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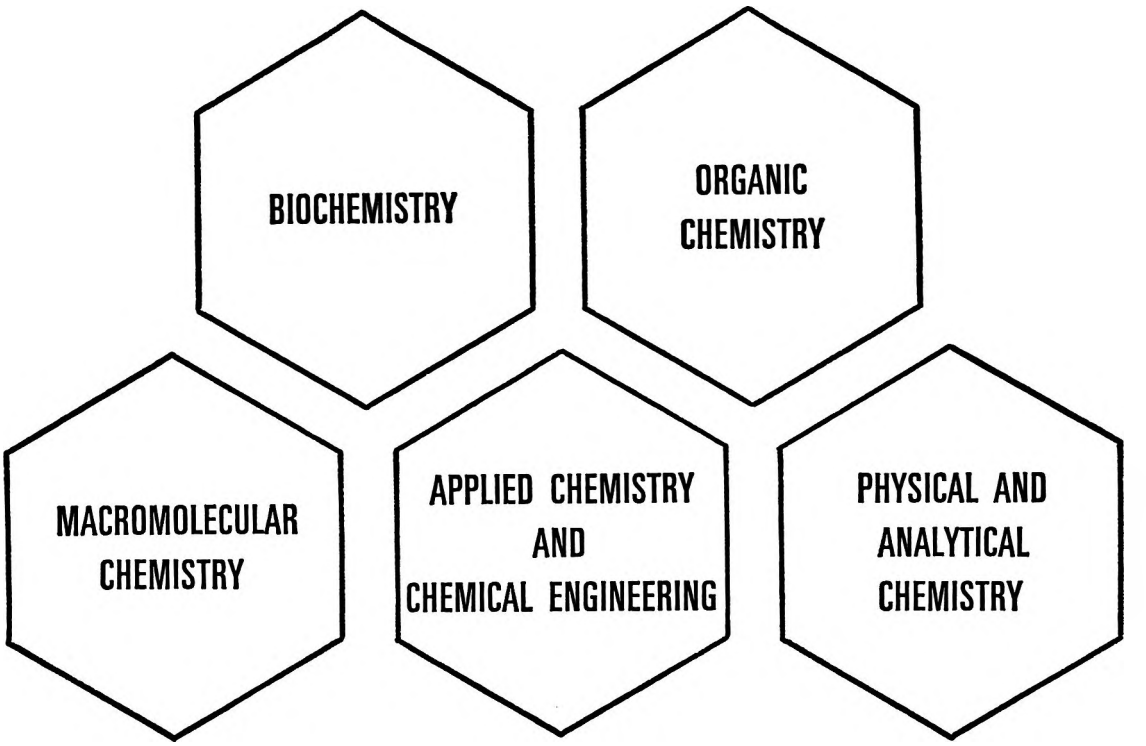

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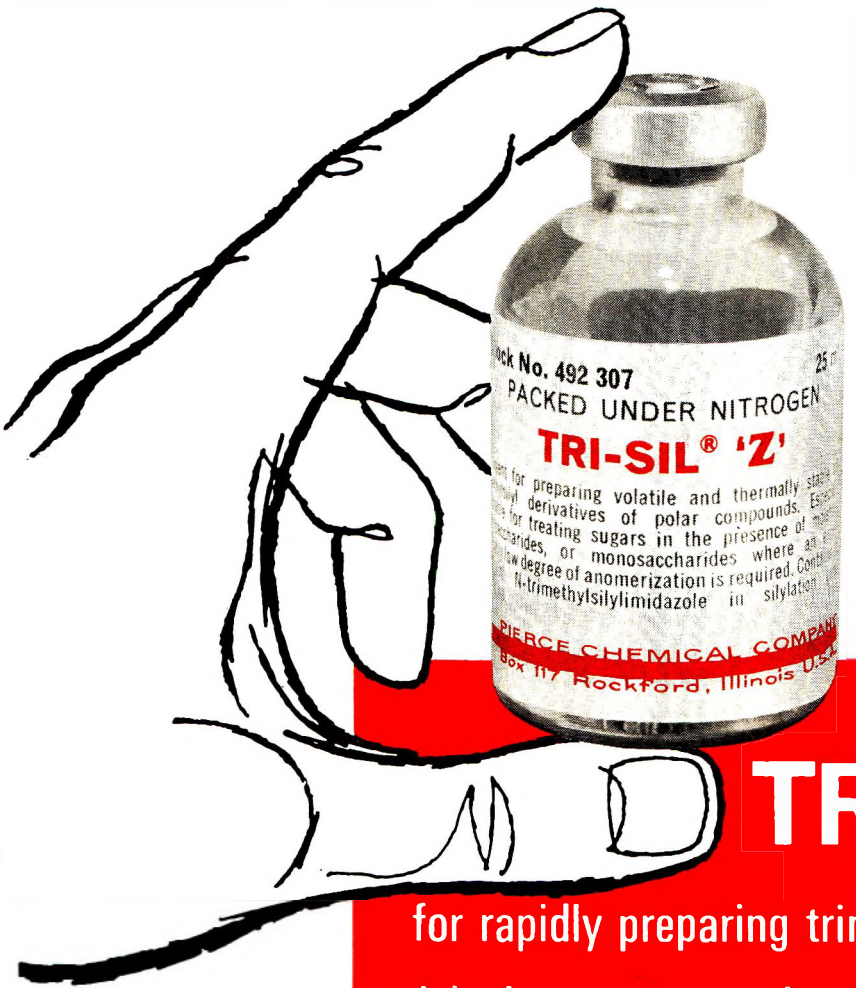

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FEBRUARY, 1969

Very Slow Reactions, Rates, and Isotope Effects in the Bromination of 2-Benzoylbutane[1]

EDWARD S. LEWIS, JAMES D. ALLEN,[2] AND EARL T. WALLICK[3]

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Received May 20, 1968

The application of a method for following very slow reactions using an isotopic dilution method is described. The particular case studied is the bromination of 2-benzoylbutane and 2-benzoylbutane-2-*d* in acetic acid containing sodium acetate. The reaction is not particularly well suited to the method, and the successful application thus illustrates the generality of the method. The rates measured are consistent with those measured at a higher temperature by a gas chromatographic method, which is also applicable to rather slow reactions. Several rates measured by this latter method are also presented. The limitations of various techniques for slow reactions are discussed. Second-order rate constants of less than 10^{-8} M^{-1} sec^{-1} are measured. The deuterium isotope effect is given by the equation $k_H/k_D = 0.99 \exp(1280/RT)$, which does not suggest that tunneling is important. The measured rate at the lowest temperature is greater than predicted by the Arrhenius equation for both protium and deuterium compounds; the source is not tunneling but may be mechanistic or experimental error.

The study of proton-transfer reactions has been a subject of interest for many years, in part because it appears to be the simplest example of the nucleophilic substitution reaction. It is also a reaction in which tunneling can contribute to the reaction rate to a significant extent. An approach to this problem is to study the temperature dependence of the reaction rate, for a simple model for tunneling has predicted that there would be significant deviations from the Arrhenius equation at low temperatures.[4] Most experimental tests of this prediction have been limited to reactions with low activating energy, which allows the measurement of the reaction rate over a wide range of temperatures and allows the measurement of reasonable rates at quite low temperatures.[5] Nevertheless, the above model for tunneling shows that, for a given barrier curvature, the tunnel correction will be larger for a high barrier.[4,6] High activation energy proton-transfer reactions have not been studied much at a variety of temperatures, largely because different techniques are necessary since the rate is so sensitive to temperature. It seemed worthwhile therefore to explore methods for studying very slow reactions to enable rates to be measured at temperatures well below those at which the rate is convenient.

Reactions can be followed by studying the concentration of product or reagent as a function of time, and slow reaction can be followed merely by making the times longer. For purposes of this paper we shall consider that we can spend no more than 3 months on a reaction. We further assume that limitations of analytical precision require us to have at least a factor of 2 change in the measured concentration during the course of the measurement. If the concentration of a reagent is followed, we can say that the half-life must be at least 3 months. A bimolecular reaction with the second reagent in excess at 1 M would then have a rate constant measurable by this method of not less than 10^{-7} M^{-1} sec^{-1}; the rates of transfer of tritium from 2-nitropropane-2-*t* to 2,4,6-trimethylpyridine of this order of magnitude have been followed this way.[7] When the reaction is followed by observing the increase in concentration of a product there is no such limitation, and if a satisfactory analysis for 1% of product is available a second-order rate constant of 10^{-9} M^{-1} sec^{-1} is measurable under the above restrictions; an accurate analysis for one part per million of product can give rate constants of 10^{-13} M^{-1} sec^{-1}. This is clearly a promising direction.

Occasionally, but not generally, the immediate product from the reaction of A and B is highly reactive, and if a reagent C is added at very low con-

(1) From the Ph.D. Theses of (a) J. D. Allen, 1962, and (b) E. T. Wallick, 1966, Rice University, Houston, Texas.

(2) Robert A. Welch Foundation Predoctoral Fellow, 1960–1962.

(3) Robert A. Welch Foundation Predoctoral Fellow, 1963–1965. National Institutes of Health Predoctoral Fellow, 1965–1966.

(4) R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959, p 210.

(5) E. F. Caldin and M. Kasparian, *Discussions Faraday Soc.*, **39**, 25 (1965); J. R. Hulett, *J. Chem. Soc.*, 430 (1965).

(6) R. P. Bell, *Trans. Faraday Soc.*, **55**, 1 (1959).

(7) E. S. Lewis and J. K. Robinson, *J. Amer. Chem. Soc.*, **90**, 4337 (1968).

centration which reacts rapidly and selectively with this reactive species then the reaction will be zero order in C, and the rate of disappearance of a very small amount of C will correspond to the rate of reaction of A with B which may proceed only to a very small extent. Thus the ionization of 2-nitropropane by pyridine bases was followed spectrophotometrically by the disappearance of iodine, which reacts very rapidly with the carbanion, and measurements of a few hours' duration afforded rate constants down to as low as 10^{-7} M^{-1} sec^{-1} in the extreme.[8] This method in practice is limited by the selectivity of the added iodine, which disappeared slowly by other routes; slower reactions could thus not be measured. Similar limitations may be quite general for this method; it is therefore less promising than the sensitive product analysis above.

The analysis for a substance in the presence of several orders of magnitude higher concentration of other substances needs to be both very sensitive and very specific. Isotopic dilution analysis is extremely sensitive, and the specificity is limited only by the extent to which radioactive contaminants can be removed by purification procedures. We present in this paper a gas chromatographic method for following a few per cent reaction and an isotopic dilution analysis which we use to follow about 1% reaction but which is easily extended to far slower reactions.

The isotopic dilution analysis method for rate measurement is not new, but most previous applications have been to cases in which the separation of radioactive reagent and radioactive product have been relatively facile. Thus Conway and Libby[9] separated carbon dioxide from alanine to measure rates of decarboxylation with half-lives of 10^5 years, Manno and Johnson[10] separated iodobenzene from inorganic iodide to measure exchange rate constants as slow as 10^{-12} M^{-1} sec^{-1}, and Kresge and Chiang[11] separated water and 1,3,5-trimethoxybenzene, measuring exchange rates as slow as 5×10^{-9} M^{-1} sec^{-1}; this last work was reported in a paper illustrating strikingly the value of measurement of very slow reaction rates.

The ionization of carbonyl compounds by bases can be a very rapid reaction or a slow one, and the rate may be roughly estimated from considerations of basicity and acidity of the two reagents.[12] Thus the transfer of a proton from ketone free from further acid-strengthening substituents to a weak base can be expected to be quite slow. The ionization of phenyl *sec*-alkyl ketones by acetate ion in acetic acid was chosen for this study because earlier work[13] showed that several such reactions are slow, and because the presence of only one ionizable proton simplifies the kinetics and the interpretation of the isotope effect. Part of the slowness might be a consequence of steric hindrance toward proton transfer, examples of which are now well established.[8,14]

(8) E. S. Lewis and L. H. Funderburk, *J. Amer. Chem. Soc.*, **89**, 2322 (1967).
(9) D. Conway and W. F. Libby, *ibid.*, **80**, 1077 (1958).
(10) P. J. Manno and W. H. Johnson, *ibid.*, **79**, 807 (1957).
(11) A. J. Kresge and Y. Chiang, *ibid.*, **83**, 2877 (1961).
(12) R. G. Pearson and R. L. Dillon, *ibid.*, **75**, 2439 (1953).
(13) W. D. Emmons and M. F. Hawthorne, *ibid.*, **78**, 5593 (1956).
(14) (a) R. G. Pearson and F. V. Williams, *ibid.*, **76**, 3073 (1953); (b) E. S. Lewis and J. D. Allen, *ibid.*, **86**, 2022 (1964); (c) J. A. Feather and V. Gold, *J. Chem. Soc.*, 1752 (1965).

Results and Discussion of Results

The rates of some brominations of phenyl alkyl ketones are given in Table I, measured by one of two methods. Method I is the spectrophotometric measurement of disappearance of bromine as described by Emmons and Hawthorne,[13] except that sodium bromide was added to keep the bromine–tribromide extinction coefficient constant (660 at 390 nm) as recommended elsewhere.[15] This method is of adequate sensitivity to measure far slower reaction rates than given here, but the solvent system slowly reduces the bromine, so that method I (see Table I) is unsuitable for slower reactions or reactions at much higher temperatures. Method II allows for this complication by using a large excess of bromine. The extent of reaction is measured by a gas chromatographic determination of the bromo ketone–ketone ratio. This method is quite adequate if the bromo ketone survives both the reaction conditions and the gas chromatography, both of these are limiting under various circumstances, and special precautions are always necessary to get any bromo ketones through the gas chromatograph.

The first three entries show that the spectrophotometric method is on the verge of having uncertain stoichiometry, since the second bromine can go in 33 times faster than the first. For extents of bromination of well under 1%, as in this work, the assumption of one bromine per molecule of acetophenone is fairly good, but di- or tribrominations become quite important and at 3% completion the rates of dibromination and monobromination are equal. In our work on this compound and on propiophenone, the zero-order plots were quite good straight lines; so there is no reason to suspect serious error from this possibility of dibromination. It may, however, distort the isotope effect a little.

A clear result from the table is the retarding effect of alkyl groups on the rate, most striking with the second one. The relatively minor effect on k_H on changing from one secondary alkyl to another suggests that most of the retardation from propiophenone is a consequence of the acid-weakening character of the alkyl group, although some steric effect may be present and is probably responsible for most of the variations in k_H of the last four entries. It is possible that the case R = $CH(CH_3)CH(CH_3)_2$ shows an unusually large isotope effect due to a steric retardation which does not interfere with tunneling, analogous to that found earlier,[8] but the evidence is hardly convincing.

