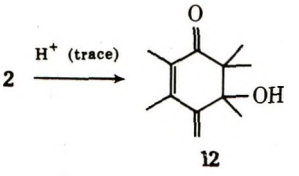


In summary, all three products from the acid-catalyzed isomerization of 1 arise from epoxide ring opening in the direction which places the positive charge remote from the carbonyl group (intermediate ion B). B may rearrange *via* either an acyl shift to give 3 or a methyl shift to give ion C, which in turn may either lose a proton to give 5 or suffer carbon–carbon bond cleavage leading to 4.

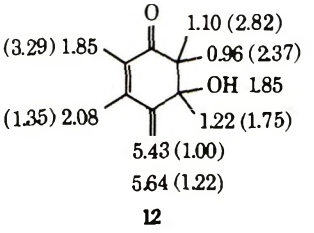
Rearrangement of 2. The epoxy enone 2 has not been previously described. It was obtained as colorless crystals, mp 48–49.5°, in high yield from the corresponding dienone 11. Its infrared and ultraviolet spectra showed that the carbonyl group was still conjugated with a double bond [$\nu_{C=O}$ 1680 cm^{-1}, λ_{max} (cyclohexane) 253 nm (ϵ 7230), 324 (240)], and the nmr spectrum was also consistent with epoxidation having occurred solely at the γ,δ double bond.



The epoxy enone 2 could be purified by chromatography over Florisil or neutral alumina, but it was sensitive to small amounts of acid. Chromatography on silica gel, or treatment with a little aqueous acid, resulted in nearly quantitative rearrangement to a hydroxy ketone assigned structure 12, based on its spectral properties and further

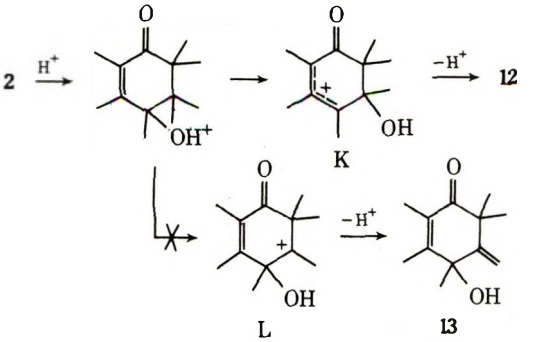


rearrangements in stronger acid (*vide infra*). The ir ($\nu_{C=O}$ 1670 cm^{-1}) and uv [λ_{max} 282 nm (ϵ 11,700), 273 (15,200), 266 (14,500)] spectra support conjugation of the carbonyl group with both double bonds. The ir spectrum also showed a terminal methylene group (960, 930 cm^{-1}) and a hydroxyl group [3620 (sharp, free OH), 3590 (sharp, intramolecular π H bond), 3500 cm^{-1} (broad, intermolecular H bond)]. The nmr spectrum was consistent with the structure.



12 is undoubtedly formed from 2 by proton loss from the intermediate cation K (Scheme IV). The alternative ring-

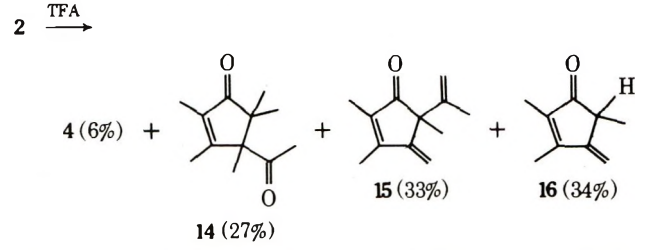
Scheme IV



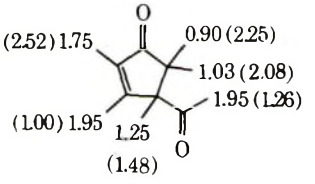
opening mode to give L would lead to structure 13, which is also reasonably consistent with the observed nmr spectrum, but which is less consistent with the uv and ir data and is conclusively eliminated by labeling results. Prepa-

ration of **2** from **11** containing CD_3 groups at C-3 and C-5[9] gave **2**-d_6 lacking methyl signals at δ 1.48 and 2.10. This in turn, with acid, gave **12**-d_6 lacking methyl signals at δ 1.22 and 2.08. Had the hydroxy ketone been **13**, the product would have contained only five deuteriums and would have lacked the vinyl proton signals.

Treatment of **2** with neat trifluoroacetic acid gave four products, only two of which were isomers (mass spectrum) of the starting epoxy enone. One of these was **4**, already identified as a rearrangement product of **1** (*vide supra*). The other products are assigned structures **14**–**16**. The product ratios depend on time, and those shown are for 20 hr at room temperature. Monitoring the products showed that **16** was formed at the expense of **15**, and independent treatment of **15** with TFA showed that it was converted cleanly to **16** and acetone.

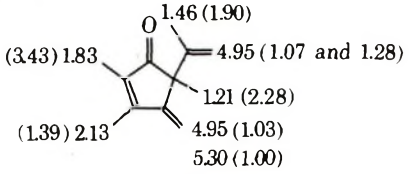


The product structures were established primarily by their spectral properties. The diketone **14** had ir and uv spectra similar to those of **3** but was isomeric with it. The nmr data fit the assigned structure; shift-reagent appears to coordinate primarily at the cyclopentenone carbonyl group. The base peak in the mass spectrum was M − 42 (loss of CH_2=C=O) and the next most intense peak (rel intensity 60) was at M − 57 (loss of CH_2=C=O and CH_3).



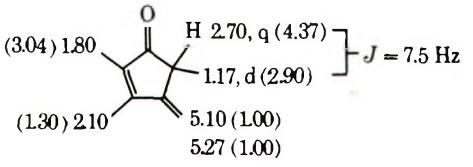
14

The product assigned structure **15** corresponded in analysis to loss of water from the epoxy enone **2**. The nmr spectrum showed four vinyl protons and three allylic methyl groups, as well as one sharp aliphatic methyl singlet. The ir spectrum was consistent with a cyclopentenone carbonyl (1710 cm^{-1}), showing strong carbon-carbon double bond absorptions (1645, 1620 cm^{-1}) and a strong terminal methylene band (915 cm^{-1}). The uv maxima [340 nm (ϵ 63), 270 (13,700)] were consistent with a conjugated dienone.



15

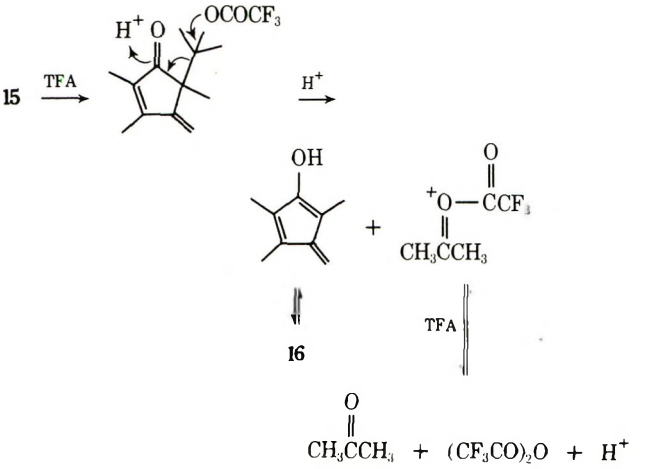
The product assigned structure **16** corresponded in analysis not only to loss of water from the epoxy enone, but a C_3H_4 fragment as well. The uv spectrum was very similar to that of **15** [267 nm (ϵ 15,200)], as was the ir spectrum ($\nu_{C=O}$ 1710, $\nu_{=CH_2}$ 905 cm^{-1}). The nmr spectrum showed two vinyl protons, two allylic methyls, and a >$CHCH_3$ moiety. The proton at δ 2.70 was readily exchanged at room temperature in $NaOCH_3$-CH_3OD, causing collapse of the doublet at δ 1.17 to a singlet.



16

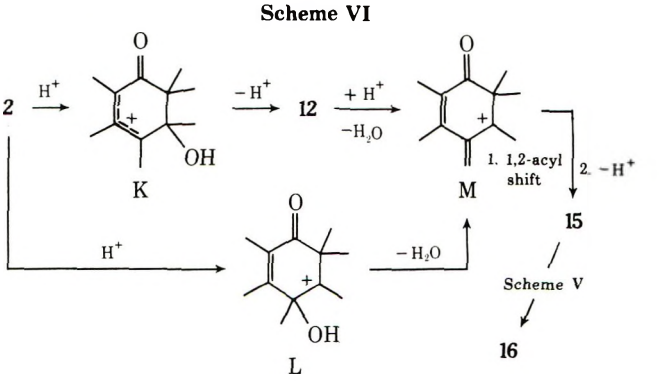
Mechanisms. Scheme V gives a plausible mechanism for the formation of **16** from **15**. When the reaction was carried out in an nmr tube, the appearance of the sharp singlet due to the acetone was observed.

Scheme V



Independent treatment of the hydroxy ketone **12** with TFA at room temperature gave only **15** and **16**, in ratios which depended on the reaction time. After 2 hr the product was 94% **15** and 6% **16**, whereas after 46 hr it was 3% **15** and 97% **16**. These products can be rationalized as in Scheme VI, either with **12** as a discrete intermediate on the route **2** → **12** → **15** → **16** or by-passing **12** *via* intermediate L. If the reaction proceeds *via* L, dehydration may precede the 1,2-acyl shift as shown in Scheme VI, or the order of these steps may be reversed. Unfortunately, no simple experiment can distinguish between these alternatives. It is clear, however, that the remaining two rearrangement products **4** and **14** are not produced from **12**.

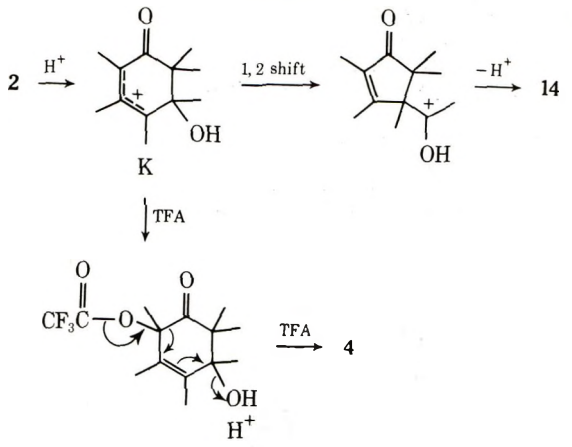
Scheme VI



Possible routes to **4** and **14** are shown in Scheme VII. The first-formed intermediate is once again K; ring contraction and proton loss lead to **14**, whereas attack of a nucleophile at the carbon α to the carbonyl group followed by an acyl shift (again, a ring contraction) and loss of hydroxyl lead to **4**.[10]

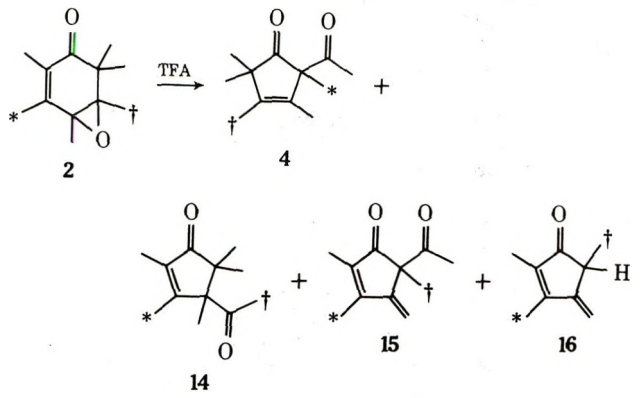
Several labeling experiments were done to test the plausibility of the mechanisms in Schemes VI and VII. The results are shown in Scheme VIII. Experiments were done with trideuterio- (**2***) and hexadeuterio- (**2***,†) epoxy ketone.[11] The mechanisms leading from **2** to **14**–**16** are fairly obvious, and the labeling results fully support the proposals in Schemes VI and VII. The route from **2** to **4** is

Scheme VII



less obvious, but the label results support the mechanism shown in Scheme VIII.[12]

Scheme VIII



In summary, the dienone epoxide **2** rearranges quantitatively in dilute acid to the hydroxy ketone **12** *via* the allylic cation K (Scheme IV). In less basic solvents (such as neat TFA) the same intermediate may rearrange by a 1,2-alkyl shift to give **14** or may, following nucleophilic attack α to the carbonyl group, undergo a ring contraction similar to a benzilic acid rearrangement, leading to **4** (Scheme VII). Product **15** may arise from protonation of **12** or may be formed by the alternate method of epoxide ring opening (*via* L, Scheme VI); product **16** is formed by dealkylation of **15** (Scheme V).

The manner in which the various methyl groups in **1** and **2**, or other substituents, may determine the mode of the acid-catalyzed rearrangements of cyclohexadienone epoxides remains to be further explored, but it is clear from these studies that such reactions can be useful for the synthesis, for example, of cyclopentenones.

Experimental Section[13]

Acid-Catalyzed Rearrangement of 2,3-Epoxy-2,3,4,4,5,6-hexamethyl-5-cyclohexenone (1). A solution containing 200 mg of **1**[2] and 2 ml of trifluoroacetic acid, prepared at 0°, was allowed to stir for 3 hr. The mixture was then poured into cold Na_2CO_3 solution and extracted several times with ether. The combined ether extracts were washed successively with Na_2CO_3 solution and saturated NaCl solution, and dried ($MgSO_4$). After solvent removal, the residue was subjected to analytical gas chromatography (vpc, 5 ft × 0.125 in. 20% FFAP on Chromosorb W, 150°) and showed three main products: **3**[2] (50%, retention time 7.1 min), **4** (35%, 2.5 min) and **5** (10%, 4.8 min). The products were separated by preparative vpc on a similar column. The mixture of **4** and **5** could also be separated from **3** by column chromatography on silica gel using hexane–ether (10:1), the last fractions being pure **3**. The mass spectrum of each product had a parent peak at *m/e* 194, establishing that they were all isomers of **1**.

2-Acetyl-2,3,4,5,5-pentamethyl-3-cyclopentenone (**4**) had ir (neat) 1740 (s), 1710 (s), 1455 (w, br), 1370 (w), 1270 (w), 1210 (w), 1140 (w), 1100 (w), 1035 cm^{-1} (w); uv (95% ethanol) 282 nm (ϵ 81), 203 (3560); nmr (CCl_4) see structure; the peaks at δ 1.60 and 1.72 were mutually coupled quartets, J = 1.5 Hz; mass spectrum (70 eV) *m/e* (rel intensity) 194 (<1), 152 (94), 137 (100), 123 (22), 109 (12), 91 (12), 81 (27), 67 (14), 43 (55).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 73.94; H, 9.41.

6-Hydroxy-4-methylene-2,3,5,5,6-pentamethyl-2-cyclohexenone (**5**) had ir (neat) 3500 (m, br), 1660 (s), 1470 (w), 1440 (m), 1380 (m), 1340 (m), 1215 (w), 1160 (w), 1125 (w), 1105 (w), 1085 (w), 1040 (m), 935 cm^{-1} (m); uv (95% ethanol) 281 nm (ϵ 7500); nmr (CCl_4) see structure; the peaks at δ 1.93 and 2.06 were mutually coupled quartets, J = 1.0 Hz.

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 73.75; H, 9.37.

Preparation and Rearrangement of 2,3-Epoxy-5-trideuteriomethyl-2,3,4,4,6-pentamethyl-5-cyclohexenone (1*). To a solution of 1.0 g of unlabeled **1**[2] in 5 ml of dimethyl sulfoxide-d_6, N_2 atmosphere, was added slowly with stirring 0.8 g of potassium *tert*-butoxide. The mixture was stirred at room temperature for 1 hr, quenched in ice–water, and extracted with ether. The organic layer was dried ($MgSO_4$) and solvent was evaporated to give a nearly quantitative yield of **1***. Its nmr spectrum was identical with that of **1**[2] except for the absence of the peak at δ 1.81 (C-5 methyl) and a sharpening to a singlet of the peak at δ 1.74 (C-6 methyl).

Treatment of **1*** with TFA as described for unlabeled **1** afforded **3*** (lacked the C-3 signal at δ 1.98, and the C-2 signal at δ 1.70 sharpened to a singlet), **4*** (lacked the C-3 signal at δ 1.60, and the C-4 signal at δ 1.72 sharpened to a singlet), and **5*** (lacked the C-3 signal at δ 2.06, and the C-2 signal at δ 1.93 sharpened to a singlet).

Rearrangement of 2,3-Epoxy-3,5-trideuteriomethyl-2,4,4,6-tetramethyl-5-cyclohexenone (1*·†). Labeled epoxy ketone, treated with TFA as described for unlabeled **1**, gave **3*·†** (sharp singlets, equal in area, at δ 1.02, 1.10, 1.70, and 2.01), **4*·†** [sharp singlets at δ 1.05 and 1.08 (total area 3 H), and at δ 1.27, 1.72, and 1.98 (3 H each)], and **5*·†** [singlets at δ 0.91 (1.5 H), 1.00 (3 H), 1.27 (1.5 H), 1.93 (3 H), 3.62 (1 H, br), 6.28 (1 H), and 6.40 (1 H)].

Cleavage of 3 with Base. A solution of **3** (100 mg) and sodium methoxide (20 mg) in 3 ml of methanol was stirred at room temperature for 8 hr. The mixture was poured into ice–water and extracted with ether. The combined ether layers were washed with water and saturated sodium chloride solution and dried ($MgSO_4$). After evaporation of the solvent, the residue was analyzed by vpc (5 ft × 0.125 in., 20% FFAP, 120°) and consisted of 80% recovered recovered **3** (retention time 21 min) and 20% of 2,3,4,4,5-pentamethyl-2-cyclopentenone (**6**), retention time 1.7 min. This product was collected by preparative vpc: ir (neat) 1700 (s), 1650 (s), 1460 (m, br), 1400 (m), 1335 (m), 1235 (w), 1100 cm^{-1} (w, br); nmr (CCl_4) see structure; the peaks at δ 1.02 (3 H) and 1.98 (1 H) were a mutually coupled doublet and quartet, respectively, J = 8.0 Hz, and the peaks at δ 1.62 and 1.92 were mutually coupled quartets, J = 1.0 Hz.

Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.75; H, 10.73.

Cleavage of 4 with Base. The reaction conditions were identical with the conditions given for the cleavage of **3**. Vpc analysis (5 ft × 0.125 in., 20% FFAP, 120°) showed that all of **4** was consumed, the sole product being 2,3,4,5,5-pentamethyl-2-cyclopentenone (**7**), retention time 1.4 min. Pure **7** was collected by preparative vpc: ir (neat) 1700 (s), 1650 (s), 1460 (m, br), 1400 (m), 1335 (m), 1040 cm^{-1} (m, br); uv (95% ethanol) 235 nm (ϵ 6000); nmr (CCl_4) see structure; the peaks at δ 1.01 (3 H) and 2.33 (1 H) were a mutually coupled doublet and quartet, respectively, J = 8.0 Hz, and the peaks at δ 1.63 and 1.95 were mutually coupled quartets, J = 1.0 Hz. Treatment of **7** with sodium methoxide in excess methanol-*d* for several hours at room temperature, followed by work-up, gave **7**-d_4 whose nmr spectrum lacked the quartets at δ 1.95 (3 H), and 2.33 (1 H), the three-proton peaks at δ 1.01 and 1.63 now becoming sharp singlets.

Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.75; H, 10.71.

Cleavage of **4**-d_3 lacking the singlet at δ 1.27 (*vide infra*) gave **7**-d_3 lacking the signal at δ 1.63 and with the peak at δ 1.95 a sharp singlet. Cleavage of **4**-d_6 lacking the methyl signals at δ 1.27 and 1.72 (*vide infra*) gave **7**-d_6 lacking the quartet at δ 1.63 and the doublet at δ 1.01, and having the signal at δ 1.95 a sharp singlet and that at δ 2.33 a broadened one-proton singlet.

Treatment of 3 with TFA. To 8 mg of vpc-collected **3** cooled in an ice bath was added dropwise 1 ml of TFA. The solution was stirred at 0° for 4 hr, then quenched with ice-cold $NaHCO_3$ solution and extracted with ether. The ether layer was washed successively with cold $NaHCO_3$ solution and saturated NaCl solution, then dried and analyzed by vpc as in the rearrangement of **1**. The only product was recovered **3**.

Treatment of 5 with TFA. To 10 mg of vpc-collected **5** cooled in an ice bath was added dropwise 1 ml of TFA. The solution was stirred at 0°. After 0.5 hr an aliquot was withdrawn, quenched, worked up, and analyzed as above. It consisted of 7% **4** and 93% recovered **5**. After 4 hr, the product consisted of 10% **4** and 90% recovered **5**.

4,5-Epoxy-2,3,4,5,6,6-hexamethyl-2-cyclohexenone (2). To a solution of 0.600 g (3.37 mmol) of 2,3,4,5,6,6-hexamethyl-2,4-cyclohexadienone (**11**)[9] in 10 ml of methylene chloride was added, at 0°, a solution of 0.620 g (3.60 mmol) of *m*-chloroperbenzoic acid in 10 ml of methylene chloride. The mixture was stirred for 2 hr at 0°, during which time *m*-chlorobenzoic acid precipitated from solution. The solvent was evaporated, petroleum ether (bp 30–60°) was added to the residue, and the *m*-chlorobenzoic acid was removed by filtration. Evaporation of the solvent from the filtrate left 0.648 g of a light yellow oil; an nmr spectrum of the crude material showed it to be >90% **2**. The crude product was chromatographed on Florisil using ether–hexane (1:10) as eluent, to give 0.523 g (2.70 mmol, 80%) of epoxide **2**: mp 48–49.5°; ir (KBr) 2970 (m), 2920 (m), 2860 (w), 1680 (s), 1465 (m), 1380 (m), 1310 (m), 1070 (m), 840 cm^{-1} (s); uv (cyclohexane) λ_{max} 253 nm (ϵ 7230); nmr ($CDCl_3$) see structure; all peaks had equal areas; all were sharp singlets except those at δ 1.82 and 2.10, which were mutually coupled quartets, J = 1.0 Hz; mass spectrum (70 eV) *m/e* (rel intensity) 194 (14), 179 (14), 178 (19), 163 (18), 152 (46), 151 (70), 147 (21), 137 (29), 135 (25), 126 (29), 124 (29), 123 (27), 109 (31), 91 (16), 81 (30), 43 (100).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.06, H, 9.32.

Similar oxidation of **11** with a CD_3 group at C-3[9] gave **2*** whose nmr spectrum lacked the quartet at δ 2.10, and with the quartet at δ 1.82 sharpened to a singlet. Oxidation of **11** with CD_3 groups at C-3 and C-5[9] gave **2***† whose nmr spectrum, in addition to the changes just cited, lacked the singlet at δ 1.48.

4-Methylene-5-hydroxy-2,3,5,6,6-pentamethyl-2-cyclohexenone (12). To a solution of **2** (0.250 g, 1.29 mmol) in ether (15 ml) at 0° was added a solution of trifluoroacetic acid (0.5 ml) in water (5 ml). After the mixture was stirred for 0.5 hr, the layers were separated, and the ether layer was washed successively with saturated $NaHCO_3$ solution, water, and saturated NaCl solution, and dried ($MgSO_4$). Evaporation of the ether left 0.238 g (95%) of the hydroxy ketone **12** as a colorless liquid which was not further purified: ir (CCl_4) 3620 (w, sharp), 3590 (w, sharp), 3500 (m, br), 2980 (s), 2930 (m), 2870 (w), 1670 (s), 1590 (w), 1460 (w), 1380 (s), several w bands from 1350–1170, 1150 (m), 1130 (w), 1070 (m), 1040 (m), 1010 (w), 960 (m), 930 cm^{-1} (m). The bands at 3620 and 3590 cm^{-1} did not change in relative intensity as a function of the concentration of **12** in CCl_4, whereas the intensity of the band at 3500 cm^{-1} decreased drastically with a decrease in concentration of **12**: uv (cyclohexane) 282 nm (ϵ 11,700, sh), 273 (15,200), 266 (14,500, sh); nmr (CCl_4) see structure; the peaks at δ 1.85 and 2.08 were broadened, all other peaks being sharp singlets; mass spectrum (70 eV) *m/e* (rel intensity) 194 (29), 179 (31), 176 (8), 161 (16), 151 (100), 137 (30), 133 (44), 123 (15), 121 (15), 109 (26), 105 (15), 91 (23), 83 (16), 79 (23), 78 (25), 67 (13), 65 (15), 56 (18), 54 (26), 51 (15), 43 (80), 39 (42).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.05; H, 9.36.

Treatment of **2***† with aqueous TFA as above gave **12**-d_6 with the following nmr spectrum: δ 0.96 (s, 3 H), 1.10 (s, 3 H), 1.85 (s, 3 H), 5.43 (s, 1 H), 5.64 (s, 1 H).

Rearrangement of 2 in Neat Trifluoroacetic Acid. A solution of 0.100 g (0.515 mmol) of **2** in 2 ml of ice-cold trifluoroacetic acid was stirred at 0° for 1 hr, then at room temperature for 20 hr. The reaction was monitored by nmr after the spectrum of each product had been determined. The reaction was quenched by pouring the mixture into ice and saturated $NaHCO_3$ solution. The products were extracted with ether, and the combined ether layers were washed successively with saturated $NaHCO_3$ solution, water, and saturated NaCl solution and dried ($MgSO_4$). Evaporation of the solvent left 0.092 g of a light yellow liquid which was analyzed by vpc (5 ft × 0.125 in., 10% FFAP on Chromosorb W, AW-DMCS 80/100, 160°, 30 ml/min). Four products (retention time in minutes, %) were observed: **4** (1.5, 6), **14** (4.4, 27), **15** (1.8, 33), **16** (1.2, 34). At 150° the retention times were respectively 3.5, 10.9, 4.0, and 2.5 min. After only 30 min reaction time, the yields follow: **4** (7%), **14** (32%), **15** (53%), **16** (8%). After 20 hr, the respective yields were 6, 27, 33, and 34%. The ratio of **4**:**14**:(**15** + **16**) was time independent, but the yield of **16** increased with reaction time at the expense of **15**.

The products from this and larger scale experiments were separated by preparative vpc (10 ft × 0.25 in., 20% FFAP on Chromosorb W P/G 30/60, 160°). The spectral data for 2-acetyl-2,3,4,5,5-pentamethyl-3-cyclopentenone (**4**) have been presented (*vide supra*).

4-Acetyl-2,3,4,5,5-pentamethyl-2-cyclopentenone (**14**) had ir (CCl_4) 2970 (s), 2940 (m), 2920 (m), 2860 (w), 1710 (s), 1660 (s), several medium-intensity bands at 1475–1400, 1380 (m), 1350 (m), 1320 (m), 1215 (m), 1150 (m), 1075 (m), 1025 (m), 960 cm^{-1} (w); uv (cyclohexane) 237 nm (ϵ 7720), 209 (6000); nmr (CCl_4) see structure; the bands at δ 1.75 and 1.95 were mutually coupled, J = 1.0 Hz; mass spectrum (70 eV) *m/e* (rel intensity) 194 (1.5), 179 (1.0), 166 (1.0), 152 (100), 137 (60), 123 (53), 109 (9), 95 (8), 93 (9), 91 (12), 81 (35), 67 (12), 55 (12), 53 (12).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.25; H, 9.29.

5-Isopropenyl-4-methylene-2,3,5-trimethyl-2-cyclopentenone (**15**) had ir (CCl_4) 3080 (w), 2965 (s), 2910 (s), 2865 (m), 1710 (s), 1645 (s), 1620 (s), 1455 (s), 1400 (s), 1370 (m), 1340 (w), 1290 (m), 1175 (w), 1160 (w), 1120 (w), 1030 (m), 1010 (w), 915 cm^{-1} (s); uv (cyclohexane) 278 nm (ϵ 10,030, sh), 270 (13,700) 262 (11,070, sh); nmr (CCl_4) see structure; the band at δ 1.46 was a doublet, J = 1.7 Hz, those at δ 1.83 and 2.13 were broadened by mutual coupling, that at δ 4.95 was a multiplet (three vinyl protons), and that at δ 5.30 was a broadened singlet. The peak at δ 1.21 was a sharp singlet: mass spectrum (70 eV) *m/e* (rel intensity) 176 (13), 161 (34), 148 (24), 133 (100), 105 (31), 91 (35), 79 (19), 77 (26), 65 (16), 53 (14), 51 (19), 41 (37), 39 (41).

Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.72; H, 9.11.

4-Methylene-2,3,5-trimethyl-2-cyclopentenone (**16**) had ir (CCl_4) 3080 (w), 2960 (m), 2925 (m), 2860 (w), 1710 (s), 1640 (s), 1620 (s), several medium-intensity bands at 1460–1375, 1340 (w), 1310 (m), 1265 (m), 1145 (w), 1120 (m), 1050 (m), 990 (m), 905 cm^{-1} (s); uv (cyclohexane) 275 nm (ϵ 10,020, sh), 267 (15,200), 258 (13,450, sh); nmr (CCl_4) see structure; the peaks at δ 1.80 and 2.10 were broadened by mutual coupling, and the singlets at δ 5.10 and 5.27 were also broad; mass spectrum (70 eV) *m/e* (rel intensity) 136 (35), 121 (13), 93 (100), 91 (37), 79 (19), 77 (36), 67 (16), 65 (13), 55 (11), 54 (23), 53 (25), 52 (12), 51 (23), 50 (10), 41 (18), 39 (44).

Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found C, 79.15; H, 9.04.

A solution of **16** (50 mg, 0.368 mmol) in 4 ml of CH_3OD containing 54 mg (1.0 mmol) of sodium methoxide was stirred for 1 hr at room temperature, then quenched with 15 ml of D_2O and extracted three times with pentane (10 ml). Combined organic layers were washed with water (twice) and saturated NaCl solution and dried ($MgSO_4$). Evaporation of the solvent left 45 mg of **16**-d_1 with the following nmr (CCl_4): δ 1.17 (s, 3 H), 1.80 (br s, 3 H), 2.10 (br s, 3 H), 5.10 (br s, 1 H), 5.27 (br s, 1 H).

Treatment of 5-Isopropenyl-4-methylene-2,3,5-trimethyl-2-cyclopentenone (15) with TFA. A solution of **15** (0.060 g, 0.34 mmol) in 1 ml of trifluoroacetic acid was allowed to stand at room temperature for 20 hr, the reaction being monitored by nmr. During the reaction, a sharp singlet appeared at δ 2.33, shown to correspond to acetone in TFA. The reaction was quenched by pouring it into ice and saturated $NaHCO_3$ solution. The mixture was extracted with ether, and the ether extract was worked up and analyzed as in the rearrangement of **2**. The sole components (determined by vpc) after 20 hr were **15** (55%) and **16** (45%). When the reaction was carried out at higher temperatures, conversion to **16** was quantitative.

Rearrangement of 5-Hydroxy-4-methylene-2,3,5,6,6-pentamethyl-2-cyclohexenone (12) in TFA. A solution of **12** (0.100 g, 0.515 mmol) in 1.5 ml of trifluoroacetic acid was stirred at room temperature. Aliquots were withdrawn at various time intervals, quenched and worked up as usual, and analyzed by vpc (5 ft × 0.125 in., 10% FFAP on Chromosorb W, AW-DMCS 80/100, 150°, N_2 flow rate 30 ml/min). Only two components were present, **15** (4.0 min) and **16** (2.5 min), identified by nmr and ir. The relative amounts at various time intervals follow: 2 hr, 94% **15**, 6% **16**; 26 hr, 32% **15**, 68% **16**; 46 hr. 3% **15**, 97% **16**.

Rearrangement of Labeled 2 in TFA. A solution of **2*** (lacking the signal at δ 2.10; 500 mg, 2.58 mmol) in 5 ml of TFA was

stirred at room temperature for 21 hr, then quenched and worked up as described for unlabeled **2**. The products had the following nmr spectra (CCl_4): **4**, δ 1.05 (s, 3 H), 1.08 (s, 3 H), 1.60 (m, 3 H), 1.72 (m, 3 H), 1.98 (s, 3 H); **14**, δ 0.90, 1.03, 1.25, 1.75, and 1.95, all s, 3 H; **15**, δ 1.21 (s, 3 H), 1.46 (d, 3 H, J = 1.7 Hz), 1.83 (s, 3 H), 4.95 (m, 3 H), 5.30 (br s, 1 H); **16**, δ 1.17 (d, 3 H, J = 7.5 Hz), 1.80 (s, 3 H), 2.70 (q, 1 H, J = 7.5 Hz), 5.10 (br s, 1 H), 5.27 (br s, 1 H).

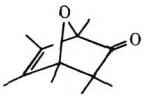
A solution of **2***·† (lacking the signals at δ 2.10 and 1.48) in TFA was allowed to rearrange in the amounts and manner described for **2***. The products had the following nmr spectra (CCl_4): **4**, δ 1.05, 1.08, 1.60, and 1.98 (all s, 3 H); **14**, δ 0.90, 1.03, 1.25, and 1.75 (all s, 3 H); **15**, δ 1.46 (d, 3 H, J = 1.7 Hz), 1.83 (s 3 H), 4.95 (m, 3 H), 5.30 (br s, 1 H); **16**, δ 1.80 (s, 3 H), 2.70 (br s, 1 H), 5.10 (br s, 1 H), 5.27 (br s, 1 H).

Acknowledgment. We are indebted to the National Institutes of Health and the National Science Foundation for their support of this research.

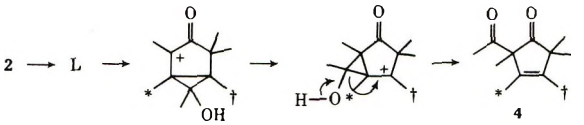
Registry No.—**1**, 40940-60-1; **1**-d_3, 50506-40-6; **1**-d_6, 50506-41-7; **2**, 50506-42-8; **2**-d_3, 50506-43-9; **2**-d_6, 50506-44-0; **3**, 40940-46-3; **3**-d_3, 50506-46-2; **3**-d_6, 50506-47-3; **4**, 50506-48-4; **4**-d_3, 50506-49-5; **4**-d_6, 50506-50-8; **5**, 50506-51-9; **5**-d_3, 50506-52-0; **5**-d_6, 50506-53-1; **6**, 50506-54-2; **7**, 50506-55-3; **11**, 3854-96-4; **12**, 50506-57-5; **12**-d_6, 50506-58-6; **14**, 50506-59-7; **15**, 50506-60-0; **16**, 29765-85-3.

References and Notes

(1) R. E. Parker and N. S. Isaacs, *Chem. Rev.*, **59**, 737 (1959); M. S. Malinovskii, "Epoxides and Their Derivatives," Daniel Davey, New York, N. Y., 1965; H. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, Menlo Park, Calif., 1972, p 320.
(2) H. Hart, M. Verma, and I. Wang, *J. Org. Chem.*, **38**, 3418 (1973).
(3) Corresponding respectively to the cyclopentenone and acetyl moieties: K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, San Francisco, Calif., 1962, p 42.
(4) Shown in δ units, with the relative downfield shifts in the presence of Eu(fod)$_3$ given in parentheses; see D. R. Kelsey, *J. Amer. Chem. Soc.*, **94**, 1764 (1972).
(5) All peaks were sharp three-proton singlets except for those at δ 1.60 and 1.72, which were homoallylically coupled (J = 1.5 Hz). The acetyl methyl (δ 1.98), allylic methyls (δ 1.60, 1.72), and aliphatic methyls are readily assigned using chemical shifts. Specific assignments within the last two categories are based on labeling experiments to be described below.
(6) This result also argues against structures **9** and **10** for the hydroxy ketone. The most plausible route to **9** would involve proton loss from B; in this event, product from **1***·† should lack the vinyl protons. The most plausible route to **10** would involve proton loss from D; in this event, product from **1***·† should lack two methyl signals. The label results fit neither of these predictions.
(7) The kinetic experiments require that, when starting from **1**, less than 3% of **4** is produced from **5**; over 97% must be obtained directly from **1**.
(8) One can envision several other plausible mechanisms for the conversion of **1** to **4**. The most attractive of these involved cyclopropylcarbinyl cations derived from participation of the double bond in B. However, none of these fit the observed labeling results.
(9) H. Hart, P. M. Collins, and A. J. Waring, *J. Amer. Chem. Soc.*, **88**, 1005 (1966). (See particularly footnote 16.)
(10) The nucleophile shown is TFA, but may also be water or may even be the hydroxyl group, *via* an intermediate such as



(11) It was from these experiments that **4**, lacking only the singlet at δ 1.27, or lacking both signals at δ 1.27 and 1.72 referred to earlier, was obtained.
(12) Plausible alternative routes from **2** to **4** can be envisioned but can be eliminated as a consequence of the labeling experiments. One example, involving cyclopropylcarbinyl rearrangements, is



(13) Melting points are uncorrected. Analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. Ir spectra were calibrated against a polystyrene film; nmr spectra are referenced against tetramethylsilane.

Notes

Acid-Catalyzed Rearrangement of an Epoxy Ketone by Competitive Protonation at Each Oxygen

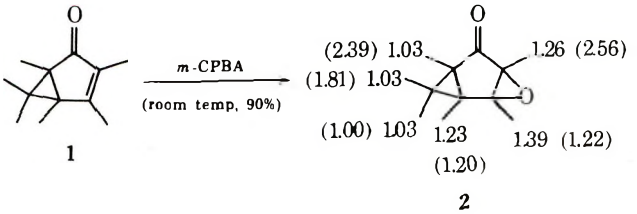
Harold Hart* and Irene Huang

Department of Chemistry, Michigan State University, East Lansing, Michigan 48824

Received September 6, 1973

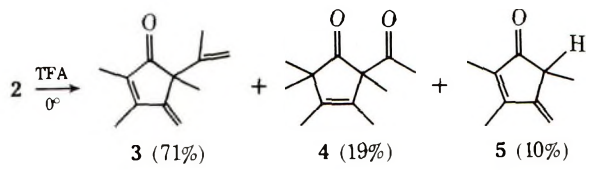
In general, the acid-catalyzed rearrangement of epoxy ketones is initiated by protonation of the epoxide oxygen atom.[1] We describe here the rearrangement of an epoxy ketone to two principal products, one of which appears to arise from protonation of the carbonyl oxygen.

3,4-Epoxy-1,3,4,5,6,6-hexamethylbicyclo[3.1.0]hexan-2-one (**2**) was prepared in good yield from the corresponding unsaturated ketone **1**[2] and *m*-chloroperbenzoic acid. The structure is based on the method of synthesis and spectral properties. The $\nu_{C=O}$ in **2** was at 1715 cm^{-1} (1690 cm^{-1} in **1**). The nmr spectrum[3] showed that all methyl signals were aliphatic (δ ≤1.39), and europium shift reagent removed the accidental degeneracy of three methyls at δ 1.03 and gave a spectrum with six sharp, equal singlets. Vpc and nmr analysis showed that only a single stereoisomer of **2** was produced; the equal chemical shifts of the two methyl groups at C-6 suggest that the epoxide ring is trans to the cyclopropane ring. Epoxide prepared from **1** with a CD_3 group at C-4 lacked the singlet at δ 1.39 (**2***); epoxide prepared from **1** with CD_3 groups at C-1 and C-4 lacked the singlet at δ 1.39, and that at δ 1.03 was reduced in area to six protons (**2***·†). The labeling and Eu-shift data support the nmr assignments shown in the structure.



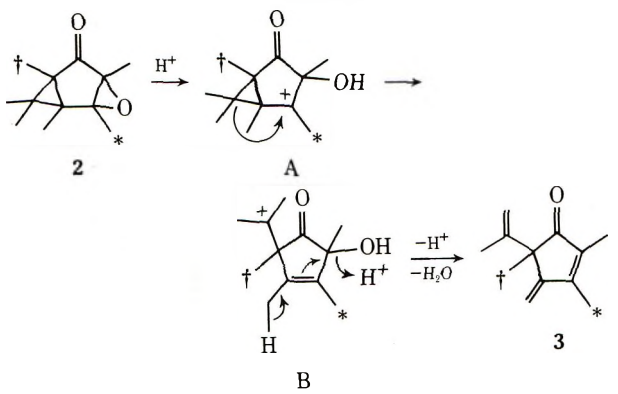
1 2

Treatment of **2** with trifluoroacetic acid (TFA) at 0° for 10 min resulted in complete rearrangement to **3** and **4**. Also formed was a small amount of **5** which is known to arise from the dealkylation of **3**.[4] The properties and structure proof of **3**–**5** are described elsewhere.[4]



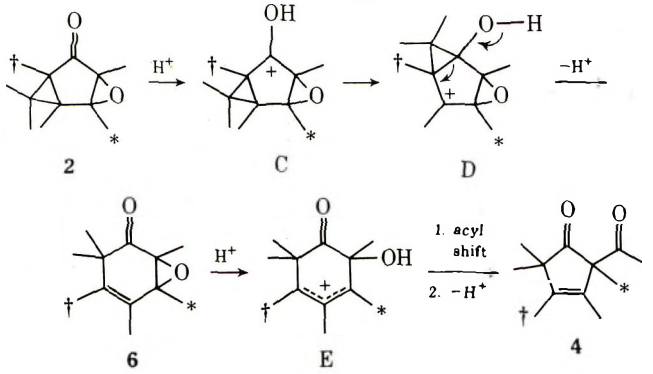
A plausible mechanistic route to 3 *is shown in* Scheme I. Protonation of the epoxide oxygen by ring opening in a direction which places the positive charge remote from the carbonyl group gives the intermediate cyclopropylcarbinyl cation A. Ring opening gives the homoallyl cation B, or alternatively B may be formed directly from protonated 2 in a concerted process. Proton loss and dehydration gives 3. Deuterium-labeling results[5] are consistent with this mechanism; 2* gave 3* and 2*·† gave 3*·†.