The values of k_D and the isotope effect are less precise than we would like, almost entirely because of the rather large light hydrogen content. Unfortunately, this is associated with isotope effects higher than we had anticipated, so that the corrections are quite large and quite sensitive to the mole fraction of light hydrogen, f_H, at the position in question. These compounds were made as we were beginning to learn about the use of nmr for these analyses; the precision is lower than that which we now achieve on this sort of analysis. Even so, the determination of f_H by nmr is more positionally specific than mass spectral analysis and is much more precise than a routine deuterium analysis by mass spectrometry. Analysis by density measure-

(15) E. S. Lewis and M. D. Johnson, *J. Amer. Chem. Soc.*, **81**, 2070 (1959).

TABLE I

RATES OF BROMINATION OF C_6H_5COR IN AQUEOUS ACETIC ACID–SODIUM ACETATE

R	Registry no.	T, °C	Method[a]	k_H[b] 10^6 sec^{-1}	k_D(obsd),[b,c] 10^6 sec^{-1}	k_H/k_D (cor)[d]
CH_3	98-86-2	27.5	I	2.36	0.354	(10.5)[e,f]
CH_2Br	70-11-1	27.5	I	78.8		
$CHBr_2$	13665-04-8	27.5	I	82		
CH_2CH_3	93-55-0	38.5	I	1.83	0.339	7.0[e]
$CH(CH_3)_2$	611-70-1	100	II	19.8	4.26	6.8
$CH(CH_3)C_2H_5$	938-87-4	100	II	6.5	1.5	5.6
$CH(CH_3)CH(CH_3)_2$	18321-24-9	100	II	6.2	(0.643)[g]	(10)[g]
Cyclohexyl	712-50-5	100	II	(8.2)[h]	h	

[a] Method I, spectrophotometric; method II, gas chromatographic; see text. [b] Pseudo-first-order rate constants in 1.83 M sodium acetate solution. [c] Measured rate constants for largely deuterated material. [d] Isotope effects corrected for incomplete deuteration by the relation $k_D = [k_D(obsd) - k_H f_H]/(1 - f_H)$, where k_D is corrected for contamination of the reagent by a mole fraction f_H of protium compound. [e] This number includes an unestablished secondary isotope effect of the other deuterium atoms. [f] The correction for protium contamination is quite large, so that we do not believe that this number is very precise. [g] Application of the correction yields $k_H/k_D = 22$, but the correction is large and there is only one determination of k_D; the isotope effect probably is fairly large and lies between $k_H/k_D(obsd) = 9.7$ and this "corrected" value of 22. [h] The gas chromatograph showed a variety of peaks, which we attribute to decomposition products of the bromo ketone. This was so serious with the deuterated ketone that no meaningful rate constant could be calculated.

ment on water produced by combustion is much better for finding the difference between 0 and 1% D in the molecule than the difference between 99 and 100% at some position. In our hands the combustion analysis is better than the nmr only under the most favorable circumstances (*i.e.*, large ratio of deuterated to unchanged positions) and only when the analyst is doing these analyses regularly.

The methods used for Table I seemed unlikely to be applicable to much slower reactions, nor could we hope for improved accuracy, which is necessary for a good interpretation of the results. We have therefore developed a third method based upon an isotopic dilution analysis for the bromo ketone. We did not try using radioactive bromine, because the short half-life (for ^{82}Br, $t_{1/2} = 35.7$ hr) limits studies to those which can be completed in a few half-lives, and because the method lacks generality. We prepared 2-benzoylbutane-4-*t* and 2-benzoylbutane-2-*d*-4-*t*, added this to the brominating medium, and after various times stopped the reaction and added 2-benzoyl-2-bromobutane in known amount. Reisolation of the 2-benzoyl-2-bromobutane in pure form and counting then allowed the calculation of the yield from the bromination reaction. The pseudo-zero-order rates were measured from the slope of a line of extent of completion *vs.* time. A typical run is illustrated in Figure 1. The results are presented in Table II.

TABLE II

RATES OF BROMINATION OF 2-BENZOYLBUTANE AND 2-BENZOYLBUTANE-2-*d* BY ISOTOPIC DILUTION ANALYSIS

T, °C	$k_H \times 10^6$ sec^{-1}	k_D(obsd) $\times 10^6$ sec^{-1}	k_H/k_D (cor)
100[a]	650[a]	150[a]	5.4[a]
79.8	146.7	23.8[b]	6.5[b]
48.50	9.86	1.47[b]	7.1[b]
32.10	3.53	0.458[b]	8.3[b]

[a] Entry from Table I by gas chromatography; the deuterated compound contained 5.7% protium compound. [b] The sample contained 1% protium compound.

The error in the entries in Table II is not readily calculated, especially since the most obvious source of error is a systematic error tending to give high results due to contamination of the bromo ketone counted with radioactive impurities. An idea may be obtained from the Arrhenius plot of Figure 2. The points for k_H at the two higher temperatures and the one at 100° by the gas chromatographic method give a respectable Arrhenius plot, with $k_H = 10^{6.25} \exp(-19{,}520/RT)$. The deviation at the lowest temperature can not be attributed to tunneling, since the deuterium compound also deviates, and the isotope effect, also shown in Figure 2, obeys the Arrhenius equation reasonably well. There is insufficient precision to exclude tunneling and Arrhenius plot curvature due to it entirely, but a further reason to question its importance comes from the iso-

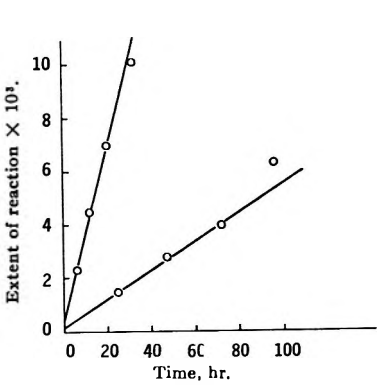


Figure 1.—Plot of extent of completion *vs.* time for two runs by isotopic dilution analysis. Upper points give k_H, lower points k_D.

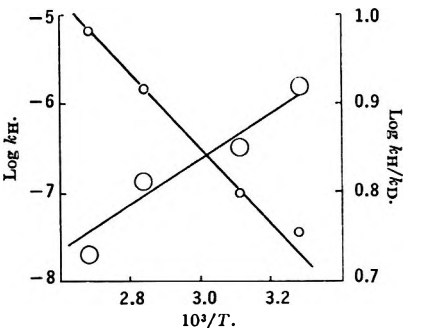


Figure 2.—Arrhenius plot for k_H (left scale, small circles), and k_H/k_D (right scale, large circles corresponding to 3% error in k_H/k_D. Left-most points by gas chromatography, others by isotopic dilution.

tope effect temperature dependence, fitted by the equation $k_H/k_D = 0.99 \exp(1280/RT)$. Neither the essentially unit A_H/A_D factor nor the reasonable $E_{a_d} - E_{a_H}$ term, although both are rough, suggests any major contribution to the isotope effect other than zero-point energy loss.[4]

The deviation of the lowest point from the Arrhenius equation could be caused by the intrusion of a new mechanism with a similar isotope effect, such as a radical[16] bromination, or a low A factor low E_a ionic mechanism, such as the concerted termolecular mechanism rejected as a major contributor under most circumstances.[17] An alternative explanation is that it is the result of experimental error. These run at the lowest temperatures were chronologically the first, and the execution of the chromatographic separations may have been less effective in these cases. Furthermore, the smaller extent of reaction due to the slower reactions exaggerates the effect of imperfect separations. There seems under these circumstances to be no reason to pursue explanations for the Arrhenius equation deviations.

Discussion of the Isotopic Dilution Method.—Isotopic dilution analyses in general depend only on the ability to isolate a pure sample of the substance in question and to determine its specific activity. The latter usually presents no problem, although in the present work dealing with difficultly volatile liquids in small amounts made the determination of the total amount of material counted impractical by weighing. The concentration of the material to be counted was therefore determined by the ultraviolet absorption of a toluene solution before adding scintillators. We estimate a minimum random error of $\pm 1\%$ in the specific activities from this source, and believe that this level of precision was very nearly attained. Statistical errors can be reduced by taking enough counts, and there was no evidence of drifts in counting efficiency over the times necessary to get at least 10^4 counts. Thus the determination of specific acitivity is not a likely source of major error.

The major problem is associated with the purity of the isolated material. Errors are of two sorts, depending on whether the contaminants are radioactive or not. The latter case is the least troublesome; thus, if the material isolated has only the fraction g ($g < 1$) of the desired substance, then the true specific activity a is related to that measured, a_{obsd}, by the relation $a = a_{obsd}/g$.[18] Thus a few per cent contamination will only produce a few per cent error in a, and, if g is reproducible, there will be no error in rate constant.

(16) All systems were protected from strong light to inhibit any photochemically initiated chain reactions, but a low level of ordinary light could account for a very slow reaction if the kinetic chain length is long. Similarly, only a very long chain length radiation induced reaction could account for the discrepancy, since the level of activity has fairly low. We can not calculate this radiation-induced rate, but by analogy with other work it must be very small.

(17) Reference 4, p 151.

(18) This is true if g is a weight fraction and the amount of substance is measured by weights, but in our case amounts are measured by uv absorption. If there is a nonradioactive contaminant Z with a mole fraction n_Z in with the desired substance Y with a mole fraction n_Y, then the appropriate g to put in is $g = \epsilon_Y n_Y/(\epsilon_Y n_Y + \epsilon_Z n_Z)$ where ϵ_Y and ϵ_Z are the extinction coefficients of Y and Z. Thus no error results from a transparent contaminant ($\epsilon_Z = 0$), but serious errors can result from contaminants with $\epsilon_Y > \epsilon_Y$, even if n_Z is small. Fortunately, compounds with high ϵ are usually strongly adsorbed on a chromatographic column, so that our purification renders such a contamination unlikely.

The more difficult problem is that of contamination by radioactive impurities. Thus, if we allow the reaction to go to 1% completion, and add an amount of cold carrier compound (Y) equal to that of the unreacted material, the specific activity of the product (Y) will only be 1% of that of the reagent (X). If we then isolate Y contaminanted by only 1% X, the specific activity measured will be too high by a factor of 2! For smaller extents of completion this error of contamination is even more serious. In the above case example, the error may be reduced by purification to a level of 99.99%; then the error due to contamination is only 1%, but small scale routine purification to this level is generally impossible. The problem is attacked by the so-called "hold-back carrier" technique.[19] If the above 99% pure Y is mixed with an equal amount of nonradioactive X and then repurified to a mixture 99% Y and 1% of X, X has now been reduced in specific activity by a factor of 100, and counting of Y now is in error by only 1%. The efficacy of this procedure can be followed by counting the X fraction, and in our studies this process was repeated until the specific activity of the X fraction was negligible.

This error can thus be overcome so long as there is a reasonably efficient separation of X and Y, and the number of powerful separation methods now available suggests that one can rely upon this being quite general.

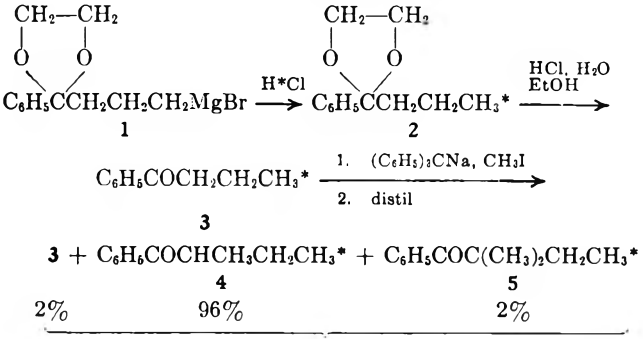
A further problem is associated with unwanted radioactive impurities in the reagent X, which may be difficultly separable from Y, or converted into difficultly separable materials under the reaction conditions. Clearly the number of these is related to the synthetic procedure for preparing X and to the point at which the radioactivity is introduced. The hazards of introducing very high levels of activity followed by dilution with carrier in introducing very high activity impurities have been pointed out[19] and taken into consideration. Clearly the optimum experimental design is to introduce the activity in the last step of the synthesis by a process that minimizes side reactions. Known contaminants can be rendered inactive by the "hold-back carrier" technique, and a rigorous purification, unaccompanied by any dilution with cold X, will then complete the process. We were unable to achieve this optimum design, but the application to a less than ideal system illustrates better the generality of the method.

The steps used in the synthesis of the radioactive reagents are illustrated in Scheme I, starting with the introduction of the radioactivity. Scheme II illustrates the purification and analysis to determine the extent of reaction. The preparation of the starting materials and some of the details are described in the Experimental Section. We were unsuccessful at preparing the Grignard reagent from 2-phenyl-2-(1-methyl-3-bromopropyl)-1,3-dioxolane, thus requiring this more devious process of introduction of the label before the methylation. We neglected to apply the "hold-back carrier" technique to the removal of active 2-benzoyl-2-methylbutane (**5**) from our sample of 2-benzoylbutane, and this oversight is probably re-

(19) E. J. Dewitt, C. T. Lester, and G. A. Ropp, *J. Amer. Chem. Soc.*, **78**, 2101 (1956).

SCHEME I

PREPARATION OF 2-BENZOYLBUTANE-4-*t* AND 2-BENZOYLBUTANE-2-*d*-4-*t*



sample A
(all specific activities about same as that of **4**)

1. $C_6H_5COCH_3CH_2CH_3$ (inactive)
2. column chromatography
3. repeat "hold-back" three times
4. preparative glpc

Sample B of **4** (3.2×10^4 dps/mmol)
<0.1% $C_6H_5COCH_2CH_2CH_3$ of negligible specific activity
≪0.1% **5**, undetectable by glpc, specific activity as in sample A

1. D_2O, $SOCl_2$
2. repeated exchange

$C_6H_5COCDCH_3CH_2CH_3$*
6
(containing 1% **4** and other impurities as in sample B)

SCHEME II

DETERMINATION OF EXTENT OF BROMINATION OF **4**

4 (sample B) or **6**
~80 mg (m_1 mol)

HOAc, H_2O
NaOAc, NaBr, Br_2
for measured time *t*

4 + $C_6H_5COCBrCH_3CH_2CH_3$* (~99%) **7** (~1%)

1. partition between petroleum ether and aqueous $Na_2S_2O_3$
2. add ~40 mg (m_2 mol) of $C_6H_5COBrCH_3CH_2CH_3$ (inactive)
3. discard aqueous layer
4. wash and dry organic layer
5. chromatograph on Florisil

fraction (mostly **4**)

fraction C (mostly **7**)

1. $C_6H_5COCHCH_3CH_2CH$ (**8**)
2. chromatograph

fraction E (mostly **7**)

fraction D (mostly **8**) count

if count of D is significant, repeat C → D + E process; if not, rechromatograph to remove residual **8**

7 (in petroleum ether)
1. replace solvent with toluene
2. determine uv spectrum (*A*)
3. add scintillation solution (count rate = *c*)
4. determine specific activity (a_{obsd})

sponsible for a good bit of the remaining kinetic uncertainties, even though this contamination of the sample used was undetectable by gas chromatography, and all low-level samples had been subjected to further column chromatography several times. Apparently the bromo ketone and the completely methylated ketone are not easily separated by the column chromatography. The removal of the labeled unmethylated ketone **3** was done very carefully, since it would be brominated rapidly, and possibly the product would be difficult to separate from the bromination product of **4**.

The specific activity a_{obsd} of the sample of bromo ketone was determined by combining the absorbance of the solution (ϵ = 153 at 327 nm) with the count rate, making suitable allowance for the volume of sample taken to count. The specific activity of the starting material, a_0, was counted under the same conditions by converting it quantitatively into bromo ketone using a rapid acid-catalyzed reaction before counting. The extent of completion (x) is then given by the equation $x = am_2/a_0m_1$. The pseudo-first-order rate constant was then calculated from the slope of a plot of x *vs.* t. These plots sometimes had intercepts greater than zero at $t = 0$. Although some of this could be attributed to a real effect of a small, rapidly brominated amount of enol in the ketone, which might easily be different from the equilibrium content, we believe that a reasonably reproducible contamination by **5** is a more likely source of this intercept. In either case the use of the slope rather than the extent of completion at any one time eliminates or reduces the error. When a bromination reaction is this slow, both steric or electronic explanations for the slowness would also suggest that bromine would not compete as well for the enolate ion (or enol) as it does in more familiar systems. If this competition were really unfavorable, bromine would enter the rate expression. This was not checked for 2-benzoylbutane, but the gas chromatographic results on 2-benzoylpropane and the spectrophotometric results on propiophenone were both independent of bromine concentration. In the latter case the use of very dilute bromine solutions (using 10-cm cells) allowed a study of the region of bromine dependency, and it was found that bromine reacted about 3×10^6 times faster than acetic acid with the reactive intermediate.[20] Since the bromine concentrations in the present work are high, it is likely that the enolate is efficiently trapped, and that the rates are genuine ionization rate measurements.

The choice of nature and position of the label calls for some comment. Either tritium or ^{14}C is required for generality for organic reactions, and tritium was chosen both because it is easier to introduce and because it is cheaper and offers minimal health hazards, even at levels far higher than we used. The label was not put in the ring, because of the (rather far-fetched) possibility of exchange. The α position was avoided since we were interested in measuring isotope effects. We avoided a label at the 1 or 3 position of the butyl group because it might be lost by β elimination from the bromo ketone. The further advantage of a label in the 4 position was that secondary isotope effects would be reduced to a trivial amount, so that the rate on the tritium compound could be compared directly with that of ordinary 2-benzoylbutane.

We conclude that we have successfully measured a slow reaction rate by this isotope dilution analysis, and that the inherent limitations have not been ap-

(20) Reference 1a.

proached, so that far slower reactions could be studied. The only practical limitation is the tedium of the numerous chromatographic separations,[21] so that the method should not be applied unless there is some real reward for the considerable effort.

Experimental Section

Materials.—Acetophenone, propiophenone, 2-benzoylpropane, and phenacyl bromide were commercially available materials. Repeated exchange of the first two with deuterium oxide in dioxane containing potassium carbonate gave acetophenone-d_2, 94% deuterated (by combustion), and propiophenone-α-d_2, 95% deuterated (by combustion). 2-Benzoylbutane was made following Bartlett and Stauffer.[22]

2-Benzoyl-3-methylbutane.—Following the plan of Nunn and Henze,[23] benzonitrile (69 g, 0.66 mol) in dry toluene (800 ml) was added to the Grignard reagent from 2-bromo-4-methylbutane (0.6 mol) in refluxing ether (700 ml). The ether was removed and the toluene solution was allowed to stand for 9 hr. The mixture was then boiled for 6 hr, cooled, and treated with 450 ml of cold saturated ammonium chloride solution. The toluene layer was extracted with cold dilute sulfuric acid, and this extract was boiled under reflux for 2.5 hr, cooled, and extracted with ether. The ketone was isolated by distillation and gave a 2,4-dinitrophenylhydrazone, mp 121–122° (lit.[24] mp 118–119°). Fractional distillation gave a compound containing only 1% contaminant by gas chromatography.

2-Benzoylpropane-2-*d*, 2-benzoylbutane-2-*d*, and 2-benzoyl-3-methylbutane-2-*d* were made by boiling the ketones with about a twofold excess of sodium hydride in suspension in tetrahydrofuran. After hydrogen evolution had ceased, usually in excess of 12 hr, deuterium oxide (in twofold excess) was added and distillation yielded the ketone in good recovery, but the deuterium contents were, respectively, 92 (nmr) (93% by combustion), 94 (nmr), and 94% (nmr) (95% by combustion). This method is not recommended. The acid-catalyzed exchange described below used for 2-benzoylbutane-4-*t* is superior. Benzoyldibromomethane was prepared following Evans and Brooks[25] by the bromination of phenacyl bromide.

2-Benzoyl-2-bromopropane.—The bromination of the ketone led to this compound.[26] Similarly, 2-benzoyl-2-bromobutane and 2-benzoyl-2-bromo-3-methylbutane, all used for gas chromatographic references, were prepared by brominating the ketone in acetic acid solution. Adsorption chromatography on alumina and Florisil, respectively, was needed to get a sample pure enough for use. The same method was used to convert 2-benzoylbutane-4-*t* into 2-benzoyl-2-bromobutane-4-*t*.

Butyrophenone-4-*t* (3).—The Grignard reagent from 2-phenyl-2-(3-bromopropyl)-1,3-dioxolane (54 g) was prepared following the procedure of House and Blaker[27] starting from ethyl benzoylacetate. Tritiated water (1 g, 10 mCi) was added slowly to boiling thionyl chloride, and the gases were passed over the ethereal solution of the Grignard reagent. Ordinary water was used to complete the transfer of the tritiated water 1 hr after the radioactive water had been added. After 5 hr, the residual magnesium was removed by filtration, and the ether was washed with water, 5% sodium carbonate, water, and saturated brine. Since the ketal is only partially hydrolyzed at this stage, isolation should not be attempted. The ether was concentrated to a total volume of 150 ml, then added to a mixture of 1 l. of 1 *M* hydrochloric acid and 400 ml of ethanol, and heated overnight on the steam bath. After conventional work-up, distillation gave 13.29 (44%) of 1-benzoylpropane-3-*t*, to which was added 5 g of ordinary butyrophenone distilled through the same apparatus to scavenge column holdup, etc.

2-Benzoylbutane-4-*t* (4).—In a flask protected from the atmosphere, equipped with a magnetic stirrer, a reflux condenser and an addition funnel was placed 10.2 g of 1-benzoylpropane-3-*t*. An ethereal solution of triphenylmethylsodium was added until the red color persisted; then methyliodide (100 ml) was added with stirring. A precipitate of sodium iodide was observed in 10 min, but the solution was stirred for 6 hr, then poured on 500 ml of water, and the layers were separated. Conventional work-up gave 8.32 g (82%) of 2-benzoylbutane-4-*t*, and a further 2.35 g of less active material was obtained by scavenging with cold material. Analytical scale glpc showed, about 2% each, peaks with retention times identical with those of the unmethylated and dimethylated ketones (**3** and **5**, respectively).

Further purification was accomplished by adding an equal amount of unlabeled butyrophenone and chromatographing on Woelm activity I alumina, with the unmethylated compound more strongly adsorbed. This treatment was repeated twice, so that only about 1 part in 10^7 of the activity was attributable to contamination by **3**, and preparative scale glpc on a silicone fluid column showed that the product contained 0.1% butyrophenone (essentially devoid of activity) and no detectable amount of the active dimethylated ketone **5**.

2-Benzoylbutane-2-*d*-4-*t* (6).—Thionyl chloride (0.8 ml) was added to deuterium oxide (10 ml, 99.5%), and the mixture heated to 90° for 1 hr to complete the hydrolysis; then 1.01 g of 2-benzoylbutane-4-*t* was added and the heating continued for 24 hr. The mixture was then extracted with petroleum ether, which was then washed and dried and the solvent evaporated. The exchange was repeated as before and the product was distilled, yielding 0.5 g of material with a deuterium content 99.0 ± 0.1 by an nmr method. This analysis involves rather difficult comparisons either of peaks of very different size, or of unestablished origin. The analysis was facilitated by the availability of a sample of intermediate deuterium content. With this sample, it was possible to integrate the relative intensities of the signal at δ 3.38 (sextet, the tertiary hydrogen) with the multiplet at 8.0 of two of the aromatic hydrogens. A protium content of 5.7% was calculated. The rough factor of 40 difference in integral was reduced to a factor of 4 by sweeping the intense one ten times as fast, a technique depending only on the constancy of speed of a synchronous motor and the number of teeth on gears, rather than relying on the precision of resistors in attenuators. This analysis was unsuitable for the more highly deuterated species since the signal to noise level was very poor on the smaller peaks of the sextet. When the sample which contained 5.7% protium compound was studied with the higher resolution and greater sensitivity of a 100-Mc instrument, a small peak was found at δ 8.19, which is presumably a ^{13}C satellite of a portion of the aromatic proton spectrum. This peak, although not rigorously assigned to any proton, was used in a peak height analysis, by comparing its height to that of the largest peak of the sextet from the tertiary hydrogen.[28]

Kinetics.—The solvent for all runs was prepared by diluting a mixture of 150 g of anhydrous sodium acetate, 15.5 g of sodium bromide, and 85 ml of water to 1 l. with glacial acetic acid. The sodium bromide is called for in the spectrophotometric runs, it was included in the others merely to keep the conditions uniform.

Spectrophotometric Kinetics.—The method of Emmons and Hawthorne[13] was followed, except that a Cary Model 14 spectrophotometer was used. The problems of temperature control in this method have been discussed elsewhere.[14b]

Gas Chromatographic Kinetics.—A weighed sample of ketone was diluted to 25 ml with the solvent and 0.4–0.8 ml of bromine was added. About 4 ml of this solution was placed in each of six ampoules, which were then sealed and placed in an oil thermostat at 100° in a darkroom. In the presence of light the results were nonreproducible. At various times an ampoule was removed and immediately cooled in ice. The ampoule was then opened and the contents were transferred to a separating funnel and partitioned between 25 ml of 0.01 *M* sodium thiosulfate solution and petroleum ether. Most of the petroleum ether was evaporated on a water bath and the residue was subjected to gas chromatographic analysis. Columns were made of glass and were packed with Chromosorb W containing 10% Dow-Corning 550 silicone oil. The bromo ketones were rather sensitive on gas chromatography and did not survive metal columns.

Blank runs showed that the bromo ketone–ketone ratio was

(21) Professor R. V. Stevens has suggested that these separations could well be carried out by preparative scale thin layer chromatography, with a great reduction in time.

(22) P. D. Bartlett and C. H. Stauffer, *J. Amer. Chem. Soc.*, **57**, 2580 (1935).

(23) L. G. Nunn and H. R. Henze, *J. Org. Chem.*, **12**, 541 (1947).

(24) A. T. Nielsen, G. Gibbons, and C. A. Zimmerman, *J. Amer. Chem. Soc.*, **73**, 4696 (1951).

(25) W. J. Evans and B. J. Brooks, *ibid.*, **30**, 406 (1908).

(26) A. Faworsky and N. Mandryka, *J. Prakt. Chem.*, **88**, 691 (1913).

(27) H. O. House and J. W. Blaker, *J. Org. Chem.*, **23**, 334 (1958).

(28) We thank Professor M. R. Wilcott for the 100-Mc nmr spectra.

unaffected by the isolation procedure, and the analysis was calibrated by known mixtures frequently.

Rate constants were calculated from the slope of a plot of bromo ketone–ketone against time, since the reactions were not carried to a large enough extent of completion to consider the variation of ketone concentration with time.

Isotopic Dilution Analysis Kinetics.—A weighed amount ($\leq$80 mg) of the tritiated ketone was mixed with the heated solvent and an excess of bromine (five- to tenfold) was added and the vessel placed in the thermostat. At the desired time (1–8 days) the reaction was quenched by cooling and dilution with petroleum ether (bp 30–60°); then a weighed amount (40–50 mg) of the inactive bromo ketone was added. Successive washings with water, 0.05 *M* sodium thiosulfate, water, 10% sodium carbonate, water, and saturated brine gave a colorless solution which was concentrated to about 1–2 ml at not greater than 50° on a rotary evaporator. Further concentration or higher temperatures sometimes led to discoloration. The concentrate was then subjected to chromatography on Florisil, from which the bromo ketone was eluted with petroleum ether and then the unchanged ketone with toluene. The bromo ketone rich fractions were mixed with inactive ketone and rechromatographed, and the ketone fraction was counted; if the activity was low enough the bromo ketone fraction was chromatographed once more before uv and radioassay, but if the activity was significant, the "holdback" separation was repeated.

After the final chromatographic separation the petroleum ether was mostly removed and replaced with toluene, again taking precautions not to overheat or remove all solvent. When the volume reached about 6 ml the uv spectrum was taken and the concentration calculated [λ_{max} 327 nm (ϵ 153) in toluene]. A 5-ml sample of the same solution was transferred to a counting vial, 15 ml of scintillator solution [4 g of 2,5-diphenyloxazole and 0.1 g of 2,2-*p*-phenylenebis(5-phenyloxazole) in 1 l. of toluene] was added and the sample was counted. Efficiency of counting was determined by automatic external standardization, and varied little except when much higher concentrations of bromo ketone were used, when some quenching appeared.

Registry No.—2-Benzoylbutane-2-*d*, 18321-26-1.

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The Mass Spectra of Cyclobutyl and Cyclopropylcarbinyl Methyl Ethers and the Methanolysis of Bicyclobutane[1]

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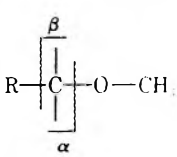
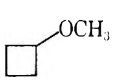
Received July 31, 1968

The mass spectral fragmentation patterns of cyclobutyl and cyclopropylcarbinyl methyl ethers were found to be similar and the mechanisms of the fragmentations were evaluated by use of deuterium-labeled material and by means of high-resolution mass spectrometry. In both materials the base peak was *m/e* 58, corresponding to the loss of ethylene. The mechanism of the acid-catalyzed addition of methanol to bicyclobutane was studied using the above mass spectral results. The addition was not concerted but proceeded *via* protonation to yield a bicyclobutonium ion (or equivalent activated complexes) which partially equilibrated before the nucleophilic attack of methanol occurred. When 1,3-butadiene in methanol was irradiated with ultraviolet light, cyclobutyl and cyclopropylcarbinyl methyl ethers were formed in low yield. These ethers were shown to be derived in a dark reaction of methanol with bicyclobutane.