Scheme I



A mechanism for obtaining 4 from 2, consistent with *the labeling results, is shown in Scheme II.* Protonation at the carbonyl oxygen gives C, which undergoes a cyclopropylcarbinyl rearrangement to D. Such rearrangements are well established and exceedingly facile in the case of protonated 1.[6] Ring opening and proton loss would lead to the α,β-epoxide of hexamethyl-2,4-cyclohexadienone (6). Further rearrangement in a normal manner[4] should lead to 4. No evidence for the presence of 6 in these solutions was obtained, and we must assume that, if formed, it rearranges to 4 under the reaction conditions.[7]

Scheme II



Experimental Section[8]

3,4-Epoxy-1,3,4,5,6,6-hexamethylbicyclo[3.1.0]hexan-2-one (2). To a solution of 1.2 g (6.75 mmol) of 1,3,4,5,6,6-hexamethylbicyclo[3.1.0]hexen-2-one (1)[2] in 20 ml of methylene chloride was added a solution of 1.25 g (7.2 mmol) of *m*-chloroperbenzoic acid in 20 ml of methylene chloride. The mixture was stirred at room temperature for 4 hr (nmr monitoring showed complete reaction *at this time), the solvent was removed by rotary* evaporation, petroleum ether (bp 30–60°) was added, and the *m*-chlorobenzoic acid was removed by filtration. The filtrate was washed with aqueous $NaHCO_3$ and saturated NaCl solution, dried ($MgSO_4$), and evaporated to give 1.17 g (90%) of 2. Vpc (5 ft × 0.125 in., 10% FFAP on Chromosorb W, 150°, 30 ml/min N_2) showed only a single peak, retention time 12.5 min: ir (neat) 1715 (s), 1460 (m), 1395 (m), 1080 (w), 1025 (w), 940 (w), 860 cm^{-1} (w); nmr (CCl_4) see structure; mass spectrum (70 eV) *m/e* 194 (M^+).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.20; H, 9.43.

Starting with 1* (lacking the methyl signal at δ 1.88),[6a] the resulting 2* had the following nmr spectrum (CCl_4): δ 1.03 (s, 9 H), 1.23 (s, 3 H), 1.26 (s, 3 H). Starting with 1*·† (lacking the methyl signal at δ 1.88 and having the singlet at δ 1.10 correspond to only 3 H)[2] the resulting 2*·† had the following nmr spectrum (CCl_4): δ 1.03 (s, 6 H), 1.23 (s, 3 H), 1.26 (s, 3 H).

Rearrangement of 2 in TFA. A solution of 2 (100 mg, 0.517 mmol) in 2 ml of TFA was stirred at 0° for 10 min, then poured into a slurry of aqueous $NaHCO_3$ and ether. The ether layer was separated, washed successively with aqueous $NaHCO_3$ and NaCl solutions, dried ($MgSO_4$), and evaporated to leave 90 mg of a light yellow oil which was analyzed by vpc (5 ft × 0.125 in., 10% FFAP on Chromosorb W, 155°, 30 ml/min N_2). There were three components (retention time, %): 5-isopropenyl-4-methylene-2,3,5-trimethyl-2-cyclopentenone (3, 1.9 min, 71), 2-acetyl-2,3,4,5,5-pentamethyl-3-cyclopentenone (4, 1.6 min, 19) and 4-methylene-2,3,5-trimethyl-2-cyclopentenone (5, 1.3 min, 10). The products were separated by preparative vpc (10 ft × 0.25 in., 20% FFAP on Chromosorb W, 160°, 25 ml/min He) and identified by comparison of their ir and nmr spectra with those of authentic samples.[4]

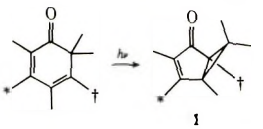
Rearrangement of Labeled 2. The same experimental procedure as described for unlabeled 2 was used. Starting with 2* the products had the following nmr spectra: 3, δ 1.21 (s, 3 H), 1.46 (d, 3 H, J = 1.7 Hz), 1.83 (s, 3 H), 4.95 (m, 3 H), 5.30 (br s, 1 H); 4, δ 1.05, 1.08, 1.98 (s, 3 H each), 1.60, 1.72 (q, 3 H each, J = 1.5 Hz).[9] Starting with 2*·† the products had the following nmr spectra: 3, δ 1.46 (d, 3 H, J = 1.7 Hz), 1.83 (s, 3 H), 4.95 (m, 3 H), 5.30 (br s, 1 H); 4, δ 1.05, 1.08, 1.60, 1.98 (s, 3 H each).

Acknowledgment. We are indebted to the National Institutes of Health for their support of this research.

Registry No.—1, 2206-69-1; 1-d_3, 50507-02-3; 1-d_6, 50507-03-4; 2, 50507-04-5; 2-d_3, 50507-05-6; 2-d_6, 50507-06-7; 3, 50506-60-0; 4, 50506-48-4.

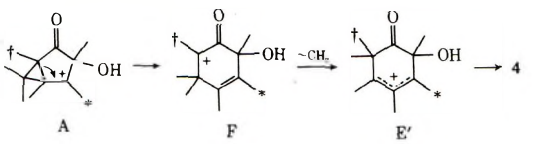
References and Notes

(1) For an example, see House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, Menlo Park, Calif., 1972, p 320.
(2) H. Hart, P. M. Collins, and A. J. Waring, *J. Amer. Chem. Soc.*, **88**, 1005 (1966).
(3) Shown in δ units, with the relative downfield shifts in the presence of Eu(fod)$_3$ given in parentheses; see D. R. Kelsey, *J. Amer. Chem. Soc.*, **94**, 1764 (1972).
(4) H. Hart, I. Huang, and P. Lavrik, *J. Org. Chem.*, **39**, 999 (1974).
(5) Hexamethyl-2,4-cyclohexadienone is labeled selectively at C-3 under mild conditions, or at C-3 and C-5 under more strenous conditions, or (by back exchange of doubly labeled material under mild conditions) at C-5. For proof, see ref 2, particularly footnote 16. Irradiation of the dienone labeled C-3 (*) and/or C-5 (†) gives specifically labeled 1 which, in turn, can be epoxidized to the required labeled 2.



1

(6) (a) D. W. Swatton and H. Hart, *J. Amer. Chem. Soc.*, **89**, 5075 (1967); (b) H. Hart, T. R. Rodgers, and J. Griffiths, *ibid.*, **91**, 754 (1969).
(7) An alternative route from 2 to 4 which involves initial protonation at the epoxide oxygen (as in Scheme I) is shown. Ring opening of A gives F; a 1,2-methyl shift gives E' (identical with E in Scheme II, except for the label), which can further rearrange to 4. This mechanism is inconsistent with the label results and can be unequivocally ruled out. Since F has a positive charge adjacent to the carbonyl group, it is probably a high-energy intermediate.



(8) Analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. Nmr spectra were internally referenced against tetramethylsilane.
(9) Compound 5 was not examined, since the mechanism of its formation from 3 has already been established.[4]

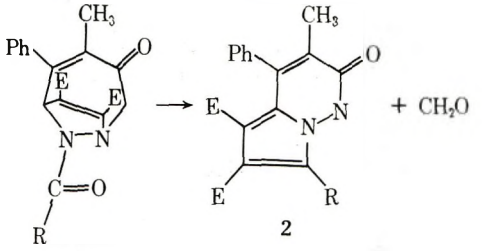
Heterocyclic Studies. 43. The Crystal Structure of 2,3,4,7-Tetrahydro-3a,4-bis(methoxycarbonyl)-2,6-dimethyl-5-phenylindazol-7-one

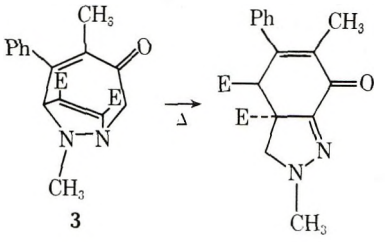
Richard C. Gearhart, Robert H. Wood, Patricia C. Thorstenson, and James A. Moore*

Department of Chemistry, University of Delaware, Newark, Delaware 19711

Received July 30, 1973

We recently described the thermal reaction of the 9-acyldiazabicyclic ketone **1** to give pyrrolopyridazine **2** and formaldehyde;[1] the same reaction occurs also on treatment of **1** with acid or base. The reactions of the 9-methyl ketone **3**[2] present a marked contrast. Different product mixtures are obtained with base, with acid, and with heat. Two rearrangement products have been isolated and characterized from thermolysis of **3**. This note describes the structure determination of one of these products, the tetrahydroindazolone **4**.

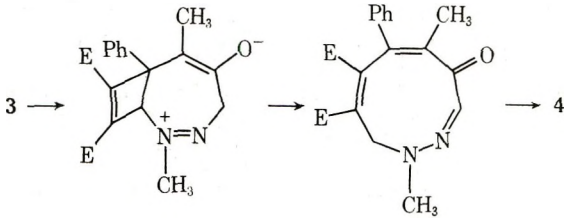




Compound **4** and an isomer were produced in approximately equal amounts (*ca.* 10–15% yields of crystalline compounds) on heating **3** for 90 min in a melt at 170°. (The same products were obtained very slowly on heating **3** in a sealed tube in benzene solution at 150°.) The products were separated by chromatography; **4** was the more polar substance. Compound **4** crystallized in pale yellow prisms; the nmr spectrum contained the expected methyl and phenyl peaks, an AB pattern at δ 3.34 (1 H) and 4.06 (1 H, J = 12 Hz) and a doublet (1 H, J = 0.8 Hz) at 4.32 ppm.

Structure **4** was established by single-crystal X-ray analysis. Table I[4] gives the fractional atomic coordinates and thermal parameters (with their respective estimated standard deviations) for the atoms comprising **4**; Figure 1 is a stereodrawing of the molecule. All bond lengths and bond angles for the structure are within the expected ranges tabulated in the literature.[3,4]

Structure **4** represents the original diazepine framework with the two carbon bridge shifted to a new location. One of several possible rationalizations of the reaction is the formation and cyclization of a diazonine intermediate. Discussion of the mechanism will be deferred until information is available on other products.



Experimental Section

Thermolysis of 3. A 0.3-g sample of the *N*-methylbicyclic ketone **3** (mp 103°) in a small test tube was heated in an oil bath at 170° for 90 min. Tlc (ether–pentane) showed the appearance of two products: A, colorless (visualized with I_2), slightly slower moving than unreacted **3**, and B, yellow, moving about one-fifth as fast as **3**.

The dark oil was chromatographed in $CHCl_3$ on 10 g of SiO_2. Two fractions were obtained; the first contained product A and unreacted **3**. Crystallization of this fraction gave 30 mg of compound A: mp 160–163°; ν (KBr) 1730, 1700, 1610 (s), 1550 cm^{-1}; δ ($CDCl_3$) 1.88 (d, 3, J = 1 Hz), 2.67 (s, 3), 3.88 (s, 3), 3.92 (s, 3), 4.49 (br s, 1), 4.74 (d, 1, J = 1.8 Hz), 4.94 (d, 1, J = 1.8 Hz) (the 4.74 and 4.94 signals are not a symmetrical AB pattern), 7.39 (m, 5). Recrystallization from ether gave colorless crystals, mp 165–167°.

Anal. Calcd for $C_{19}H_{20}N_2O_5$: C, 64.03; H, 5.66; N, 7.86. Found: C, 63.26, H, 5.51; N, 7.60.

The second fraction from the column contained product B, identified as indazolone **4**. Preparative tlc gave a bright yellow band from which 40 mg of yellow crystals of **4** were obtained: mp 117–119°; ν (KBr) 1720, 1650, 1620 (w), 1550; nmr, see text.

Anal. Calcd for $C_{19}H_{20}N_2O_5$: C, 64.03; H, 5.66; N, 7.86. Found: C, 64.00; H, 5.60; N, 7.86.

Slow crystallization from ether gave well-formed crystals, mp 120°, used for X-ray analysis.

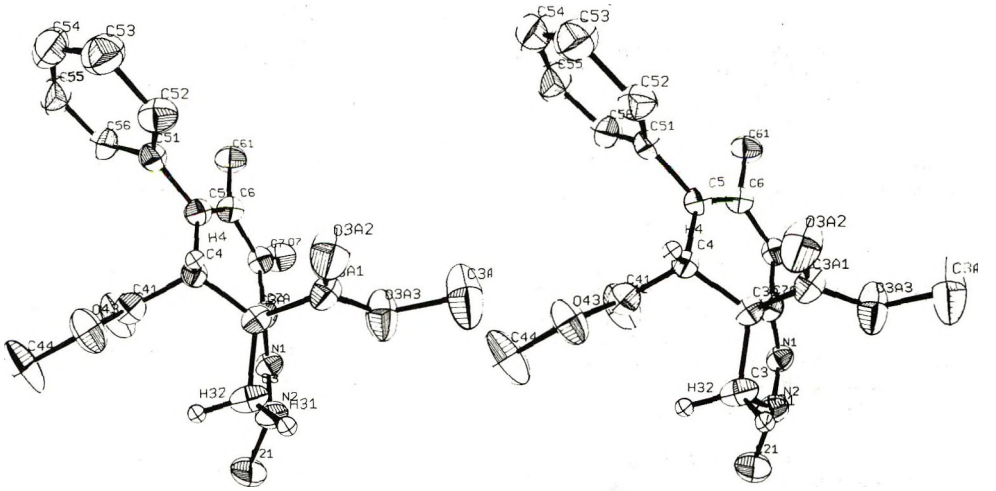


Figure 1. ORTEP stereodrawing of 2,3,4,7-tetrahydro-3a,4-bis(methoxycarbonyl)-2,6-dimethyl-5-phenylindazol-7-one showing 50% probability ellipsoids. For clarity, ring and methyl hydrogens are excluded.

X-Ray Crystallography. Crystals were received as prismatic needles; a sample showing good crystal quality under microscopic examination, with and without polarized light, was chosen from the batch. The sample was approximately 0.3 × 0.2 × 0.5 mm and was mounted with the largest dimension as the goniometer rotation axis.