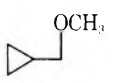
Alkyl ethers undergo two major fragmentation reactions upon electron impact in the mass spectrometer. These are "α" cleavage of the carbon–oxygen bonds leading to carbonium ions and "β" cleavage leading to oxonium ions.[3,4] The oxonium ions of ethers where both groups are larger than methyl undergo further rearrangements[3,4] which are of no concern to the present study. Generally, β cleavage has been found to yield the base peak of methyl ethers.[3]



In the course of a study of the photochemistry of 1,3-butadiene in methanol,[5] it was discovered that the mass spectra of cyclobutyl methyl ether (CBME), **1**, and cyclopropylcarbinyl methyl ether (CPCME), **2**, have one main feature which distinguishes them from the spectra reported for other methyl ethers. The



1



2

base peaks for **1** and **2** are at *m/e* 58, corresponding neither to α cleavage nor to β cleavage, but to the loss of the elements of ethylene. It was considered that these fragmentations involve cleavage of the cyclobutane and cyclopropane rings as shown in eq 1–2. In accord with eq 1 are the mass spectra of several cyclobutane derivatives which were recently reported.[6] In each case it was found that fission of the cyclobutane ring leads to the most abundant ion. Similarly it has been suggested that fission of the cyclopropane ring gives rise to the M − 28 peak in the mass spectrum of benzylcyclopropane.[7] It is of interest, however,

(1) This work was supported in part by PHS Grant No. AM-00709, National Institute for Arthritis and Metabolic Diseases, U. S. Public Health Service.

(2) (a) NASA Predoctoral Trainee, 1964–1967; (b) NSF Postdoctoral Fellow, 1964.

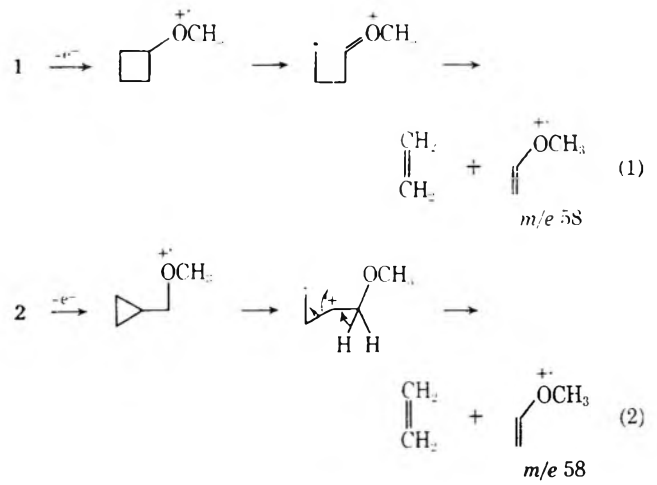
(3) F. W. McLafferty, *Anal. Chem.*, **29**, 1782 (1957).

(4) C. Djerassi and C. Fenselau, *J. Amer. Chem. Soc.*, **87**, 5747 (1965).

(5) J. H. Smith J. Saltiel, and W. G. Dauben, unpublished results.

(6) D. A. Bock and K. Conrow, *J. Org. Chem.*, **31**, 3608 (1966).

(7) N. J. Turro D. C. Neckers, P. A. Leermakers, D. Seldner, and P. D. 'Angelo, *J. Amer. Chem. Soc.*, **87**, 4097 (1965).



that, unlike 2, cyclopropylcarbinyl *sec*-butyl ether shows no M − 28 peak.[8] Mechanisms 1 and 2 have now been investigated using specifically labeled ethers.

Cyclobutyl Methyl Ether.—CBME-1-d_1 was prepared by reducing cyclobutanone with lithium aluminum deuteride followed by reaction of the resulting alcohol with sodium hydride and methyl iodide. The infrared spectrum of the ether showed a peak at 2092 cm^{-1}, corresponding to the C–D stretching frequency. The nmr spectrum showed no detectable α proton on the cyclobutane ring and the integration of the spectrum suggested one deuterium. It was not possible by mass spectrometry to determine directly the per cent deuterium in the ether since both the molecular ion and the M − 15 peaks were very weak and since there was an appreciable M − 1 peak. As can be seen in Figure 1, the *m/e* 58 peak has moved entirely to *m/e* 59, and, assuming that all the deuterium is in the *m/e* 59 ion, it can be estimated that the percentage of deuterium in **3** is 99% 1-*d*. This figure sets the lower limit of the isotopic purity of the sample. Furthermore, the fact that at least 99% of the *m/e* 58 ion from unlabeled CBME occurs as a deuterated moiety in the mass spectrum of the deuterated ether supports the mechanism proposed in eq 1.

In the undeuterated CBME (1), the other peaks which are larger than 5% of the base peak are *m/e* 43 and 55. A small peak is found at *m/e* 71 (0.4%). Cleavage of the carbon–oxygen bonds account for the *m/e* 55 and 71 while *m/e* 43 requires a hydrogen migration. Mechanisms leading to these ions are suggested below and the results shown in Figure 1 substantiate the proposals. As expected, ions *m/e* 71, 55, and 43 all increase by 1 mass unit in the deuterated species. Two pathways can be suggested for the formation of *m/e* 43 ion (Scheme I). the ion being either $C_3H_7^+$ or $C_2H_3O^+$; high-resolution mass spectral results obtained with cyclopropylcarbinyl ether (see later) indicate the involvement of only the latter ion.

Cyclopropylcarbinyl Methyl Ether.—CPCME-1-d_2 was prepared by reduction of methyl cyclopropylcarboxylate with lithium aluminum deuteride followed by methylation of the resulting alcohol. The ether possessed a maximum in the infrared spectrum at 2068 cm^{-1}, characteristic of C–D bonds and the nmr

(8) S. Meyerson and J. D. McCollum, *Advan. Anal. Chem. Instr.*, **2**, 213 (1963).

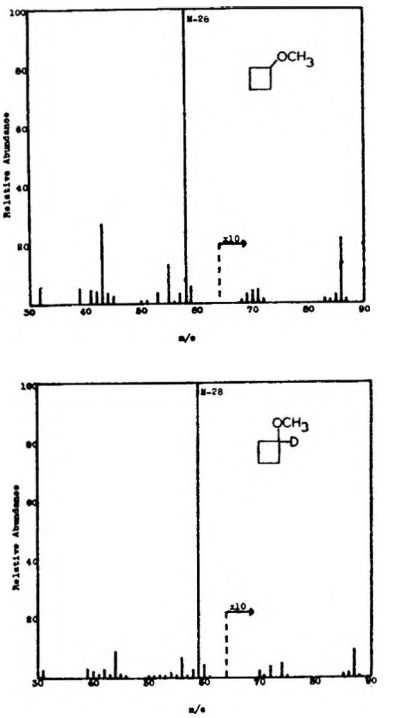
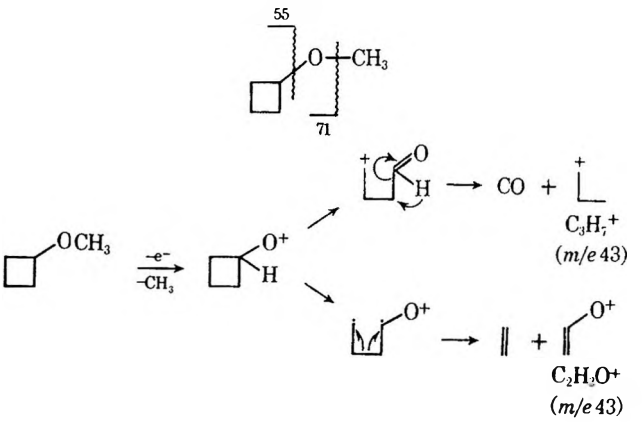


Figure 1.—Mass spectrum of cyclobutyl methyl ether.

SCHEME I



spectrum showed that absorption of the α-methylene protons was less than 5% of that for the corresponding peak in undeuterated material. The calculated isotopic distribution is 96% 2-*d*, 3% 1-*d*, and 1% O-*d*, assuming that all α-methylene protons are in the *m/e* 58 peak which moves to *m/e* 60 in the dideuterio ether (see Figure 2). Such an assumption is reasonable since the *m/e* 58 peak was shown to be $C_3H_6O^+$ by high-resolution mass spectroscopy (see Figure 3). These mass spectrographic values agree well with the nmr results and set the lower limit for the per cent of dideuterated material. The finding that the *m/e* 58 peak moves to 60 (containing all of the deuterium) strongly supports the mechanism proposed in eq 2.

Other peaks of CPCME (1) found in greater abundance than 5% of the base peak are *m/e* 43 (24%), 45 (53%), 53 (8%), and 55 (31%). In addition, the M − 1 peak at *m/e* 85 is 2%; the M − 15 peak at *m/e* 71 is 1%. The fragmentation pathways given in Scheme II can be proposed to account for these ions.

The results shown in Figure 2 substantiate these proposals; in the dideuterated species the original

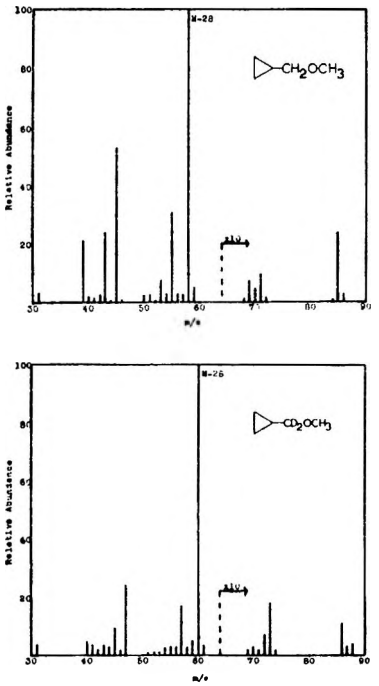


Figure 2.—Mass spectrum of cyclopropylcarbinyl methyl ether.

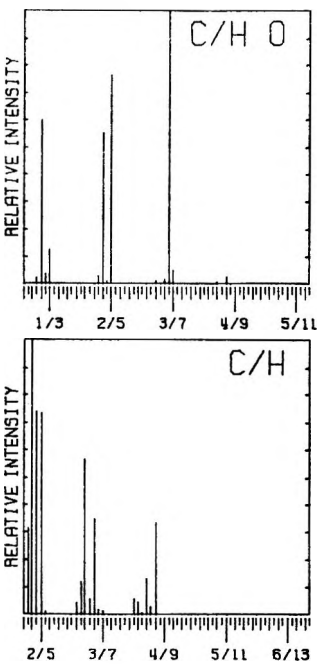


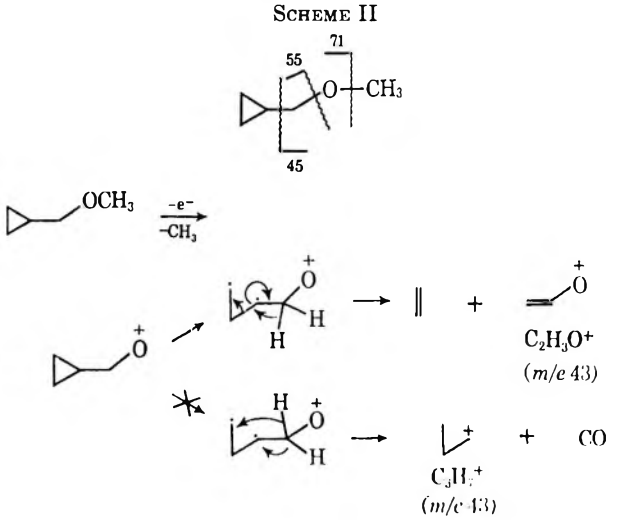
Figure 3.—High-resolution mass spectrum of cyclopropylcarbinyl methyl ether.

major peaks at *m/e* 43, 45, 55, and 71 all increase by two mass units. The high-resolution mass spectrum of CPCME is shown in Figure 3 and it proves that the compositions of the peaks found in the low-resolution spectra are, indeed, those predicted by the mechanism and, in addition, shows that the *m/e* 43 peak is due to $C_2H_3O^+$. The findings of large amounts of $C_2H_3^+$ and $C_2H_4^+$ support the mechanism for the loss of ethylene to give the *m/e* 58 peak. The nature of peak *m/e* 53 is undetermined.

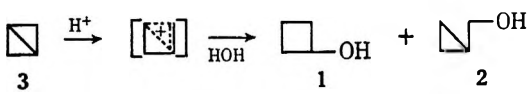
When this work was completed, it was learned that Hofman had published the high-resolution mass spectrum of cyclopropylcarbinol.[9] In this spectrum the base peak was at *m/e* 44, corresponding to the loss of ethylene. His suggested fragmentation mechanism is essentially the same as that discussed above. He also proposed detailed fragmentation pathways leading to the other major peaks, substantiating many of the suggestions by observations of related metastable peaks. His results support the mechanism proposed in this investigation.

(9) H. J. Hofman, Ph.D. Thesis, University of Amsterdam, 1966.

SCHEME II



The Acid-Catalyzed Addition of Methanol to Bicyclobutane.—Numerous workers have reported that bicyclobutane (BCB, **3**) and its derivatives are unstable in the presence of dilute acid.[10] Considering the simplest case first, Wiberg[10e] found that BCB in deuterium oxide at pH 2.3 yields cyclopropylcarbinol and cyclobutanol.[10e] Moore,[10a] Doering,[10c] and Wiberg[10e] suggested that, since these products resemble those obtained from reactions thought to involve bicyclobutonium ions,[11] the same intermediate might be formed when BCB (or its derivatives) is attacked by a proton. The present study has yielded additional evidence in support of this proposal.



3 **1** **2**

A solution of BCB in neutral methanol was prepared and after an initial decrease of 10% within 13 hr, possibly attributable to oxygen in the sample tube since an equal decrease was observed when benzene was used as the solvent, no decrease in the concentration of BCB was observed after 88 hr at 50°. When a solution of BCB in methanol containing a small amount of dilute perchloric acid was allowed to stand for a short period of time, three ethers were formed: CBME, 44%; CPCME, 51%; and homoallyl methyl ether, 5%. These ethers were isolated by preparative vpc and shown to be identical with authentic samples.

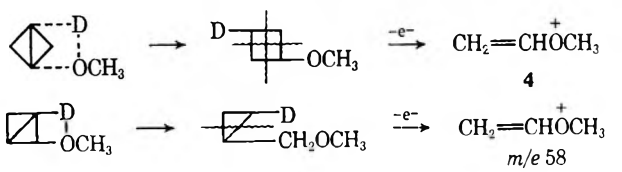
To study the mechanism of the reaction, BCB was allowed to react with methanol-O-*d* in the presence of

(10) (a) W. R. Moore, H. R. Ward, and R. F. Clark, *J. Amer. Chem. Soc.*, **83**, 2019 (1961); (b) W. G. Dauben and W. T. Wipke, *Pure Appl. Chem.*, **9**, 539 (1964); (c) W. von E. Doering and J. F. Coburn, Jr., *Tetrahedron Lett.*, 991 (1965); (d) R. B. Turner, P. Goebel, W. von E. Doering, and J. F. Coburn, Jr., *ibid.*, 997 (1965); (e) K. B. Wiberg, G. M. Lampman, R. P. Ciula, D. S. Connor, P. Schertler, and J. Lavanish, *Tetrahedron*, **21**, 2749 (1965); (f) E. P. Blanchard and A. Cairncross, *J. Amer. Chem. Soc.*, **88**, 487 (1966).

(11) For discussions of this ion, see L. Birladeanu, T. Hanafusa, B. Johnson, and S. Winstein, *ibid.*, **88**, 2316 (1966); P. von R. Schleyer and G. W. VanDine, *ibid.*, **88**, 2321 (1966).

acid; the resulting ethers were analyzed by mass spectrometry. Two samples of BCB in methanol-O-*d* were prepared, one containing 0.075 *M* perchloric acid and the other containing 0.0007 *M* acid. CBME and CPCME were isolated from each sample by preparative vpc of the crude, neutralized reaction mixtures. The mass spectra of each ether from the two sources (see Table I) showed a slightly different deuterium distribution, indicating that the concentration of acid had an effect on the products formed. As discussed earlier, an important fragment from CBME and CPCME is the vinyl ether ion (**4**), *m/e* 58 (Scheme III).

SCHEME III

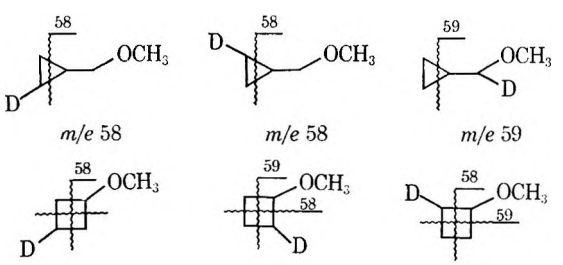


The finding of an *m/e* 59 ion (greater intensity than expected from natural abundance of ^{13}C) requires deuterium from the solvent on the α or β carbon atoms of these two ethers. Concerted addition of methanol-O-*d* to BCB would yield CBME-3-d_1 and CPCME 2-d_1, and the fragmentation of each should show no *m/e* 59 ion in the mass spectra. The finding of a significant *m/e* 59 ion is in agreement with the earlier suggestion that the acid-catalyzed addition of methanol to BCB involves an initial protonation step to give an intermediate carbonium ion which can rearrange before nucleophilic attack of methanol can occur.

TABLE I
DISTRIBUTION OF DEUTERIUM IN ETHERS

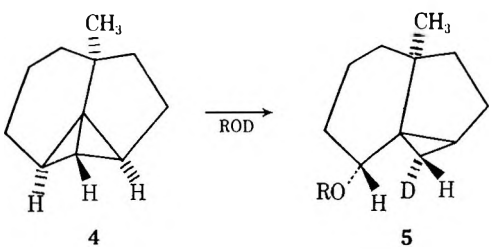
Ethers	Concn of acid, *M*	Relative amounts of $C_3H_6O^+$ and $C_3H_5DO^+$, % *m/e* 58	% *m/e* 59	% of statistical distribution
CBME	0.0007	85	15	46
	0.075	81	19	56
CPCME	0.0007	86	14	42
	0.075	83	17	50

In the carbonium ion formed, if the deuterium is statistically distributed among the methylene carbons prior to reaction with methanol, CPCME should have 33% of the deuterium on the α carbon atom. The



possible locations for the deuterium in these materials are shown above. Since in CPCME there is only one fragmentation pathway to the $C_3H_6O^+$ ion, only one of the three deuterated isomers will yield a *m/e* 59 peak and the ratio of the *m/e* 59:58 peaks should be 1:2. Consideration of the possible locations of the deuterium in CBME and the fragmentation pattern shows again that the *m/e* 59:58 ratio should be 1:2 since there are four ways to obtain the *m/e* 58 peak and only two ways to get the *m/e* 59 peak.[12] The mass spectral values (see Table I) show that the distribution of deuterium is between 42 and 56% of the statistical values. These similar data for deuterium scrambling in both CBME and CPCME may be accommodated by collapse of a protonated BCB to a bicyclobutonium ion (or rapidly equilibrating cyclobutyl and cyclopropylcarbinyl cations) whose short lifetime does not allow complete scrambling; *i.e.*, partial equilibration occurs prior to the irreversible attack of the nucleophile.

The foregoing results are in complete accord with earlier published work which indicated the involvement of similar ionic species.[10e,13] Recently, the concept of "twist" bent bonds was postulated and the concept was applied to the reactions of bicyclobutanes.[14] It was suggested that reaction of a protic solvent with the bicyclobutane derived from 3,5-hexalins[10e,15,16] might proceed by an initial nucleophilic attack by the solvent. In view of the complete parallelism of the reactions of all of the bicyclobutanes studied and a carbonium ion process, there appears to be little basis for considering a nucleophilic process in the reactions of bicyclobutanes containing only alkyl substituents. For example, the protolysis of the bicyclobutane **4** occurs with retention of configuration leading to the carbonium ion by reaction from the *endo* side of the ring, the side which has been suggested to be electron rich.[17] The subsequent addition of the anion occurs from the opposite side, a result anticipated by the involvement of a bicyclobutonium-type cation, to yield the cyclopropylcarbinyl ether **5** resulting from



4 **5**

inversion of C-6. The absence of product derived from cleavage of the center bond of the bicyclobutane cannot be taken as proof that such a bond was not initially broken[18] since the resulting cyclobutyl cation could readily rearrange to the cyclopropylcarbinyl cation. This stepwise addition has been found to occur with all bicyclobutanes containing only alkyl substituents.[13] With 1-cyano-3-methylbicyclo[1.1.0]-

(12) This analysis assumes that there is no deuterium isotope effect in the fragmentation reaction as deuterium is not directly involved in the reaction leading to the loss of ethylene; *cf.* J. K. MacLeod and C. Djerassi, *Tetrahedron Lett.*, 2183 (1966).

(13) W. G. Dauben and C. D. Poulter, *Tetrahedron Lett.*, 3021 (1967).

(14) P. G. Gassman, *Chem. Commun.*, 793 (1967).

(15) W. G. Dauben and F. G. Willey, *Tetrahedron Lett.*, 893 (1962).

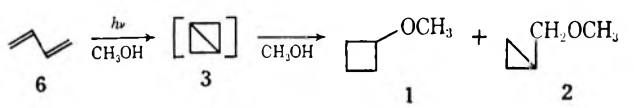
(16) G. Just and V. DiTullio, *Can. J. Chem.*, **42**, 2153 (1964).

(17) M. Pomerantz and E. W. Abrahamson, *J. Amer. Chem. Soc.*, **88**, 3970 (1966).

(18) K. B. Wiberg, *Tetrahedron*, **24**, 1083 (1968).

butane, however, electronic effects of the substituents greatly affect the reaction of the ring system and an *endo-cis* addition occurs.[10f,19] Elucidation of the mechanistic details of the reactions of this latter type of bicyclobutane awaits further study.

The Irradiation of 1,3-Butadiene in Methanol.—When a solution of 1,3-butadiene (6) in methanol contained in a flask which had not been base washed before use was irradiated through quartz with a 450-W Hanovia mercury lamp, about equal amounts of CBME (1) and CPCME (2) were isolated in a total yield of about 3%. Repetition of this reaction in methanol-O-*d* as the solvent gave ethers with the same deuterium distribution as the ethers obtained by the acid-catalyzed addition of the deuterated solvent to BCB (3).



When the irradiation of 1,3-butadiene was conducted in quartz tubes which had been washed with concentrated ammonium hydroxide and dried for 12 hr at 110°, no ethers were formed. The vpc trace of the total reaction mixture showed a peak corresponding in retention time to BCB (3). Upon addition of perchloric acid to make the solution 0.1 *M* in acid, the BCB peak immediately disappeared and peaks corresponding in retention time to the ethers appeared.

These studies show that in the direct irradiation of 1,3-butadiene in methanol there is no light-induced addition of solvent. This result is similar to that found[20,21] for other unconstrained 1,3-dienes and shows that the light-induced addition of a protic solvent to a 1,3-diene occurs only when the diene is constrained from adopting a nonplanar excited state.

Experimental Section

Physical Measurements.—Infrared spectra were taken in carbon tetrachloride, unless otherwise noted, using a Perkin-Elmer Model 137 Infracord. Nuclear magnetic resonance spectra were determined using a Varian Model A-60 spectrometer with samples in carbon tetrachloride containing tetramethylsilane as internal standard, unless otherwise specified. Combustion analyses were carried out by the Microanalytical Laboratory, College of Chemistry, University of California at Berkeley. Mass spectra were obtained on a CEC Model 21-103C spectrometer which was equipped with an ion multiplier and run at 70 eV. The high-resolution mass spectrum was determined on a Model CEC 110 mass spectrometer.

Cyclobutyl Methyl Ether (1).—A slurry of 297 mg (7.9 mmol) of lithium aluminum hydride in 7 ml of dry ether was cooled to 0°. A solution containing 562 mg (7.9 mmol) of cyclobutanone in 1.3 ml of dry ether was added dropwise to the cooled slurry. The reaction flask was protected from moisture with a drying tube and stirred at 0° for 0.5 hr. The aluminum salts were precipitated with saturated aqueous ammonium chloride solution. The ether was decanted from the salts, which were washed three times with ether. The combined ether layers were filtered through sodium sulfate and concentrated under a stream of nitrogen to about 2 ml.

A 1.7-g (38 mmol) sample of 53% sodium hydride suspended in mineral oil was washed twice with dry ether, suspended in 10 ml of ether, and cooled to 0°. The above ethereal solution of cyclobutanol was added dropwise to the cooled suspension. The mixture was allowed to come to room temperature and stirred for 4 hr. Methyl iodide (0.98 ml, 16 mmol) was added; the flask was stoppered and stirred for 4 days. Vpc of the crude reaction mixture showed that all of the cyclobutanol had reacted and only cyclobutyl methyl ether (CBME) had formed.

To decompose the unreacted methyl iodide, 3.8 ml (16 mmol) of tri-*n*-butylamine was added, and stirring continued for another 2 days. Vpc showed that no methyl iodide remained after this treatment.

The ethereal solution was filtered and the CBME collected by preparative vpc: $\nu_{max}^{CHCl_3}$ 1351, 1236, 1125, 1027; nmr τ 6.3 (1 H, complex multiplet, α H), 6.90 (3 H, singlet, methoxy H), 7.6–8.8 (6 H, complex multiplet, methylene H).

Cyclobutyl-1-d_1 methyl ether was prepared in an identical manner starting with 630 mg (15 mmol) of lithium aluminum deuteride and 2.13 g (30.5 mmol) of cyclobutanone. The product was isolated by preparative vpc: ν_{max} 2092, 1255, 1176, 1055, 929 cm^{-1}; nmr (external TMS) τ 6.98 (3 H, singlet, methoxy H), 7.7–8.8 (6 H, broad multiplet, methylene H).

Cyclopropylcarbinyl Methyl Ether (2).—Following the exact procedure described above, 7.0 g (81.3 mmol) of cyclopropanecarboxylic acid was reduced with 2.8 g of lithium aluminum hydride. After the methylation the solvent was distilled through a spinning-band column. All higher boiling material was collected in one fraction and the CPCME purified by preparative vpc: ν_{max} 3090, 1109, 1018, 978, 897 cm^{-1}; nmr (external TMS) τ 6.76 (3 H, singlet, methoxy H), 6.85 (2 H, doublet, J = 6.1 cps, α H), 8.8–9.2 (1 H, multiplet, cyclopropylmethyne H), 9.2–10.0 (4 H, multiplet, cyclopropylmethylene H).

Cyclopropylcarbinyl-1-d_1 methyl ether was prepared in an identical manner using 1.5 g of lithium aluminum deuteride and 7 g of methyl cyclopropylcarboxylate. The product was isolated by preparative vpc: ν_{max} 3088, 2155, 2068, 1181, 1121, 1022, 937, 901 cm^{-1}; nmr (external TMS) τ 6.76 (3 H, singlet), 8.8–9.2 (1 H, multiplet), 9.2–10.0 (4 H, multiplet).

Rate of Decomposition of Bicyclobutane in Methanol.—In a Pyrex nmr tube which had never contained acidic material but had not been rigorously base washed was sealed a solution of 100 μl (1.3 mmol) of BCB[10e] and 75 μl (1.7 mmol) of benzene in 0.50 ml of methanol (solution A). In a similar tube was sealed a solution of 100 μl (1.88 mmol) of toluene and 100 μl (1.3 mmol) of BCB in 0.50 ml of benzene (solution B). The sealed tubes were placed in an oil bath which was heated to 49.99 ± 0.01°. The reaction was followed by nmr spectroscopy. The concentration of BCB was determined in reference to the internal aromatic hydrocarbon standards. The concentration was checked at 0, 12.9, 39.1, and 87.7 hr. The concentrations of BCB in mmoles per milliliter were as follows: solution A, 1.69 ± 0.03, 1.54 ± 0.04, 1.52 ± 0.05, 1.53 ± 0.05; solution B, 2.56 ± 0.10, 2.36 ± 0.06, 2.33 ± 0.06, 2.38 ± 0.10.

Acid-Catalyzed Decomposition of Bicyclobutane in Methanol.—A solution containing 0.9 ml (12 mmol) of bicyclobutane[10c] in 3 ml of methanol was cooled to 0° in a graduated test tube. A 0.05-ml aliquot of 0.2 *N* perchloric acid in methanol was added. The reaction was immediate and violent. Vpc showed that this solution contained 5% homoallyl methyl ether, 44% CBME, and 51% CPCME. After neutalization with a few milligrams of solid potassium bicarbonate, the three components were isolated from the crude reaction mixture by preparative vpc.

Acid-Catalyzed Decomposition of Bicyclobutane in Methanol-O-*d*.—Into two 5-ml pear-shaped flasks was weighed the following: flask A, 16.3 mg (0.12 mmol) of 70% perchloric acid; flask B, 0.1 mg (0.007 mmol) of 70% perchloric acid. A solution of 0.80 ml (10 mmol) of bicyclobutane[10e] in 3 ml of methanol-O-*d* (>97% D) was prepared. A 1.5-ml aliquot of this solution was added to flask A to give a solution containing 3 *M* BCB and 0.075 *M* acid. A 1.0-ml aliquot was added to flask B to give a solution containing 3 *M* BCB and 0.0007 *M* acid. The flasks were stoppered and placed in the refrigerator for 3 days. The solutions were each subjected to preparative vpc and the deuterated ethers, CPCME and CBME, collected as before, The mass spectra of these ethers were obtained and reported in Figures 1 and 2.