Preliminary precession camera investigation showed the unit cell to be monoclinic with a choice of either $P2_1/c$ or $P2_1/n$ as the space group; because of the near-cubic geometry of the resulting unit cell, $P2_1/n$ was chosen for indexing [general positions $\pm(x,y,z; x+\frac{1}{2}, y-\frac{1}{2}, z+\frac{1}{2})$].

Precision lattice constants were obtained by least-squares refinement[5] of 2θ diffractometer angular settings on 18 independent reflections within the range $23 < 2\theta < 43°$ (λ 0.7107 Å, Mo Kα radiation). This calculation gave a = 14.148 (4), b = 11.432 (1), c = 11.318 (4) Å, β = 97.50 (4)°. Assuming four formula units per cell, the calculated density, ρ_{calcd}, was found to be 1.304 (6) g/cm^3, which agrees favorably with the experimental density (determined by immersion in a mixed solvent of equal density) of 1.32 g/cm^3 at room temperature.

The linear absorption coefficient, μ, for the compound is 1.04 cm^{-1} for Mo Kα radiation. An absorption correction for data collected using Mo Kα radiation was, therefore, deemed unnecessary.

Approximately 2400 independent reflections in the range $0.05 < \sin\theta/\lambda < 0.75$ were measured by the θ–2θ scanning technique using a card-controlled Picker diffractometer. With 235 parameters to be set in the final anisotropic model (excluding hydrogens), this gives approximately ten reflections per parameter to be set.

Diffracted intensities were measured at a take-off angle of about 2°; the range of each scan, at a rate of 2°/min, consisted of a reflection base width of 2° and an increment, $\Delta(2\theta) = (0.285 \tan\theta)°$, to allow for spectral dispersion. Background counts, for 30-sec duration, were taken at the limits of the scan. The intensities of three standard reflections were monitored at intervals of 50 data points as alignment checks while these three plus three others were used at roughly 12-hr intervals as decomposition checks. Through the data collection period, these monitored reflections showed no noticeable trend. The criteria for distinguishing observed from unobserved reflections was set such that, to be "observed," $F_{obsd} > 3.0\sigma_F$, where σ_F is the standard deviation on F_{rel} as computed from scan and background counts corrected for instrumental instability (estimated as 0.5%).

The structure was resolved using direct method techniques: Karle–Hauptmann statistics[6] and symbolic addition.[7] This led to determination of 288 phases with high probability of being correctly determined (approximately 11 reflections per nonhydrogen atom; 26 nonhydrogen atoms in the molecule). An E map using these phased reflections was then searched for the 26 largest peaks; 25 were easily chosen, the 26th had several possibilities and so was ignored in this first screening. The program OR-TEP-II[8] was used to "search" for a "molecule" amoung these 25 peak positions, working out from the highest one and using criteria of reasonable ranges for bond lengths;[3] each peak position was tested in each of the four possible positions allowed by the general positions of the space group. The resulting "molecule" was then drawn in stereo on a graphics display terminal[9] and studied for chemical sense.

This trial molecule was found to be entirely satisfactory in all chemical respects; the position of the 26th atom previously ignored was determined visually and found to agree with the position of a peak on the E map. Chemical considerations also readily led to the definition of atom types (C, N, or O) in all positions but the two positions occupied by C3 and N1 (refer to Figure 1) where the question of which position should be carbon and which nitrogen depended entirely on nmr data. The initial model defined the atoms in these two positions as they are shown in Figure 1.

A test of the model was made by performing two cycles of full-matrix least-squares on the nonhydrogen atoms of this model; unit weights and individual isotropic thermal parameters were used. The two cycles caused "R" to fall from an initial value of 0.24 for the raw model to 0.13; at the end of the two cycles, the model appeared quite reasonable with respect to individual atomic thermal parameters, bond lengths, and angles, and the appearance of a difference Fourier synthesis.

At this time, weights and anisotropic thermal parameters were introduced for all nonhydrogen atoms; hydrogen positions were introduced by calculation;[10] and cycles of full-matrix least-squares were continued. Hydrogen positions were recalculated at the close of each cycle according to shifts in the nonhydrogen atoms. The weighting function used was $w = 1/|\Delta F|^2$, where $|\Delta F| = A + B|F_{obsd}|$, and A and B are obtained from a plot of $|\Delta F|$ *vs.* F_{obsd} for 20 groups of reflections, each group containing about the same number of reflections. The plot was linear and gave values of 2.80 and 0.0492 for A and B, respectively. The final cycle gave a conventional R value of 0.064 and weighted R of 0.072.

A final structure factor calculation was made using σ values from counting statistics as weights. The weighted R value for this calculation did not differ significantly from the above weighted R value.

As a test of the possibility that C3 and N1 should be interchanged, two additional cycles of full-matrix least squares were made for the entire molecule with these two atoms interchanged as to atomic type. The resultant R value, changes in atomic parameters, and the appearance of a subsequent difference Fourier map were used as criteria of the correctness of this alternative structure. It was found that the R value increased to 0.076, thermal parameters for C3 (now defined as a nitrogen) became smaller while those for N1 (now defined as a carbon) became larger (atomic coordinate values for all nonhydrogen atoms did not change appreciably; thermal parameters for all nonhydrogen atoms but C3 and N1 did not change appreciably), and, on the difference Fourier, a hole was noted at the position of C3 while a peak was noted at the position N1 (all other atom positions showed neither appreciable peaks nor holes). This evidence led to the conclusion that C3 and N1 were correctly defined from the start.

A final difference Fourier synthesis, on the correct model, having a maximum electron density of 1 e/Å^3 was judged to be free of significant features. Because the goal of this structure determination was to find the molecular architecture of this compound rather than details of accurate bond lengths and thermal parameters, additional refinement cycles were deemed unnecessary. As a final observation, only five of the original 288 reflections phased by direct method techniques were found to be incorrect.

Supplementary Material Available. Tables of bond distances and bond angles (with their estimated standard deviations), and atomic coordinates, will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 Sixteenth Street, N.W., Washington, D. C. 20036. Remit $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-1007.

Registry No.—**3**, 35324-31-3; **4**, 50378-65-9.

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(3) "International Tables for X-ray Crystallography," Vol. III, Kynoch Press, Birmingham, England, 1968.
(4) See paragraph at end of paper regarding supplementary material.
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(9) The Burroughs B-6700 at the University of Delaware Computing Center was employed for all programs used for this structure.
(10) Hydrogen positional parameters were calculated with ATMCAL, adapted from a general hydrogen position calculating program supplied by Dr. Lloyd D. Guggenberger, Du Pont, Wilmington, Del.

A Novel Synthesis of 4-Hydroxycoumarin-3-carboxamides

Stanley A. Lang, Jr.,* and Elliott Cohen

Lederle Laboratories, A Division of American Cyanamid Company, Pearl River, New York 10965

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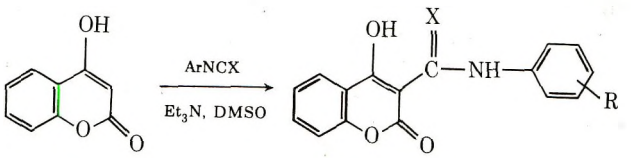
The formation of amides of 4-hydroxycoumarin-3-carboxylic acid has been well documented.[1-5] These methods

Scheme I



I

IIa, X = O; R = H
b, X = O; R = *p*-Cl
c, X = S; R = *p*-F

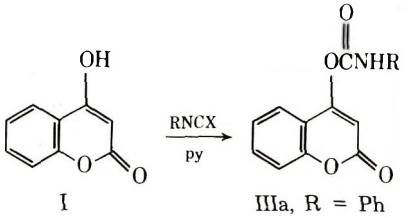
employ thermal activation in one form or another. The amides are formed by the thermal reaction of 4-hydroxycoumarin with isocyanates at 160°,[1-4] or by the reaction of 3-carbethoxy-4-hydroxycoumarin[5] in refluxing anilines.[2-4]

The room-temperature reaction of 4-hydroxycoumarin with aryl isocyanates or aryl isothiocyanates in DMSO containing triethylamine yields cleanly in one step the desired materials,[6] amides of 4-hydroxycoumarin-3-carboxylic acid. For example, 4-hydroxycoumarin and *p*-chlorophenyl isocyanate in DMSO (1 equiv of triethylamine) gave in 71% yield[7] 3-(*p*-chlorophenylcarbamoyl)-4-hydroxycoumarin (IIb, Scheme I), mp 218–220° (lit.[1,3] mp 219–221°). Similarly the reaction of 4-hydroxycoumarin with *p*-fluorophenyl isothiocyanate gave 3-(*p*-fluorophenylthiocarbamoyl)-4-hydroxycoumarin (IIc) in 82% yield[7] (Scheme I), mp 220–223°.[6]

This reaction is complete in 0.5–2 hr and is successful only with aryl isocyanates and isothiocyanates. Alkyl isocyanates and isothiocyanates yield some starting coumarin and polymeric materials. Those aryl isocyanates and isothiocyanates which have a limited solubility in DMSO (at room temperature) gave very poor yields.

The use of pyridine as a solvent yields urethanes. Thus 4-hydroxycoumarin and phenyl isocyanate in pyridine at room temperature gave 4-hydroxycoumarin, carbanilate (IIIa, Scheme II) in 60% yield, mp 210–213° (lit.[3] mp 206–209°).

Scheme II

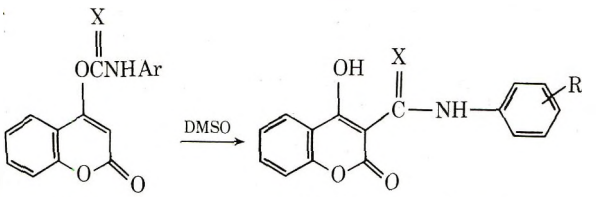


I

IIIa, R = Ph
b, R = *n*-Bu

This reaction was successful with both aryl and alkyl isocyanates and isothiocyanates. 4-Hydroxycoumarin and *n*-butyl isocyanate in pyridine gave 4-hydroxycoumarin *n*-butylcarbamate (IIIb), mp 168–171°. The aryl urethanes rearrange in DMSO (at room temperature) to the 3-carboxamides. Thus 4-hydroxycoumarin carbanilate is cleanly and quantitatively rearranged by overnight stirring in DMSO (containing several drops of triethylamine) to 3-phenylcarbamoyl-4-hydroxycoumarin (Scheme III, IIa),

Scheme III



III

IIa, X = O; R = H
d, X = O; R = *m*-Cl

yield 100%, mp 215–216° (lit.[1-4] mp 219–221°). Likewise 4-hydroxycoumarin *m*-chlorocarbanilate yields 3-*m*-chlorophenylcarbamoyl-4-hydroxycoumarin (IId), yield 95%, mp 191–193° (lit.[1] mp 190–192°). Alkyl urethanes fail to give amides, instead yielding polymer-like materials.

Experimental Section

All commercial reagents were used as received and all solvents were dried over molecular sieves. Melting points are uncorrected.

3-Phenylcarbamoyl-4-hydroxycoumarin (IIa). 4-Hydroxycoumarin (5 g, 0.031 mol), triethylamine (3.1 g, 0.031 mol), and phenyl isocyanate (1 equiv), added in the listed sequence to 50 ml of dry DMSO, were stirred at room temperature for 2 hr. The solution was poured into 100 ml of 3 *N* HCl, and the solid was filtered, air dried, and recrystallized from acetone, giving 6.1 g (70%) of a white powder, mp 215–216° (lit.[1,3] mp 219–221°).

3-(*p*-Fluorophenylthiocarbamoyl)-4-hydroxycoumarin (IIc). The procedure described for IIa gave IIc in 82% yield, mp 220–223°.

Anal. Calcd for $C_{16}H_{10}FNO_3S$ (283.32): C, 60.94; H, 3.20; N, 4.44; S, 10.17; F, 6.03. Found: C, 60.69; H, 3.22; N, 4.50; S, 9.99; F, 5,80.

4-Hydroxycoumarin Carbanilate (IIIa). A solution of 5 g (0.031 mol) of 4-hydroxycoumarin in 50 ml of pyridine was treated in a dropwise fashion with 4 g (1 equiv) of phenyl isocyanate. After stirring for 3 hr at room temperature, the solution was poured into water, and the solid was collected, air dried, and recrystallized from chloroform–hexane, mp 210–212° (yield 5.6 g, 60%).

Rearrangement of Urethanes to Amides. A suspension of 250 mg of 4-hydroxycoumarin carbanilate in 5 ml of DMSO containing several drops of triethylamine was stirred overnight at room temperature. The solution was poured into 25 ml of 1 *N* HCl and the solid IIa was collected, mp 212–215° (250 mg, 100%). The spectral properties of the samples are identical with those of samples previously prepared.

Acknowledgment. We wish to acknowledge Mr. L. Brancone and staff for required microanalytical data, Mr. W. Fulmor, Mr. G. O. Morton, and coworkers for spectral information and interpretation, and Dr. G. Van Lear for his mass spectral considerations.

Registry No.—IIa, 14206-95-2; IIc, 50600-32-3; IIIa, 37982-58-4; 4-hydroxycoumarin, 1076-38-6; phenyl isocyanate, 103-71-9; *p*-fluorophenyl isocyanate, 1544-68-9.

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(6) All new materials had proper physical constants and correct elemental analyses.
(7) Isolated and recrystallized yields.

Product Evidence for an Enamine Mechanism in the Acid-Catalyzed Cleavage of β-Amino Alcohols. Independence of Mechanism on Nature of Acid[1]

Stephen A. Fine* and Jeffrey Shreiner

Department of Chemistry, Lafayette College, Easton, Pennsylvania 18042

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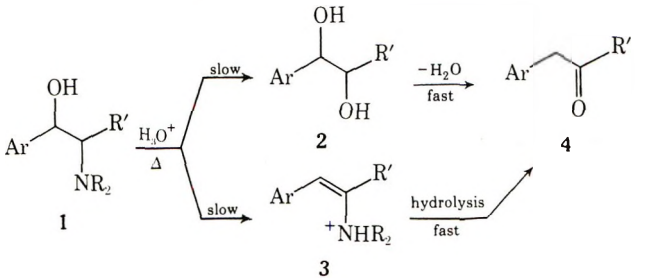
Two mechanisms have been suggested to explain the acid-catalyzed cleavage of α-aryl-β-amino alcohols to β-carbonyl compounds.[2-4] These mechanisms involve a gly-

Table I
Reaction of Compounds 1a, 1b, and 2a (= 2b) with Various Acids

Compd	Acid	Reflux period, hr	Products (yields, %)
1a	12 *M* HCl	7	**4a** (54)[a]
1b	12 *M* HCl	80	No reaction[b]
1b	48% HBr	25	**4b** (34)[a]
2a	12 *M* HCl	6	*p*-$CH_3C_6H_4(C_6H_5)CHCH{=}O$ (75), **4a** (~12), **4b** (<3)[c,d]
1a	6 *M* H_2SO_4	7	**4a** (68)[a]
1b	6 *M* H_2SO_4	27	**4b** (38)[a]
2a	6 *M* H_2SO_4	3	*p*-$CH_3C_6H_4(C_6H_5)CHCH{=}O$ (70),[c] **4a** (~11), **4b** (<2.5)
1a	85% H_3PO_4	2	**4a** (24)[a]
1b	85% H_3PO_4	4.5	**4b** (11)[b]
2a	85% H_3PO_4	4	*p*-$CH_3C_6H_4(C_6H_5)CHCH{=}O$ (47), **4a** (~33), **4b** (<6)[c]

[a] Yield after recrystallization; glc analysis of crude product showed no evidence of *p*-tolylphenylacetaldehyde or of the other, *a priori*, possible ketone product. [b] As shown by recovery of unreacted starting material in high yield. [c] Yields determined by glc analysis of crude product mixture and comparison with known mixtures of authentic samples. [d] Treatment of the glycol with 20% sulfuric acid has previously been reported to afford *p*-tolylphenylacetaldehyde. See ref 8.

col intermediate[2,3] and an enamine intermediate,[2,4] respectively. The reader is referred to a recent paper[5] for details of the mechanisms. Recent work[6] provides strong kinetic evidence for an enamine mechanism in the reaction of 2-(*N,N*-diethylamino)-1-phenylethanol derivatives with hydrochloric acid. However it is claimed,[2] although experimental details are vague, that glycols have been isolated from the reaction of similar amino alcohols with concentrated phosphoric acid.



a, R = Et; Ar = *p*-tolyl; R′ = phenyl
b, R = Et; Ar = phenyl; R′ = *p*-tolyl

One difficulty in resolving the problem is that all previously synthesized α-aryl-β-amino alcohols (**1**) have had alkyl or hydrogen R′ groups[7] and these would be expected to yield the same ketonic products in the event of either a glycol or an enamine mechanism. We have examined the reactions of two amino alcohols (**1a** and **1b**) with various types and concentrations of acid. The amino alcohols were chosen so that they would afford different enamine intermediates but a common glycol intermediate (**2a** = **2b**) if, indeed, the reactions involved such intermediates. An authentic sample of the glycol was prepared independently and was subjected to reaction conditions similar to those of the amino alcohols. Authentic samples of the two possible ketone products (**4a** and **4b**) were also prepared independently for comparison purposes. The results of the acid-catalyzed reactions are summarized in Table I.

The glycol **2a** yielded, as the major product, *p*-tolylphenylacetaldehyde[8] *via* rearrangement along with ketones **4a** and **4b**. Ketone **4a** was always predominant, an expected result since the rate-determining step in the dehydration of the glycol involves formation of a more favorable *p*-methyl benzylic carbonium ion.

The amino alcohols **1a** and **1b** afforded ketones **4a** and **4b**, respectively, as the only products (see Table I, footnote *a*). These results are consistent with an enamine intermediate but not with a glycol intermediate, since both amino alcohols must furnish the same glycol, hence the same products.[17] An enamine mechanism likely involves, as the rate-determining step, development of a benzylic carbonium ion by removal of the protonated hydroxyl group of the amino alcohol.[5,6] A feature of such a mechanism is the observed result that **1a** was consistently more reactive than **1b**, in agreement with previous kinetic data.[6] The unknown stereochemistry of **1a**, **1b**, and **2a** does not alter the validity of these results, since benzylic alcohols racemize rapidly in acidic solution.[9]

The results fail to show any variation in mechanism with the type of acid used; even with concentrated phosphoric acid the outcome is inconsistent with a glycol intermediate, in opposition to the earlier conclusion.[2] We believe that the present data, along with previous kinetic results,[6] no longer justify the possibility of a glycol mechanism of amino alcohol cleavage.

Experimental Section[10]

2-(*p*-Tolyl)-1-phenyl-2-(*N,N*-diethylamino)ethanol (1b). α-Bromo-α-(*p*-tolyl)acetophenone[11] (17.9 g, 0.062 mol) was added in small portions, under nitrogen, to diethylamine (62 ml) at 0° with stirring. After addition was complete the mixture was stirred for 3 hr at 0° and then refrigerated overnight. The diethylamine hydrobromide was filtered off and excess diethylamine was removed from the filtrate by evaporation under reduced pressure. The crude product was dissolved in cold, dilute HCl and washed with ether. The aqueous layer was neutralized with dilute NaOH and extracted with ether and the ether extract was dried ($MgSO_4$). Evaporation of ether followed by vacuum distillation of the product afforded 13.3 g (77%) of the amino ketone as a viscous yellow liquid, bp 145–146° (0.4 mm).

A solution of the amino ketone (13.2 g, 0.047 mol) in dry ether (50 ml) was added dropwise to a stirred solution of $LiAlH_4$ (1.33 g, 0.035 mol) in dry ether (50 ml) at a rate such that gentle refluxing was maintained. The mixture was then refluxed over a steam bath for 30 min. Excess $LiAlH_4$ was destroyed by cautious, dropwise addition of water with stirring followed by removal of solid material by filtration. The ether layer was washed with water, dried, and evaporated under reduced pressure, leaving a yellow-white solid residue. Recrystallization from pentane afforded white crystals: 9.1 g (70%); mp 71–73°; ir (CCl_4) 3400 cm^{-1} (broad, OH), no C=O; nmr δ 7.1 (m, 10, aryl H), 5.2 (d, J = 5 Hz, 1, >**CH**OH), 3.7 (d, J = 5 Hz, 1 >**CH**NEt_2), 3.3 (s, 1, OH), 2.65 (dq, J = 7 Hz, 8, -CH_2CH_3), 2.3 (s, 3, -$C_6H_4CH_3$), 0.9 (t, J = 7 Hz, 6, -CH_2CH_3).

Anal. Calcd for $C_{19}H_{25}NO$: C, 80.52; H, 8.89; N, 4,94. Found: C, 80.72; H, 8.93; N, 4.64.

1-(*p*-Tolyl)-2-phenyl-2-(*N,N*-diethylamino)ethanol (1a) was prepared from α-bromobenzyl *p*-tolyl ketone[12] by the same procedure as above. The intermediate amino ketone had bp 155–160° (0.9 mm). The crude amino alcohol was vacuum distilled, bp 150–153° (0.75 mm). The distillate solidified on standing and was recrystallized from petroleum ether (bp 30–60°): mp 61–63°; ir (CCl_4) 3400 cm^{-1} (broad, OH), no C=O; the nmr spectrum was nearly indistinguishable from the spectrum of **1b**, all δ values and multiplicities being identical.

Anal. Calcd for $C_{19}H_{25}NO$: C, 80.52; H, 8.89; N, 4.94. Found: C, 80.43; H, 9.08; N, 4.82.

1-(*p*-Tolyl)-2-phenyl-1,2-ethanediol (2a = 2b). The method of Jenkins[13] was adapted to the synthesis of α-hydroxybenzyl *p*-tolyl ketone. A suspension of α-bromobenzyl *p*-tolyl ketone[12] (20 g, 0.069 mol) in absolute ethanol (400 ml) was added dropwise to a stirred solution of sodium ethoxide (0.21 mol) in absolute ethanol (200 ml). The reaction mixture was stirred overnight at room temperature and then added to a cold solution of 3 *M* HCl (400 ml). After cooling to induce crystallization the solid was collected and recrystallized from ethanol–water to yield 9.2 g (59%) of α-hydroxybenzyl *p*-tolyl ketone, mp 106–108° (lit.[14] mp 108–109°).

Sodium borohydride (0.80 g, 0.021 mol) was added in small portions to a suspension of the hydroxy ketone (9.2 g, 0.041 mol) in ethanol (200 ml). After addition was complete the mixture was stirred at room temperature for 15 min, then refluxed on a steam

bath for 15 min. The volume of the mixture was reduced by ½ by distillation. Water was added to the boiling solution to the point of saturation; on cooling the diol precipitated as a mixture of stereoisomers: 7.5 g (80%); mp 104–168° (lit. mp[8] 94°, 129° for each racemic pair of enantiomers, respectively); ir ($CHCl_3$) 3590 cm^{-1} (OH), no C=O.

Reaction of 1-(*p*-Tolyl)-2-phenyl-1,2-ethanediol with Acid. General Procedure. A stirred mixture of the diol (1.0 g) and acid (50 ml) was refluxed (see Table I for acids and reaction times). After cooling to room temperature and pouring into water, the reaction mixture was extracted with ether four times. The combined ether extracts were washed with water, dried ($MgSO_4$), evaporated under reduced pressure, and weighed. The crude product mixture was then subjected to glc analysis using authentic samples of *p*-tolylphenylacetaldehyde,[8] and ketones **1a** and **1b**[15] for comparison. The results of the reactions are shown in Table I.

Reaction of Amino Alcohols 1a and 1b with Acid. General Procedure. A stirred mixture of the amino alcohol (0.2–1.3 g) and acid (15–50 ml) was refluxed for the periods indicated in Table I. After cooling and dilution with water the reaction mixture was extracted with ether. The combined ether extracts were washed with water, dried ($MgSO_4$), and evaporated under reduced pressure. The crude products were subjected to glc analysis. In every reaction of **1a** only ketone **4a** could be detected; likewise **1b** furnished only **4b**. The crude solid products were purified[16] by recrystallization and their identities were further confirmed by melting point and mixture melting point and by their infrared spectra, which were identical with those of authentic samples of the ketones. In the reactions with 85% H_3PO_4 the crude products were reddish pastes from which the pure products were extracted by trituration with hot petroleum ether, followed by filtration and cooling.

In the reaction of **1b** with 12 *M* HCl, the reaction mixture contained solid material which was filtered off prior to extraction with ether. This material was then remixed with the aqueous layer and the mixture was neutralized with excess 3 *M* NaOH. Extraction of the alkaline mixture with $CHCl_3$ followed by work-up gave unreacted amino alcohol (80%).

Registry No.—**1a**, 50600-27-6; **1b**, 50600-28-7; **2a**, 50600-29-8; **4a**, 2430-99-1; **4b**, 2001-28-7; *p*-$CH_3C_6H_4(C_6H_5)CHCH{=}O$, 50600-30-1; amino ketone, 50600-31-2.

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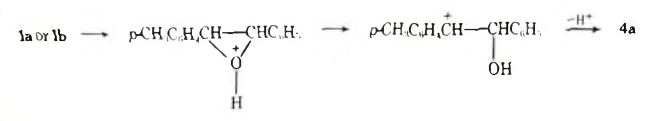
(17) The results also rule out the possibility of an epoxide intermediate, since amino alcohols **1a** and **1b** would both furnish the same epoxide, hence the same product.



Conformational Preference of Cyclohexanespiroaziridine As Determined by Low Temperature Carbon-13 Magnetic Resonance

Gerald W. Buchanan* and Robert Kohler

Department of Chemistry, Carleton University, Ottawa, Ontario, Canada K1S 5B6

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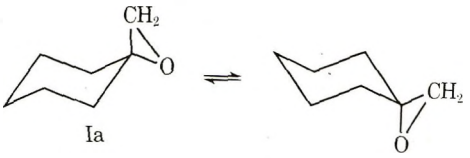
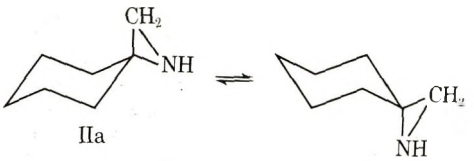
Considerable effort has been recently directed toward the elucidation of conformational preferences of spirocyclohexane derivatives. Cyclohexanespirooxirane (I) has been studied *via* kinetic,[1] low-temperature ^1H nmr,[2] and electric dipole moment[3] methods. The preference of *ca.* 0.27 kcal/mol for the conformation in which the oxygen is quasi-axial (Ib) is evident.



Ia Ib

By contrast, attempts to study the analogous spiroaziridine II by electric dipole moments have not permitted definitive conformational conclusions.[3]



IIa IIb

The low-temperature ^1H nmr peak area procedure cannot be applied to the problem owing to the accidental overlap of the aziridine methylene resonance (δ 1.45) with the cyclohexane ring methylene protons (δ 1.25–1.75). It is expected, however, that ^{13}C nmr should afford a solution, since it is now well established that carbon shieldings are an order of magnitude more sensitive to steric factors than proton shifts in favorable cases.[4,5] Furthermore, the likelihood of peak overlap in carbon spectra is considerably reduced. Accordingly, a sample of II 61% ^{13}C enriched at the aziridine methylene carbon was prepared and examined.

At room temperature under conditions of complete proton noise decoupling the aziridine methylene carbon of II appears as a sharp singlet at δ 31.84 downfield from internal TMS. When a 0.5 *M* solution of II in CD_2Cl_2 is cooled the absorption for this carbon gradually broadens and at $-80 \pm 2°$ the coalescence temperature is reached. Further cooling leads to the separation of the signal into completely resolved components separated by 6.4 Hz.

The resonance of higher integrated intensity appearing at lower field is assigned to conformer IIb. This is consistent with the observations for methylcyclohexane at low temperature,[6] where the equatorial methyl group is at considerably lower field than its axial counterpart. The peak areas were determined by a cutting and weighing procedure and the conformational energy of the spiroaziridine function was calculated from the equation $-\Delta G° = RT \ln K$. Results are shown in Table I, which indicate that conformer IIb is the more stable by 0.16 kcal/mol.