Irradiation of 1,3-Butadiene in Methanol.—A 40-ml aliquot of a 0.56 *M* solution of 1,3-butadiene in methanol (concentration determined by uv spectroscopy) was diluted to 750 ml with methanol. This solution was irradiated for 24 hr through quartz in the usual manner. The glassware was not base washed before use. An additional 10 ml of the 0.56 *M* butadiene solution was

(19) E. P. Blanchard and A. Cairncross, private communication.
(20) W. G. Dauben and W. A. Spitzer, *J. Amer. Chem. Soc.*, **90**, 802 (1968).
(21) W. G. Dauben and C. D. Poulter unpublished observation.

added and the irradiation continued for 20 hr. The vpc trace (using an internal standard) showed a 3% yield of ethers which were composed of CBME and CPCME in a ratio of 47:53 and a trace of homoallyl methyl ether. These yields represent minimum values due to the loss of butadiene during the irradiation under the conditions employed.

The crude irradiation mixture was distilled through a 24-in. spinning-band column and the first 100 ml of distillate collected. The distillate was diluted with an equal volume of water and extracted with two 15-ml portions of pure pentane. The pentane solution was dried and the pentane distilled through a 24-in spinning-band column. The residue was purified by preparative vpc and the CBME and CPCME possessed nmr and mass spectra identical with those of authentic samples.

When the reaction was run in methanol-O-*d*, the ethers obtained possessed mass spectra identical with those reported above for the deuterated species derived from BCB.

Irradiation of 1,3-Butadiene in Methanol in the Absence of Acid.—A 0.10 *M* solution of butadiene in methanol which had been freshly distilled from magnesium was prepared in base-washed glassware. The sample also contained 1,2-*trans*-dimethylcyclohexane (3.4×10^{-4} *M*), which is used as an internal standard. Aliquots (3 ml) of this solution were placed in rigorously base washed quartz tubes,[22] degassed, and sealed. The irradiation was performed in the merry-go-round apparatus using no filter. After 4.5 hr a sample was withdrawn. The concentration of butadiene, measured by uv spectroscopy, was 0.084 *M*. The vpc trace showed a new peak corresponding in retention time to bicyclobutane; no ethers were observed. A 3-μl sample of 70% aqueous perchloric acid was added to the solution, which was allowed to stand a few minutes and analyzed again. There was no peak corresponding to BCB and two new peaks, shown by coinjection with authentic materials to be CBME and CPCME, were found.

Registry No.—**1**, 18593-33-4; **1** (1-d_1), 18593-34-5; **2**, 1003-13-0; **2** (1-d_2), 18593-36-7; **3**, 157-33-5.

Acknowledgment.—We wish to thank Professor A. L. Burlingame, Dr. C. Fenselau, and Miss Sherri Firth for their interest and cooperation in the investigation of the mass spectra of the materials reported.

(22) G. S. Hammond, J. Saltiel, A. A. Lamola, N. J. Turro, J. S. Bradshaw, D. O. Cowan, R. C. Counsell, V. Vogt, and C. Dalton, *J. Amer. Chem. Soc.*, **86**, 3197 (1964).

Free-Radical Reactions of 3,3-Dimethylbutene, 3-Methyl-3-phenylbutene, and *t*-Pentylbenzene Induced by Di-*t*-butyl Peroxide[1]

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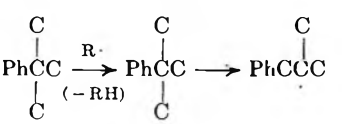
Received June 18, 1968

The effect of di-*t*-butyl peroxide (DTBP) at 150° upon skeletal isomerization of some model hydrocarbons was investigated. The hydrocarbons used for this study were 3,3-dimethylbutene, 3-methyl-3-phenylbutene, and *t*-pentylbenzene. The 1,2-vinyl migration in the olefins was not observed. The methyl radical, produced from the decomposition of the DTBP, added to the olefinic double bonds. 3,3-Dimethylbutene formed 2,2-dimethylpentane and the corresponding olefins, and 2,2,3-trimethylpentane. The addition of the methyl radical to 3-methyl-3-phenylbutene was accompanied by phenyl migration leading to the ultimate formation of 2-methyl-3-phenylpentane and of the corresponding olefins. *t*-Pentylbenzene underwent skeletal isomerization in the presence of DTBP at 150° with the production of 2-methyl-3-phenylbutane, 2-benzylbutane, and 2-methyl-2-phenylpentane. The methyl radical was also noted to add to the aromatic ring to form *p*-*t*-pentyltoluene.

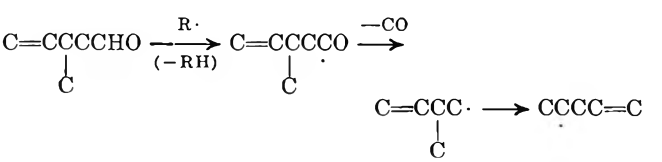
Recent studies in this laboratory have demonstrated that free-radical intermediates are involved in the aromatization of alkanes[2] and cyclanes[3] and in the dehydrogenation of alkylbenzenes[4] over "nonacidic" chromia–alumina catalyst. These free radicals were responsible for the skeletal isomerization accompanying the dehydrogenation reaction either through a phenyl and/or vinyl migration. This was demonstrated in the case of 2-phenylbutane-2-^{14}C, which rearranged to a mixture of 1-phenylbutenes-1-^{14}C and 1-phenylbutenes-2-^{14}C.[4c]

In order to obtain a better understanding of free-radical participation in the catalytic dehydrogenation reactions, it was decided to investigate the behavior of free-radical-induced reactions of hydrocarbons formed under mild conditions by the decomposition of di-*t*-butyl peroxide (DTBP).

It has been shown previously by one of us that *t*-butylbenzene refluxed in the presence of DTBP undergoes isomerization to isobutylbenzene.[5]



More recently, 1,2-vinyl migration had been observed to occur during the decarbonylation of 3-methyl-4-pentenal and *trans*-3-methyl-4-hexenal.[6]



(1) This research was supported by the Atomic Energy Commission Contract AT-(11-1)-1096, COO-1096-19.

(2) H. Pines and C. T. Goetschel, *J. Org. Chem.*, **30**, 3530 (1965).

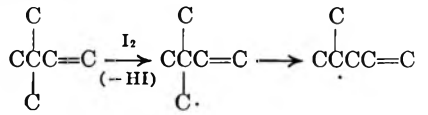
(3) (a) H. Pines, W. R. Fry, N. C. Sih, and C. T. Goetschel, *ibid.*, **31**, 4094 (1966); (b) W. F. Fry and H. Pines, *ibid.*, **33**, 602 (1968).

(4) (a) H. Pines and C. T. Goetschel, *J. Amer. Chem. Soc.*, **87**, 4207 (1965); (b) H. Pines and C. T. Goetschel, *J. Catal.*, **6**, 371 (1966); (c) H. Pines and C. T. Goetschel, *ibid.*, **6**, 380 (1966); (d) H. Pines and M. Abramovici, *J. Org. Chem.*, **34**, 70 (1969).

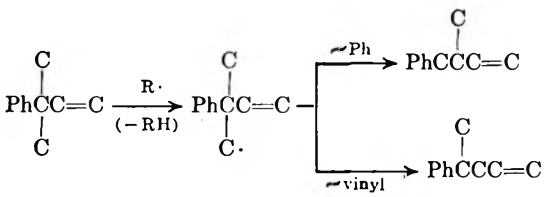
(5) H. Pines and C. N. Pillai, *J. Amer. Chem. Soc.*, **82**, 2921 (1960).

(6) L. K. Montgomery, J. Matt, and J. R. Webster, Abstracts, 147th National Meeting of the American Chemical Society, Philadelphia, Pa., April 1964, p 29N.

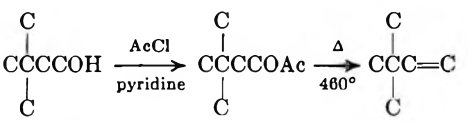
The present paper deals with the effect of free radicals, generated by the decomposition of DTBP, upon 3,3-dimethylbutene, 3-methyl-3-phenylbutene, and *t*-pentylbenzene. Since vinyl migration was noted in the case of iodine-initiated free-radical reactions at 500°,[7] it was of interest to determine if an analogous reaction would occur in 3,3-dimethylbutene under present conditions.



3-Methyl-3-phenylbutene was elected for this study in order to determine whether DTBP would cause it to undergo a phenyl and/or a vinyl migration; and, if this occurred, to assess the relative ease of their migrations.



3,3-Dimethylbutene.—The title hydrocarbon was synthesized in purity greater than 99% by the sequence of reactions shown.



The reaction of 3,3-dimethylbutene with DTBP was carried out in a 125-cc-capacity stainless steel rotating autoclave, heated at 140–150° for 3.5 hr. The autoclave was then cooled, and both liquid and gaseous reaction products were collected and analyzed using a F & M Model 720 programmed temperature gas chromatograph. The results are given in Table I. From the data obtained it was calculated that the molar ratio of olefin reacted to free radicals ($C_3CO\cdot$) produced was 1.35.

The composition of the "monomeric" product showed that the expected 4-methyl-1-pentene which would be formed through a 1,2-vinyl migration was absent. The reaction products result from the double bond reacting with the methyl radical formed from the decomposition of the peroxides, and can be explained by eq 1–9.

3-Methyl-3-phenylbutene was synthesized in over 99% purity according to Scheme I.

The free-radical reaction was made in a round-bottomed flask provided with a 6-in. distilling column. The flask was heated at 135–140° for 24 hr, and the products boiling below that temperature were removed. Table II summarizes the experimental results.

The expected products, to be formed through a 1,2-phenyl migration and/or 1,2-vinyl migration, were absent. Instead, the reaction products, as shown in

(7) J. H. Raley, R. D. Mullineaux, and C. W. Bittner, *J. Amer. Chem. Soc.*, **85**, 3180 (1963).

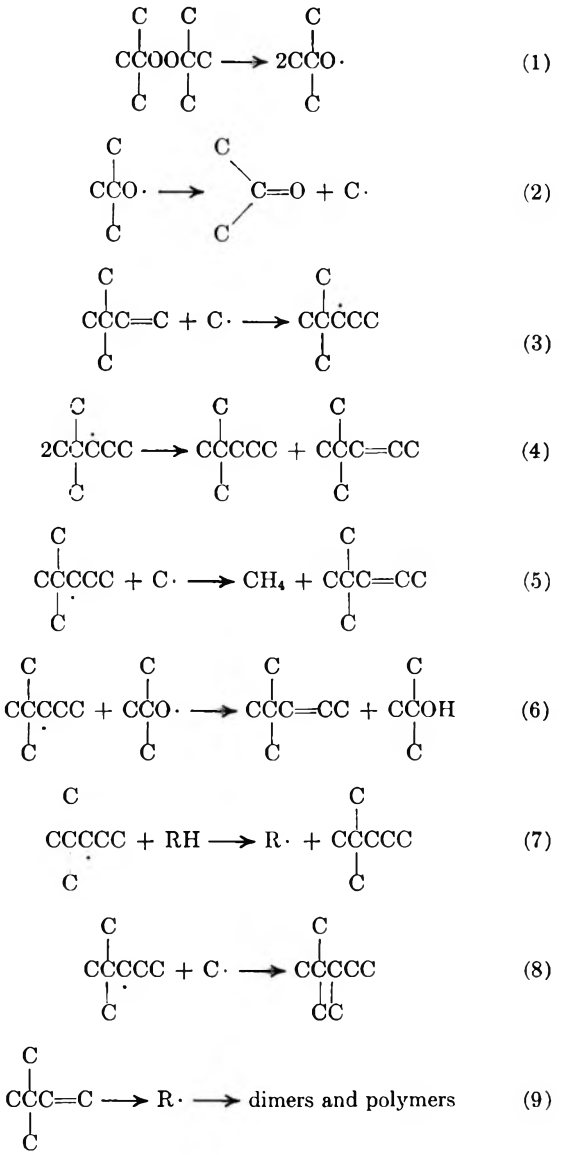


Table II, resulted from a novel type of reaction resulting from a methyl radical addition to the olefinic double bond, followed by a 1,2-phenyl migration to form a new free radical. This free radical may then lose a hydrogen atom to form an alkenylbenzene, or it may abstract a hydrogen to produce an alkylbenzene (steps 10–13).

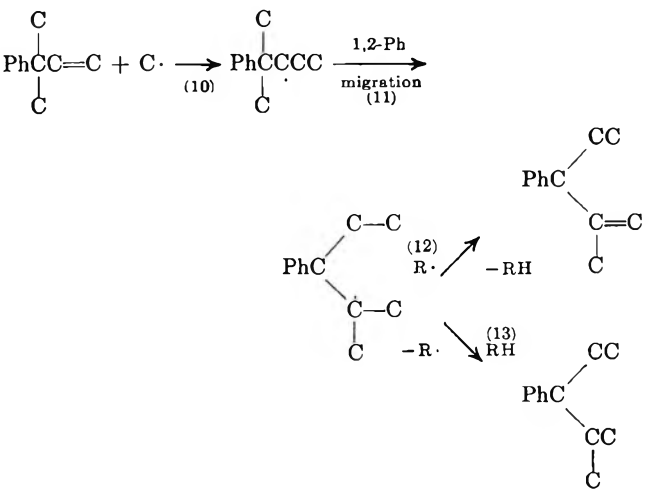
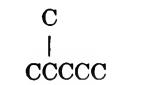
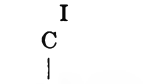
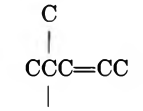
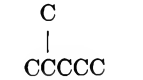


TABLE I

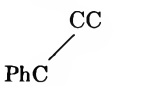
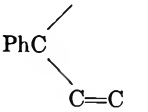
REACTION OF 3,3-DIMETHYLHEXENE WITH DI-*t*-BUTYL PEROXIDE (DTBP)[a]

Material	Amt charged, g (mol)	Amt reacted, mol (mol %)	Monomeric Product[e] Kind[e]	Mol %[b]	Mol %[c]	Yield,[d] %
3,3-Dimethylbutene	28.0 (0.33)	0.29 (88.0)		58.0	11.6	16.4
DTBP	19.5 (0.133)	0.107 (80.5)	I			
				18.3	3.7	5.1
			cis IIa			
				8.9	1.8	2.3
			trans IIb			
				14.4	2.9	4.2
			III			

[a] Conditions: autoclave, 125-cc capacity; temperature, 140–150°; duration, 3.5 hr. [b] Composition of "monomeric" product. [c] Based on reacted 3,3-dimethylbutene. [d] Based on reacted DTBP; assuming $2(CH_3)_3CO\cdot$ per mole of DTBP reacted. [e] Liquid product formed (based on converted olefin): monomeric 20%, di- and polymeric 80%; gas produced, 450 cc (99% methane).