It is apparent that the preference for conformer IIb is much less than that predicted on the basis of the difference between the conformational free energy of the Me (1.7 kcal/mol) and the NHMe (1.0 kcal/mol) groups.[7] No doubt the small angle of the aziridine ring causes appre-

ciable reduction in the nonbonded interactions between the quasi-axial CH_2 group and the syn-axial ring hydrogens. Notably the preference of the spiroaziridine group is appreciably smaller (by 0.1 kcal/mol) than that of the spirooxirane. This is consistent with the fact that $-\Delta G°$ for the NHMe function is 0.2–0.4 kcal/mol higher than for the OMe moiety in the monosubstituted cyclohexanes.[7]

Under conditions of complete proton noise decoupling, nuclear Overhauser effects (NOE's) are operative and thus may affect the observed integrated intensity ratios. In order to verify that no differential NOE has occurred in these experiments the coupled spectrum was recorded. $J(^{13}CH)$ is 166 Hz and no detectable change in the *relative* intensities of the resonances at low temperature was found compared to the decoupled spectra. This is consistent with expectation, since the directly bonded methylene protons will be essentially the only contributors to dipole–dipole relaxation and we have found that these protons have nearly identical chemical shifts below −80°.

Attempts to evaluate the effect of medium on the equilibrium IIa ⇄ IIb were unsuccessful. In toluene-d_8 below −80° no resolvable chemical shift difference between the two conformers was found. Choice of solvents in this study was severely limited owing to the necessity for a deuterium lock signal when an XL-100 nmr spectrometer is used for ^{13}C investigations.

Experimental Section

Spectra. Carbon-13 spectra were recorded at 25.2 MHz on a Varian XL-100-12 spectrometer using 5-mm sample tubes. Temperatures were calibrated using a copper–constantan thermocouple (in a dummy nmr tube) and are judged accurate to ±2°. Conditions of complete proton noise decoupling were used.

To ensure that nonsaturating radiofrequency (rf) conditions were employed, spectra were initially recorded at widely different rf powers, and the relative peak areas were measured. Final conditions were then chosen where the slope of the relative peak area *vs.* rf power graph was zero. Integration of the areas under the peaks was done by the cutting and weighing procedure. Each value represents an average of five determinations at a given temperature. Error limits quoted (±0.01 kcal/mol) represent the standard deviation.

Table I
$-\Delta G°$ Values for the Equilibrium IIa ⇄ IIb (±0.01 kcal/mol)

Temp, ±2°C	$-\Delta G°$, kcal/mol
−88	0.16
−92	0.17
−96	0.16

Materials. ^{13}C enriched (61%) methyltriphenylphosphonium bromide was prepared from triphenylphosphine and methyl bromide-^{13}C (61%, obtained from Stohler Isotope Chemicals, Montreal) according to the procedure of Trippett.[8] A Wittig reaction[9] between cyclohexanone and the ^{13}C-enriched phosphonium salt yielded labeled methylenecyclohexane in 65% yield. This material was converted to the spiroaziridine II in 68% yield according to the procedure of Fowler, Hassner, and Levy.[10]

Acknowledgment. We thank the National Research Council of Canada for financial support.

Registry No.—II, 185-69-3.

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The Reaction of Lithium Naphthalenide with Quaternary Ammonium Salts

Summary: The reaction of aliphatic and aromatic trimethylammonium iodide salts with lithium naphthalenide occurs selectively with elimination of trimethylamine.

Sir: The reaction of aromatic radical anions with halogen containing organic compounds has been shown to produce radicals plus halide ions *via* dissociative electron transfer.[1,2] Although tosylates,[3] sulfonamides,[4] and polyphenylethanes[5] have been cleaved with sodium naphthalenide to form alcohols, amines, and polyphenylmethanes, reactions with other functional groups such as quaternary ammonium salts do not appear to have been studied.[6]

We are pleased to report that several alkyl- and aryltrimethylammonium iodide salts listed in Table I undergo reductive cleavage with lithium naphthalenide in tetrahydrofuran (THF). The carbon–nitrogen bond to the larger R group is cleaved preferentially to form radicals and trimethylamine.

The formation of radicals is inferred from the reaction of 5-hexenyltrimethylammonium iodide, **5**, where 4% of methylcyclopentane is formed together with 35% of 1-hexene. The reasons why formation of methylcyclopentane serves as evidence for the presence of 5-hexenyl radical have been given by Garst and his coworkers for reactions of 5-hexenyl halides with sodium naphthalenide.[7]

Analysis of the results on benzhydryltrimethylammonium iodide, **1**, to form *sym*-tetraphenylethane, **6**, also suggests that some of the **6** is formed by α coupling of two benzhydryl radicals (path A). Radicals formed in the presence of an aromatic radical anion are expected to be reduced to carbanions faster than they can couple to dimer.[1] Path B, summarized in eq 1, involves two sequential one-electron reductions during which benzhydryl radical is reduced by a second equivalent of naphthalenide ion to form a diphenylmethyl carbanion which then displaces trimethylamine from **1** yielding **6**.

$$\underset{\mathbf{1}}{(C_6H_5)_2\overset{+}{C}HN(CH_3)_3I^-} \xrightarrow{C_{10}H_8^-} (C_6H_5)_2CH\cdot \xrightarrow{C_{10}H_8^-} (C_6H_5)_2CH:^- \xrightarrow{1} \mathbf{6} \quad (1)$$

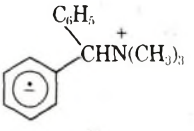
In experiments which use equimolar amounts of naphthalenide and **1**, if the mole percentage of unreacted salt (Table I) is a measure of the maximum amount of carbanion formed by path B, it can be concluded that 22% of **6** is formed by path B and 35% by path A. Additional support for path A was reported recently for benzylic halides analogous to **1** reacting with naphthalenide under conditions which militate against path B, namely, the slow dropwise addition of naphthalenide to halide.[8]

This reductive cleavage of a carbon–nitrogen bond by naphthalenide ion is analogous to the sodium in liquid ammonia fission of quaternary ammonium salts which have been studied systematically by Grovenstein.[9,10] The most surprising difference between our results with lithium naphthalenide and those reported earlier is that tetramethylammonium iodide did not react with lithium naphthalenide after 3 days at 25°. Sodium in liquid ammonia on the other hand readily cleaved tetramethylammonium bromide completely within 1.0–2.0 hr.[9b]

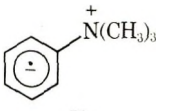
Whereas reductions with sodium in liquid ammonia can be complicated by the presence of strongly basic amide ions, aromatic radical anions are weakly basic and complications due to Sommelet–Hauser and Stevens rearrangements are not encountered.[12]

Normally in reductions with naphthalenide ion 1 equiv of naphthalene must be separated from the products. Although it is possible to use α-dimethylaminonaphthalene's radical anion as the reducing agent,[6] we have cleaved **1** (13.76 g, 0.039 mol) to give **6** (88–100% yields) using a catalytic amount of naphthalene (1 g) by the portionwise addition of 1 equiv of lithium to a suspension of **1** in THF (100 ml).

The reductive cleavage of a carbon–nitrogen bond by naphthalenide ion may form the same type of intermediate (*e.g.*, **1′** or **3′**) as is generated in the synthesis step of the radical anion chain mechanism[13] for substitution at tertiary carbon in *p*-nitrocumyl chloride and α,*p*-dinitrocumene by tertiary amines.[14] An alternate possibility is



1′



3′

that naphthalenide ion transfers the electron directly into the valence shell of the nitrogen atom to form an unstable intermediate which eliminates the more stable radical and a tertiary amine.

In summary, a new method for the chemical cleavage of the more complex organic grouping from a quaternary ammonium iodide salt has been discovered.

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Table I
Reactions of Lithium Naphthalenide with Quaternary Ammonium Iodide Salts in THF[a]

$RN^+(CH_3)_3I^-$	No.	Reaction time, minutes	% RR	% RH	% recovd salt	% $(CH_3)_3N$	% $RN(CH_3)_2$
$(C_6H_5)_2CH$	**1**	<5	57[b]	22[c]	22	81–85[b]	5
$(C_6H_5)CH_2$	**2**	<5	6[c]	72[c]	9	87[b]	8[b]
C_6H_5	**3**	15	4[c]	39[c]	48	18[b]	10[c]
1-$C_{10}H_7$[d]	**4**	90	0.2[c]	45[c]	44	80[b]	17[c]
$CH_2{=}CH(CH_2)_4$	**5**	120		4[e] 35[f]	38	80[b]	...

[a] One equivalent of naphthalenide ion per each equivalent of salt; dry salt is added to naphthalenide ion in one portion. [b] Trimethylamine was distilled, derivatized with methyl iodide, and tetramethylammonium iodide was isolated. [c] Quantitative gas chromatography. [d] Lithium biphenylenide was used. [e] Methylcyclopentane. [f] 1-Hexene.

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Department of Chemistry
Brooklyn College of the
City University of New York
Brooklyn, New York 11210

Isaac Angres[15]
Herman E. Zieger

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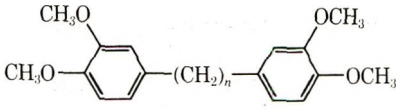
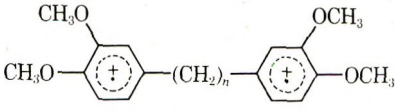
Electrosynthesis of Medium- and Large-Sized Rings by Oxidative Cyclization of Bis(3,4-dimethoxyphenyl)alkanes

Summary: On anodic oxidation in trifluoroacetic acid (TFA)–dichloromethane, diarylalkanes, $Ar(CH_2)_nAr$ where Ar = 3,4-dimethoxyphenyl and $n \geq 6$, undergo a novel dimerization–cyclization reaction with formation of a $(2n + 8)$-membered ring compound (**3**-*n*).

Sir: We report the anodic synthesis of cyclic compounds containing rings with as many as 40 members starting from the bis(3,4-dimethoxyphenyl)alkanes (**1**-*n*). These reactions involve two-electron oxidations to give the intermediate dication diradicals (**2**-*n*) which undergo coupling



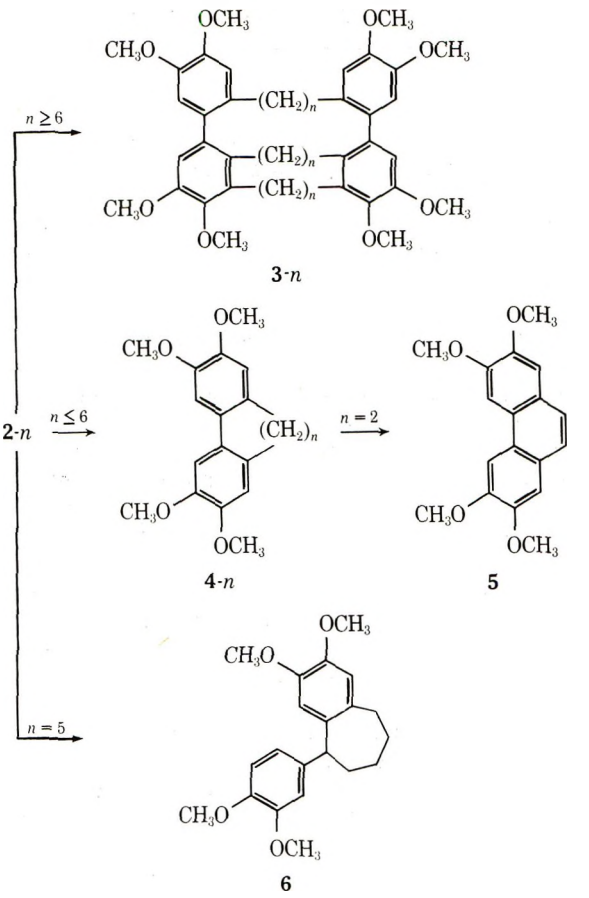
1-*n*



2-*n*

simultaneously at both ends with a neighboring ion. Dication diradicals have recently been implicated as intermediates in the intramolecular cyclization of methoxybibenzyls.[1] While the synthesis of medium- and large-sized rings has its own inherent interest, the results presented here are particularly novel since all previous attempts to prepare such compounds by anodic coupling reactions have been entirely unsuccessful.[2]

Scheme I



3-*n* **4**-*n* **5** **6**

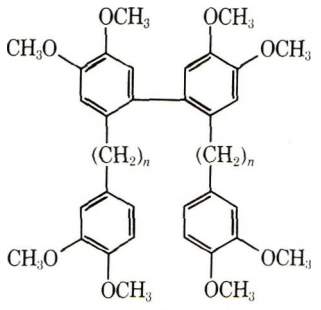
The synthesis were carried out by anodic oxidation of the substrates (5.0 mmol) in TFA–dichloromethane (1:3) containing *n*-Bu_4NBF_4 (1 g in 200 ml of solvent) in a closed two-compartment cell. Constant current (current density 0.16 mA/cm^2) oxidation was carried out at a platinum anode (150 cm^2) at −20° under nitrogen until 3.0 Faradays/mol had been passed. Zinc dust (3 g) was added and stirring was continued for an additional hour at −20°. After work-up, the oily residue was chromatographed on silica gel (200 g, toluene–ethyl acetate gradient, 25-ml fractions). The fractions were analyzed by tlc and nmr and mass spectroscopy. The results, along with those obtained by oxidation with manganic tris(acetylacetonate)[3,4] (MTA) are summarized in Table I.