TABLE II

REACTION OF 3-METHYL-3-PHENYLBUTENE WITH DI-*t*-BUTYL PEROXIDE (DTBP)[a]

Material	Amt charged, g (mol × 10^{-2})	Amt reacted, mol × 10^{-2} (mol %)	Monomeric Product[e] Kind[e]	Mol %[b]	Mol %[c]	Yield,[d] %
3-Methyl-3-phenylbutene	11.0 (7.52)	4.27 (56.8)		56.9	6.8	5.7
DTBP	4.4 (3.01)	2.53 (84.1)		43.1	5.1	4.3
				Traces		

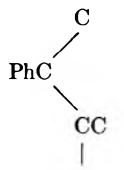
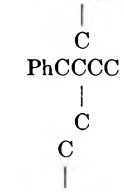
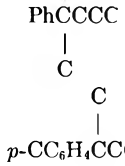
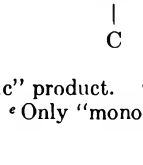
[a] Conditions: temperature, 135–140°; duration, 24 hr. [b] Composition of "monomeric" product. [c] Based on reacted 3-methyl-3-phenylbutene. [d] Based on converted DTBP, assuming $2(CH_3)_3CO\cdot$ per mole of DTBP reacted. [e] Composition of product (based on hydrocarbon reacted): monomeric 12%, di- and polymeric 88%. Gaseous hydrocarbons formed 275 cc; composition, methane 96.5%, ethane 3.3%, ethylene and propane 0.2%.

The possible driving force which causes phenyl migration, step 11, is the greater stability of the tertiary over the secondary free radical.

***t*-Pentylbenzene.**—Commercially available hydrocarbon was used and purified by means of preparative glpc to over 99% purity. The apparatus used was the same as described for 3-methyl-3-phenylbutene. The experimental conditions and results are shown in Table III. The reaction products are assumed to be formed through steps 14–22. The statistical probability of forming the primary free radical compared with the secondary free radical on the β carbon atom to the

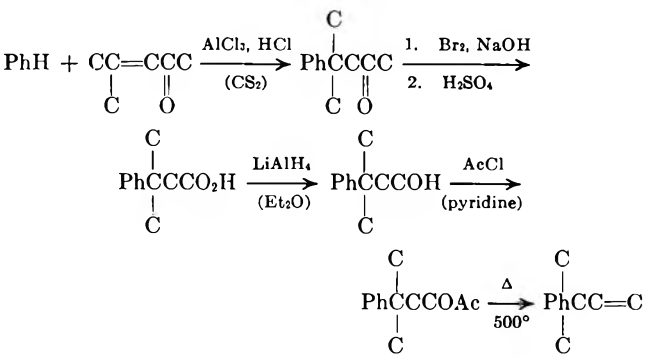
Table III

Reaction of *t*-Pentylbenzene with Di-*t*-butyl Peroxide (DTBP)[a]

Material	Amt charged, g (mol × 10^{-2})	Amt reacted, mol × 10^{-2} (mol %)	Monomeric product[e] Kind[d]	Mol %[b]	Mol %[c]	Yield,[d] %
t-Pentylbenzene	9.2 (6.20)	0.84 (13.5)		45.9	6.2	8.4
DTBP	3.6 (2.48)	2.26 (91.0)		34.8	4.7	6.4
				8.9	1.2	1.8
				10.4	1.4	2.0

[a] Conditions: temperature, 135–140°. [b] Composition of "monomeric" product. [c] Based on reacted *t*-pentylbenzene. [d] Based on converted DTBP, assuming $2(CH_3)_3CO\cdot$ per mole of DTBP reacted. [e] Only "monomeric" product was formed.

Scheme I



phenyl group, steps 14 and 17, is 3:1. The ratio of the products formed in steps 19 and 16 is 45.9/34.8 = 1.32. From this it can be concluded that the propensity of the formation of a secondary free radical relative to a primary free radical is equal to 1.32 × 3 ≅ 4, which corresponds to the values reported in the literature.[8] Both of these two free radicals are most likely stabilized by the proximity of a phenyl group through the formation of a phenonium-type radical intermediate.[4]

The presence of *t*-hexylbenzene can be explained by steps 20 and 21. It is less likely that this compound could have been produced by the addition of a methyl radical to 3-methyl-3-phenylbutene, which could have been generated by the loss of hydrogen from the radicals formed in steps 17 and 20. Such an addition is usually accompanied by a 1,2-phenyl migration as demonstrated by step 11.

The aromatic ring methylation, step 22, leading to the formation of *p*-*t*-pentyltoluene, is a scarcely known reaction under the present conditions.

(8) H. B. Hass, E. T. McBee, and P. Weber, *Ind. Eng. Chem.*, **27**, 1190 (1935).

Conclusions

The present study has shown that the expected 1,2-vinyl migration was not detected in the reactions of 3,3-dimethylbutene and of 3-methyl-3-phenylbutene with the free radicals generated from di-*t*-butyl peroxide. The reactivity of the above hydrocarbons toward the free-radical initiator was uniquely the reaction of their olefinic double bonds toward the attacking methyl radical. The addition of the methyl radical to the olefinic bond of 3-methyl-3-phenylbutene is followed by 1,2-phenyl migration. The free-radical-induced reaction of *t*-pentylbenzene is accompanied by 1,2-phenyl migration. Methylation of the aromatic ring leading to *p*-*t*-pentyltoluene was also observed.

Experimental Section

Synthesis of Hydrocarbons. 1. 3,3-Dimethylbutene. a. 3,3-Dimethylbutyl Acetate.—3,3-Dimethyl-1-butanol[9] (102 g, 1 mol) was allowed to react with 94 g (1.2 mol) of acetyl chloride in the presence of 158 g (2 mol) of pyrdine at 0°. The acetate thus obtained amounted to 128 g (89% yield).

b. 3,3-Dimethylbutene.—The olefin was obtained in over 99% purity by passing the acetate at 460° through a reaction tube filled with quartz chips.

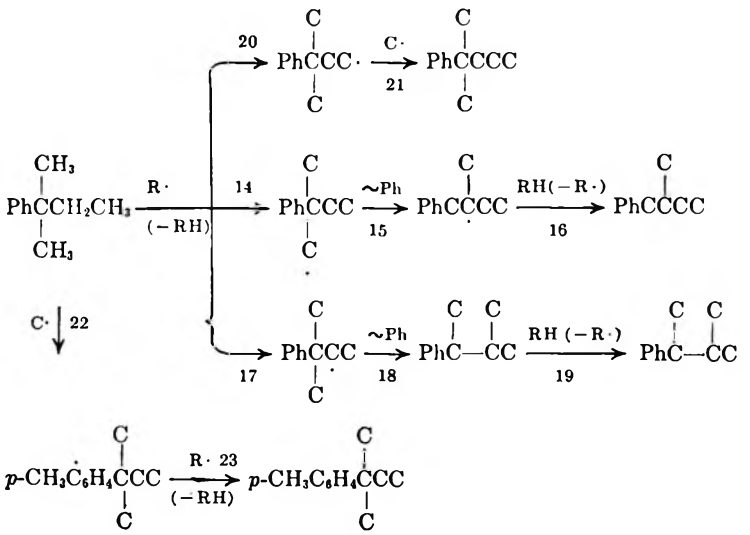
2. 3-Methyl-3-phenylbutene. a. 4-Methyl-4-phenyl-2-pentanone was prepared by treating 468 g (6 mol) of benzene with 294 g (3 mol) of mesityl oxide in the presence of 600 g of carbon disulfide as solvent and 480 g (3.6 mol) of anhydrous aluminum chloride, according to the procedure described previously.[10] The yield of the ketone was 68%, based on mesityl oxide; it distilled at 130–133° (10 mm), $n^{20}D$ 1.5110.

b. 3-Methyl-3-phenylbutyric Acid.—The ketone obtained above, 176 g (1 mol), was allowed to react with 479 g (3 mol) of bromine in the presence of a solution of 330 g (8.25 mol) of sodium hydroxide in 2.8 l. of water. The yield of the title acid thus obtained was 75%, bp 160–162° (10 mm).

c. 3-Methyl-3-phenylbutanol was prepared by the reduction of the 3-methyl-3-phenylbutyric acid, 133 g (0.75 mol), with 36

(9) V. N. Ipatieff, W. W. Thompson, and H. Pines, *J. Amer. Chem. Soc.*, **73**, 553 (1951).

(10) V. N. Ipatieff, H. Pines, and R. C. Olberg, *ibid.*, **70**, 2123 (1948).



g (0.94 mol) of lithium aluminum hydride in 800 cc of anhydrous ether, according to the described procedure.[11] The alcohol which was obtained in 90% yield distilled at 137–142° (16 mm), $n^{25}D$ 1.5207.

d. **3-Methyl-3-phenylbutyl Acetate.**—The acetylation was made at 0° by the usual procedure employing 110 g (0.67 mol) of the alcohol, 63 g (0.8 mol) of acetyl chloride, and 140 g (1.8 mol) of pyridine. The yield of the acetate was 92%, bp 131–133° (10 mm).

e. **3-Methyl-3-phenylbutene.**—The acetate was pyrolyzed at 462° over quartz chips, the conversion per pass being 25–30%. The recovered acetate was repassed through the pyrolytic tube. The title hydrocarbon thus produced was over 99% pure.

Apparatus and Procedure.—The experiments were carried out by the methods already described in the former sections.

The starting materials and the reaction products were analyzed by vapor phase chromatography using a F & M Model 720 dual column programmed temperature gas chromatograph.

A "polar" 0.25 in. × 10 m column, filled half of its length with 10% GEXF 1100 on Gas Pack W 80/100 and the other half with 10% Carbowax 20M on the same support, was used alternately with a "nonpolar" 0.25 in. × 5 m column filled with 15% silicone gum SE-30 on 60/80 WAB (White Celite).

The same silicone gum column was used for the analysis, at room temperature, of the gases evolved during the reactions.

For the separation of reaction products, a $^3/_8$ in. × 5 m preparative gas chromatography column filled with 12% silicone 550 on Chromosorb P 30/60 was used.

(11) H. Pines and L. Schaap, *J. Amer. Chem. Soc.*, **80**, 4378 (1958).

A 0.25 in. × 2.5 m column filled with 18% Carbowax 20M on Chromosorb P 60/80 was used to determine the amount of DTBP which was consumed during the reactions. The column was kept at 40°, the injection port at 90°, and the detector at 300°, in order to avoid the decomposition of the DTBP during the run, inside the instrument.

As a general procedure, the reaction products were tentatively identified by comparison of their retention times with known samples, using the above-mentioned analytical gas chromatographic columns.

The initial identification trial was followed by separation of the products with the use of preparative gas chromatography, and then the indices of refraction, ir spectra, and occasionally the nmr and uv spectra were taken, analyzed and compared with those of known samples.

The position of the double bond, which led to the characterization of 2-methyl-3-phenyl-1-pentene, was determined with the help of uv spectroscopy. The spectrum obtained, using a Cary 14 instrument, showed lack of conjugation between the aromatic ring and the side-chain olefinic double bond.

Selective hydrogenations using 10% Pd–C as catalyst, in a Paar microhydrogenator, were carried out to prove the olefinic character of some reaction products, and also to identify their structure by comparison of their hydrogenation products with known, readily available samples.

Registry No.—3,3-Dimethylbutene, 558-37-2; 3-methyl-3-phenylbutene, 18321-36-3; *t*-pentylbenzene, 2049-95-8; di-*t*-butyl peroxide, 110-05-4.

The Oxychlorination of Ethylene at High Temperatures

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Received April 1, 1968

The mechanism of ethylene oxychlorination to vinyl chloride (VCl) at 500–550° with an iron oxide containing catalyst has been established by deuterium labeling experiments. The data are consistent with a mechanism involving 1,2-dichloroethane (DCE) as the VCl precursor. The 2-chloroethyl radical or cation intermediate may directly contribute to VCl formation if certain kinetic requirements are satisfied, but neither direct substitution on ethylene *via* a vinyl radical nor any mechanism involving ethyl chloride contributes significantly.

The term "oxychlorination" describes a process whereby chlorination (usually of hydrocarbons) is achieved with hydrogen chloride and oxygen in the presence of a catalyst. These reactions are usually carried out in the vapor phase using a flow reactor. The catalysts are usually chlorides (and occasionally oxides) of metals with variable oxidation states.[1] Oxidation of the metal chloride is likely an important step in this catalytic process. The oxidized metal

$$2M^{+n}Cl_n + 2HCl + 0.5O_2 \longrightarrow 2M^{+(n+1)}Cl_{(n+1)} + H_2O$$

chloride can itself be the chlorinating agent for olefins at low temperatures (220–320°),[2] but, at higher temperatures, these metal chlorides catalyze the equilibrium among hydrogen chloride, oxygen, chlorine, and water. Under these conditions, elemental chlorine could be the important chlorinating agent.[3]

The use of iron oxide as a catalyst in the oxychlorination of saturated hydrocarbons has appeared in the patent literature.[1a,b] However, there are no reports regarding the mechanism of ethylene oxychlorination using this catalyst. Celite (trade name for diatomaceous earth) is a convenient source of low concentrations of iron oxide and was used in our experiments. When impregnated with manganese metaphosphate, it is an active catalyst for the oxychlorination of ethylene to vinyl chloride (VCl). A 50% conversion of ethylene with a 60% yield of vinyl chloride can be achieved at 550°.

The objective of this study was to establish the route followed by ethylene in its ultimate conversion into VCl. The three routes which we have considered are shown in Scheme I. In route 1 we consider the possibility that ethyl chloride is an intermediate. It is known that hydrogen chloride readily adds to ethylene at elevated temperatures. Although the equilibrium concentration of ethyl chloride is low at 550°,[4] it still must be considered, particularly if this equilibrium is established rapidly. Subsequent chlorination of ethyl chloride would likely occur in the 1 position as shown.[5] In route 2 we consider a vinyl radical as the intermediate in the so-called direct substitution route. The direct substitution route has been proposed in the chlorination of ethylene to VCl with elemental chlorine at elevated temperatures.[6] It has also been proposed in certain oxyehlorination reactions.[7] Finally, in route 3 we consider 1,2-dichloroethane (DCE) and 2-chloroethyl radical or cation as the VCl precursors.

In this paper are reported two deuterium-labeling experiments which demonstrate that ethylene follows route 3 in its conversion into vinyl chloride.