Large-ring compounds (**3**-*n*) are only formed on the oxidation of compounds containing a saturated chain of six or more carbons. As indicated in Table I, both the yield and the nature of the oxidation products of **1**-*n* depend dramatically upon the carbon chain length. In spite of this, we feel that the initial oxidation product is *2-n* in all cases.[5] The reactions which the various dication diradicals (**2**-*n*) undergo are summarized in Scheme I. When *n* is 4 or smaller intramolecular cyclization giving the bridged biphenyls (**4**-*n*) is the exclusive reaction pathway. In the specific case of *n* = 2, the phenanthrene **5** is the product isolated.[1] The case where *n* = 5 (**1**-5) is unique. Cyclization here occurs between one ring and the position α to the other ring to give **6**. It is of interest that the yield of **3**-*n* is low for *n* = 6 or 7, reaches a maximum at *n* = 8 or 9, and diminishes sharply at *n* = 16. Also at *n* = 16 the

Table I
Oxidation of Bis(3,4-dimethoxyphenyl)alkanes (1-*n*) in TFA–Dichloromethane

Compd	Anodic oxidation: Conversion (%)	Anodic oxidation: Products (yield %)	MTA oxidation,[a] products (yield %)	Mp,[b] °C	Nmr, δ (ppm)[c]	*m/e*[d]
1-1	98	**4-1** (95)	**4-1** (45)	183–184	4.03 (s, 3 H), 4.18 (s, 3 H), 4.20 (s, 2 H), 6.77 (s, 2 H), 7.20 (s, 2H)	286 (M^+)
1-2	95[e]	**5** (95)[e]	**4-2** (45), **8** (19)	211–213 (for **8**)	2.80 (m, 2 H), 3.92 (s, 12 H), 4.00 (s, 12 H), 4.08 (m, 2 H), 6.75 (s, 4 H), 7.15 (s, 4 H) (for **8**)	598 (M^+)
1-3[f]	98	**4-3** (94)	**4-3** (60)	158–159	2.40 (m, 6 H), 3.91 (s, 12 H), 6.80 (s, 2 H), 6.96 (s, 2 H)	314 (M^+)
1-4	97	**4-4** (93)	**4-4** (90)	115–116	1.10–2.90 (m, 8 H), 3.81 (s, 6 H), 3.82 (s, 6 H), 6.73 (s, 2 H), 6.76 (s, 2 H)	328 (M^+)
1-5[g]	95	**6** (38)	**6** (25)	Oil	1.93 (m, 6 H), 2.80 (m, 2 H), 3.63 (s, 3 H), 3.86 (t, 9 H), 6.33 (s, 1 H), 6.78 (m, 4 H), 4.16 (m, 1 H)	342 (M^+)
1-6	96	**3-6** (4)	Only polymers	120–122	1.16 (m, 16 H), 2.40 (m, 8 H), 3.83 (s, 12 H), 3.95 (s, 12 H), 6.63 (s, 4 H), 6.80 (s, 4 H)	712 (M^+) 356 (M^{2+})
1-7	94	**3-7** (12)	Only polymers	129–130	1.16 (m, 20 H), 2.32 (m, 8 H), 3.83 (s, 12 H), 3.95 (s, 12 H), 6.64 (s, 4 H), 6.80 (s, 4 H)	740 (M^+) 370 (M^{2+})
1-8	100	**3-8** (43)	**3-8** (8)	153–154	1.16 (m, 24 H), 2.30 (m, 8 H), 3.83 (s, 12 H), 3.95 (s, 12 H), 6.65 (s, 4 H), 6.80 (s, 4 H)	768 (M^+) 384 (M^{2+})
1-9	100	**3-9** (42)	**3-9** (7)	93–94	1.31 (m, 28 H), 2.33 (m, 8 H), 3.83 (s, 12 H), 3.95 (s, 12 H), 6.66 (s, 4 H), 6.83 (s, 4 H)	796 (M^+) 398 (M^{2+})
1-10	100	**3-10** (38)	**3-10** (5)	133–134	1.16 (m, 32 H), 2.36 (m, 8 H), 3.83 (s, 12 H), 3.95 (s, 12 H), 6.66 (s, 4 H), 6.83 (s, 4 H)	824 (M^+) 412 (M^{2+})
1-16	100	**4-16** (16), **3-16** (8)	**4-16** (4)	95–97 (for **4-16**) 60–62 (for **3-16**)	1.21 (m, 56 H), 2.28 (m, 8 H), 3.78 (s, 12 H), 3.87 (s, 12 H), 6.55 (s, 4 H), 6.71 (s, 4 H) (for **3-16**)[h]	992 (M^+, **3-1**) 496 (M^{2+}, **3-1**) 496 (M^+, **4-16**)

[a] Three mole of MTA per mole of substrate in TFA–dichloromethane was added during 1 hr to a cooled (−20°) 25 m*M* solution of the diarylalkane in TFA–dichloromethane under N_2 with stirring. When all of the substrate had been consumed (tlc) the reaction mixture was worked up as the electrolysis mixtures. [b] Compounds **4-1**, **4-3**, and **4-4** were recrystallized from ethanol and compounds **3-6** to **3-10**, **3-16**, and **4-16** from ether–pentane (4:1). All new compounds gave satisfactory elemental analysis. [c] Recorded in $CDCl_3$ with TMS internal standard. In the starting compounds (**1-***n*) the CH_2 protons appear at 1.43 [m, (2*n* − 4) H] and 2.50 (m, 4 H), the methoxy protons at 3.85 (br s, 12 H), and the aromatic protons at 6.70 ppm (narrow m, 6 H). [d] For all compounds M^+ was the base peak. For all compounds **3-***n* a strong peak appeared at M/2 identified as M^{2+} by the presence of a C-13 satellite at M/2 + 0.5. [e] From ref 1. [f] With this particular compound the same result was obtained in acetonitrile buffered with solid sodium carbonate. [g] Only 2 Faradays of current/mol of substrate was passed through the cell in this experiment. [h] The 60-MHz nmr for **4-16** is identical with that of **3-16**.



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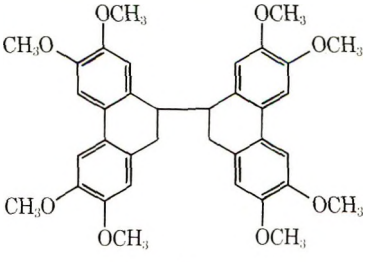
intramolecular cyclized product, **4-16**, is obtained in moderate yield.[6]

That the dication diradicals (**2-***n*) are the initial oxidation products of **1-***n* does not in itself explain why good yields of the cyclic dimers (**3-***n*, *n* = 8–10) are obtained. A random orientation of the molecules would bring about intermolecular coupling and the formation of polymeric products. This appears to be the case for *n* = 6 or 7 where polymeric materials account for most of the substrate consumed. In the cases where high yields are obtained (*n* = 8–10), it appears that the saturated carbon chains orient in a parallel fashion in the relatively polar medium.

In general, the yields of cyclized products are lower when MTA is the oxidant. This reflects the difference between a concerted reaction involving **2-***n* and a reaction involving stepwise oxidation of the two aryl groups in **1-***n*[7] and stepwise formation of the bonds in **3-***n*. Another difference in the anodic and MTA oxidations is seen for *n* = 2. Anodically, **4-2** is oxidized cleanly to **5** while MTA brings about formation of the intermolecular dimer **8**.



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Application of this novel reaction to synthesis of other large rings, in particular crown ethers, is presently under investigation.

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References and Notes

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(4) Thallium trifluoroacetate and $[Fe(DMF)_3Cl_2][FeCl_4]$ where DMF means dimethylformamide were also tried and found inferior to MTA.
(5) Voltammetric data indicates that a saturated carbon chain separating two identical electroactive aryl groups insulates the two groups from each other and allows both groups to lose an electron at about the same potential giving the dication diradical.[1] The same argument applies equally well to the compounds discussed here.
(6) It should be noted that it is impossible to distinguish between structures **3**-*n* and **4**-*n* by elemental analysis or nmr spectroscopy and all compounds were first believed to have structure **4**-*n* until both molecular ions and doubly charged ions were found in the high resolution mass spectra.
(7) Simultaneous oxidation of both aryl groups of **1**-*n* would require an unlikely trimolecular reaction.

Organic chemistry 2 **Alvin Ronlán***
The Lund Institute of Technology
Chemical Center
P.O. Box 740, S-220 07 Lund 7, Sweden

Department of General and
Organic Chemistry **Vernon D. Parker***
The H. C. Ørsted Institute
University of Copenhagen
Universitetsparken 5
DK-2100 Copenhagen, Denmark

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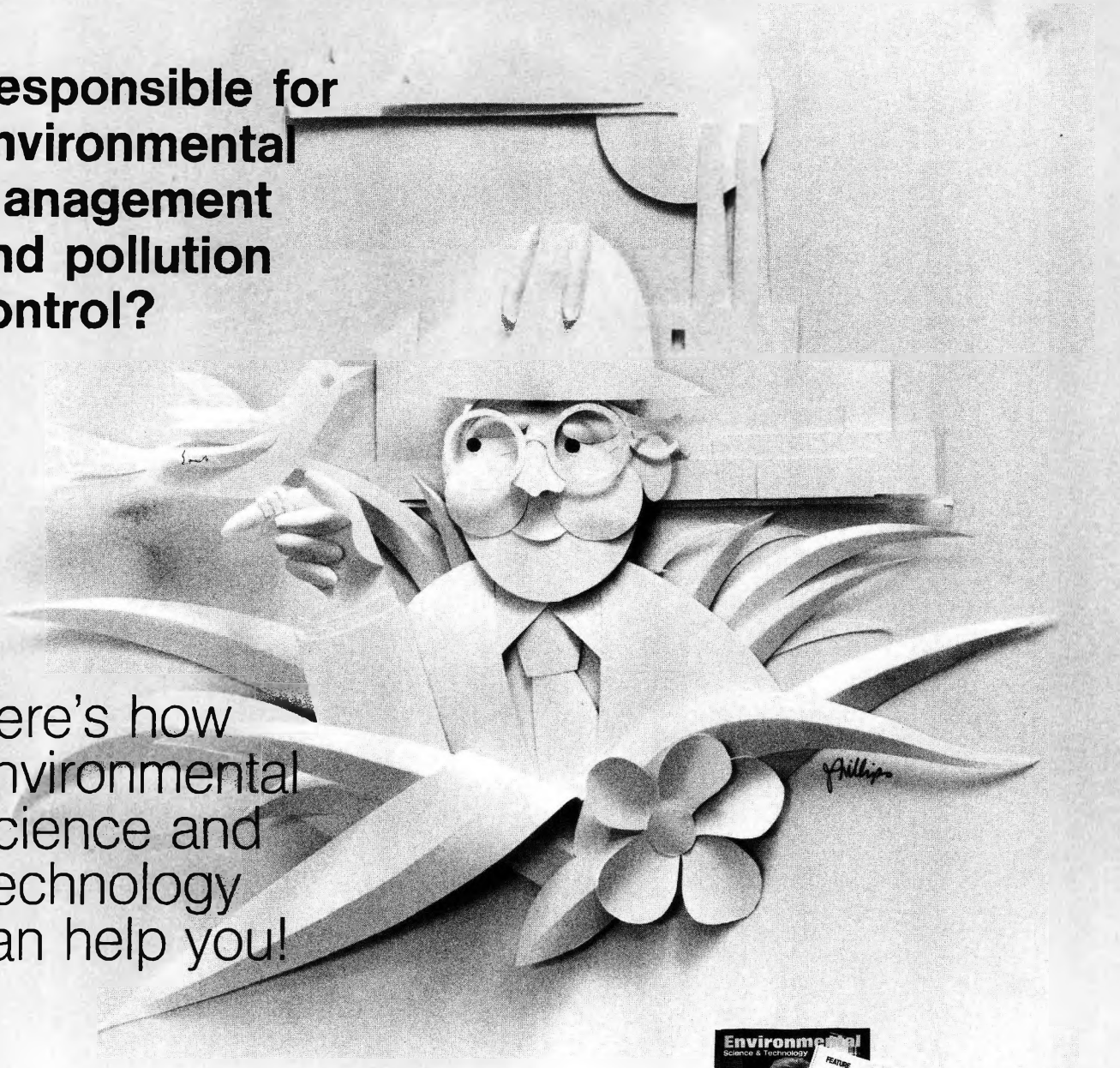

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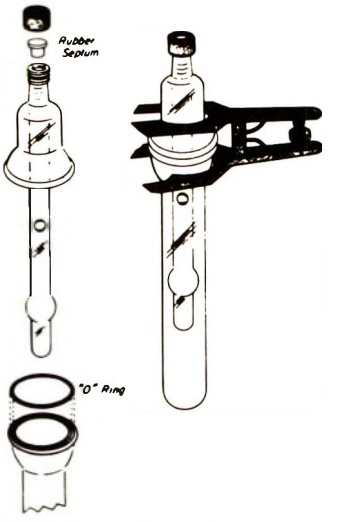

Figure 1. Apparatus for preparing diazomethane • **Z10,100-1 and Z10,102-8**

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The standard preparation of diazomethane involves adding MNNG to a cold 50% aqueous potassium hydroxide solution covered with ether, and then codistilling the diazomethane with the ether. Diazomethane has been reported to be explosive, particularly on contact with ground glass joints, and so generations of chemists have watched this codistillation with trepidation. We now offer two sets of apparatus which allow safe, more convenient generation of diazomethane either with or without distillation.

The first of these enables the preparation of diazomethane from MNNG **without distillation.**[3] Thus, MNNG is placed in the inner chamber and cold ether is introduced into the outer chamber of the apparatus (fig. 1, millimole or micromole size). 5*N* sodium hydroxide is then injected through the silicon septum onto the MNNG and diazomethane collects in the ether, ready for use. Higher diazoalkanes can be prepared from our other *N*-alkyl-*N'*-nitro-*N*-nitrosoguanidines (ethyl, propyl, butyl, are available), as can their deuterated and tritiated analogs.[4,5] Our Diazald® Kit for the generation of diazomethane from Diazald® features smooth Clear-Seal® joints which avoid the hazards associated with ground glass joints. Deuterated diazomethane is easily prepared using our Deutero Diazald® Prep Set which contains instructions and chemicals necessary for generating 50 mmoles of deuterated diazomethane.

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Z10,025-0	**Diazald® Kit $69.50**
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† Denotes molar unit

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Aldrich Chemical Company, Inc.

Home Office:
Aldrich Chemical Co., Inc.
940 W. St. Paul Ave.
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