Results and Discussion

If route 1 were operative, then the oxychlorination of ethylene with deuterium chloride should produce a large amount of VCl-*d*. No less than 66.6% of the VCl should be deuterated even if one ignores the expected deuterium isotope effect in the dehydrochlorination step,[8] but at 550° with a feed comprising DCl/C_2H_4/air = 2.5/1/2.5, we obtained only 13.9 ± 1.1% VCl-*d* (mass spectroscopy). Most of this can be accounted for in terms of hydrogen–deuterium exchange in ethylene. Analysis of the unreacted ethylene showed it to be 20 ± 0.9% deuterated. These data clearly rule out any significant contribution of route 1.

A choice between the remaining two routes was made on the basis of the deuterium isotope effects found in the oxychlorination of a nearly equal mixture of ethylene-d_0 and ethylene-d_4. In route 3, only a slight secondary isotope effect might be expected in the formation of DCE. Subsequent dehydrochlorination (k_9) by either the radical chain mechanism[9] or possibly a metal-catalyzed E2 mechanism[10] should provide a significant primary deuterium isotope effect. If VCl is derived from DCE, then the sum of the deuterated DCE and deuterated VCl should equal the sum of undeuterated DCE and undeuterated VCl, but this would not be sufficient evidence to exclude a contribution from step k_7. If this step was much faster than 2-chloroethyl radical or cation formation then the above equality would still hold.

A large primary deuterium isotope effect would be expected in k_1 of route 2. Therefore a significant contribution of route 2 to VCl production would cause a large difference in the sums of deuterated and undeuterated products.

(1) (a) British Patent 1,303,369 (1966); (b) O. Reitlinger, U. S. Patent 2,674,633 (1954); (c) E. Gorin, U. S. Patent 2,451,821 (1948); (d) G. W. Hearne, U. S. Patent 2,399,488 (1946); (e) A. J. Johnson and A. J. Cherniavsky, U. S. Patent 2,746,844 (1956).

(2) (a) R. R. Arganbright and W. F. Yates, *J. Org. Chem.*, **27**, 1205 (1962); (b) P. P. Nicholas and R. T. Carroll, *ibid.*, **33**, 2345 (1968).

(3) W. F. Engel and M. J. Waale, *Chem. Ind.* (London), 76 (1962).

(4) G. Todos and L. F. Stutzman, *Ind. Eng. Chem.*, **50**, 413 (1958).

(5) P. H. Dirstine and E. L. Dance, U. S. Patent 2,628,259 (1953).

(6) (a) W. E. Vaughan and F. F. Rust, *J. Org. Chem.*, **5**, 449 (1940); (b) H. Groll, G. Berkeley, J. Burgin, and D. LaFrance, U. S. Patent 2,167,927 (1939).

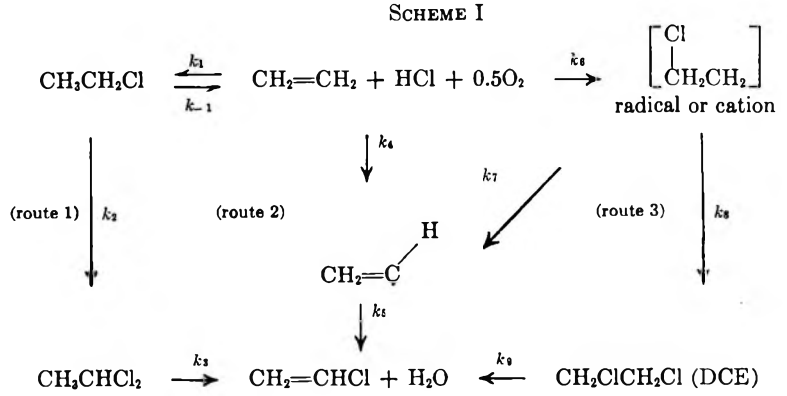
(7) K. Nawmbury, G. Schwedler, and G. Emig, *Chem.-Ing.-Tech.*, **39**, (9, 10), 505 (1967).

(8) D. H. Barton and K. E. Howlett, *J. Chem. Soc.*, 169 (1940).

(9) D. H. Barton and K. E. Howlett, *ibid.*, 115 (1949).

(10) H. Woller, *Angew. Chem. Intern. Ed. Eng.*, **7**, 232 (1968).

SCHEME I



The results shown in Table I were those obtained at 550° with a feed comprising $HCl/C_2H_4/C_2D_4/air$ = 2.5/0.47/0.53/2.5. These data are entirely consistent with the results expected for route 3. The small differences between the expected and observed sums of products in Table I can be attributed to the hydrogen–deuterium exchange in our ethylene mixture (Table II). Route 3 is further supported by the absence of a deuterium isotope effect in ethylene consumption.

TABLE I

DEUTERIUM DISTRIBUTION IN PRODUCTS FROM THE OXYCHLORINATION OF A C_2D_4–C_2H_4 MIXTURE

	Observed				Expected route 3	
Run no.	[DCE-d_4/DCE-d_0][a]	[VCl-d_3/VCl-d_0][a]	[DCE-d_4 + VCl-d_3]	[DCE-d_0 + VCl-d_0]	[DCE-d_4 + VCl-d_3]	[DCE-d_0 + VCl-d_0]
1	2.9	0.75	47.9	52.1		
2	*b*	0.85				
3	3.2	0.85	50.2	49.8		
Av	3.1	0.81	49.1	50.9	52.6[c]	47.4[c]

[a] Traces of VCl-d_2 and -d_1, and DCE-d_3 and -d_2 were detected. [b] Mass spectroscopy showed DCE sample contaminated. [c] The 1.9% ethylene-d_2 present in our ethylene mixture was not considered in these values.

TABLE II

DEUTERIUM DISTRIBUTION IN UNREACTED ETHYLENE[a]

	Run no.		
	1	2	3
d_0	50.5	50.2	48.6
d_1	1.5	1.5	2.5
d_2	2.0	3.5	0.5
d_3	3.0	3.5	3.3
d_4	43.0	41.0	44.8

[a] Starting mixture d_0 = 46.4%; d_2 = 1.9%; d_4 = 51.6%.

The rate of oxychlorination is at least three times faster than the rate of ethylene-d_4 exchange to lesser deuterated ethylenes. Therefore, this exchange would not be expected to cause a large deviation from the expected results.

We can, therefore, conclude that route 3 is likely the exclusive route in the conversion of ethylene into vinyl chloride under our conditions. This mechanism is analogous to the addition–elimination mechanism proposed for the liquid phase chlorination of benzene.[11] Consistent with this conclusion is the fact that under these conditions, DCE is converted into VCl much more rapidly than ethylene.

(11) A. S. Rodgers, D. M. Golden, and S. W. Benson, *J. Amer. Chem. Soc.*, **89**, 4578 (1967).

Experimental Section

General.—The chlorinated compounds were analyzed using an F & M 810 gas chromatograph on a 4 ft × $^3/_{16}$ in. column containing 20% Ucon LB 550X, 60/80 mesh, on Chromosorb R. Ethylene and CO_2 were analyzed on a P.E. 154 gas chromatograph using a 2 ft × $^3/_{16}$ in. column containing 30/60 mesh silica gel. The oxygen, nitrogen, and CO were analyzed on the same instrument with a 1 ft × $^3/_{16}$ in. column containing 30/60 mesh Linde 5A Molecular Sieves. Mass spectra were obtained on a C.E.C. Model 21-103C.

Apparatus.—The oxychlorination reactions were carried out in a 4 in. × 0.25 in. Pyrex reactor wrapped with chromel heating wire. A thermocouple placed in a thermowell extending through the center of the reactor was connected to a temperature controller. Fisher-Porter and Matheson flowrators were calibrated and used for the various gaseous feeds. The lecture bottle containing the deuterium chloride was cooled to −78° to help to maintain a constant back-pressure as the gas was consumed.

Reagents.—Deuterium chloride (5 l., anhydrous, 99.0% minimum purity) and 2 l. of perdeuterioethylene 99.0% minimum purity were supplied by Merck Sharp and Dohme of Canada Ltd. The C_2D_4 was diluted with 2 l. of C_2H_4. The ethylene and hydrogen chloride both 99.0% minimum purity were supplied by Matheson Co. The gases were used without further purification.

The catalyst was a pelletized Celite impregnated with manganese metaphosphate. It was prepared by adding a solution of 15.4 g (0.07 mol) of $MnCl_2 \cdot 4H_2O$ and 26.6 g (0.23 mol) of H_3PO_4 (85%) to Celite, evaporating the water, and then heating for 24 hr at 550°. It has a surface area of 4.43 m^2/g and a total pore volume of 3.32 × 10^{-3} cc/g. Fresh catalyst (20 cc of 4/18 mesh) was used for each experiment.

Procedure.—With air passing through the catalyst bed, the reactor was heated to within 10° of the desired temperature. The hydrogen chloride and ethylene were then mixed at room temperature and immediately introduced into the catalyst zone. The reaction was run for 15 min to allow the system to equilibrate. Then the reactor effluent was directed through a scrub flask containing water, dried, and then passed through the gas chromatograph's sample loops. After the reaction had run for 15 more min, the feed gases were shut off and the gas chromatography lines were sealed. A gc sample was taken immediately for quantitative calculation of the product distribution. After this analysis was performed, the desired components were isolated by preparative gc and analyzed for deuterium content by mass spectrometry.

Oxychlorination of Ethylene with Deuterium Chloride.—The conditions for oxychlorination were as follows: $DCl/C_2H_4/air$ = 2.5/1/2.5; temperature 540–550°; contact time = 7.0 sec. The products (per cent yield based on ethylene) were CO (34.4); CO_2 (2.2); VCl (58.9); 1,1-dichloroethylene (2.2); *trans*-1,2-dichloroethylene (1.1); *cis*-1,2-dichloroethylene (1.1); other samples ±3% these results; conversion C_2H_4 47.1%; carbon balance 101.6%.

Oxychlorination of Ethylene-d_0–Ethylene-d_4 Mixture.—The

conditions for oxychlorination were as follows: $HCl/C_2H_4/C_2D_4/air = 2.5/1/2.5$; temperature 490–505°; contact time = 7.0 sec at 500°. The products (per cent yield based on total ethylene) were CO (9.7); CO_2 (2.4); VCl (61.8); 1,1-dichloroethylene (3.2); CCl_4 (0.8); *trans*-1,2-dichloroethylene (4.8); *cis*-1,2-dichloroethylene (4.8); DCE (9.7); 1,1,2-trichloroethylene (0.8); 1,1,2-trichloroethane (2.4); other samples ±6% these results; conversion (C_2H_4 + C_2D_4) 50.7%; carbon balance 90.1%.

Registry No.—C_2D_4, 683-73-8; C_2H_4, 74-85-1.

Acknowledgments.—We want to thank A. E. Sir Louis and G. L. Chonko for technical assistance. We also want to thank Dr. P. Zakriski, P. Lightner, and B. Boose for performing and interpreting the mass spectra. Also we wish to thank Professor P. D. Bartlett for helpful discussions.

Selective Autoxidation of Some Phenols Using Bis(salicylaldehyde)ethylenediiminecobalt Catalysts

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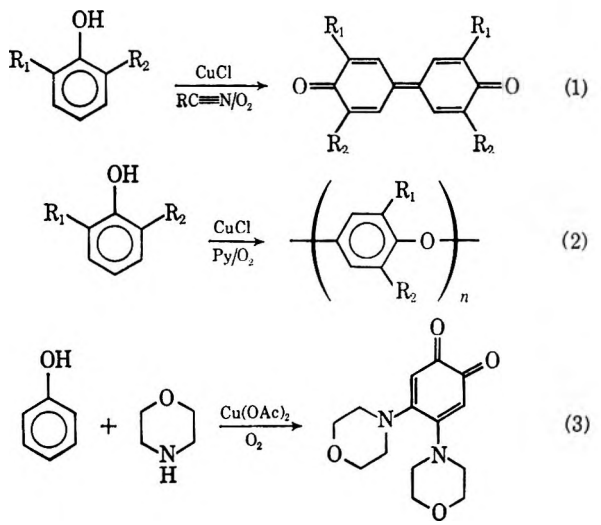
Catalyzed oxidation of phenols can result in hydroxylations, Diels–Alder coupling, aminations, benzoquinones, diphenoquinones, or polymers, depending on the particular catalyst system employed. We have found that two catalysts belonging to the salcomine [bis(salicylaldehyde)ethylenediiminecobalt (II)] family of complexes can be used to produce selectively 2,6-substituted benzoquinones, 3,3′,5,5′-tetrasubstituted diphenoquinones, or 2,6-substituted phenylene oxide polymers from several 2,6-substituted phenols. Conditions favoring the benzoquinone formation employ the salcomine monopyridine catalyst in high concentration and low temperature whereas the diphenoquinone is favored using the O_2-bridged salcomine dimer in low concentration and at high temperature. 2,6-Phenylene oxide polymers form when an amine is added to the system catalyzed by the O_2-bridged salcomine dimer. Evidence is presented for an equilibrium between a mononuclear salcomine and its O_2-bridged dimer. Selectivity of the catalysts may be associated with this equilibrium.

The catalyzed autoxidation of phenols is interesting both in mechanistic studies and in various syntheses.[1,2] Tetraalkyldiphenoquinones (eq 1), polyphenylene ethers (eq 2), and *o*-benzoquinones (eq 3) can be selectively prepared by proper choice of catalyst, solvent, and phenol.[3–6]



It is probable that the only function of oxygen in any of these reactions is to reoxidize copper from the 1+ to the 2+ state.[7,8] The suggestion that phenoxyl radicals are intermediates fails to account for the dramatic effects that result when the ligands on the copper catalyst are changed.

Recent work by van Dort and Geursen[9] and workers at Dynamit Nobel[10] has shown that copper is not the only metal that can be used in these reactions. Cobalt, as a salcomine,[11] produces all three classes of products (eq 4).

A similar reaction in chloroform gave a 26% yield of benzoquinone, an 11% yield of polymer, and no detectable diphenoquinone. It is curious that in contrast to the copper catalyst,[6] the cobalt catalyst produced little or no *o*-benzoquinone even with phenols having open 2 positions.

Although 13 other examples are given, only 2,6-diphenylphenol gave all three products. In the other cases, the benzoquinones were often the only identified product in yields ranging from 80% for 2,6-di-*t*-butylphenol to 36% with 2,3-dimethylphenol.

Until recently, nearly all of the interest in salcomines has been in the area of physical chemistry with surprisingly little emphasis on their chemical reactions, even though it has been known for about 25 years that certain salcomines can combine reversibly with molec-

(1) J. L. Bolland and P. ten Have, *Discussions Faraday Soc.*, **2**, 252 (1948); C. E. Boozer, G. S. Hammond, C. E. Hamilton, and J. N. Sen, *J. Amer. Chem. Soc.*, **77**, 3233, 3238, 3380 (1955).

(2) C. D. Cook, *J. Org. Chem.*, **18**, 260 (1953); E. Muller, A. Schick, R. Mayer, and K. Scheffler, *Ber.*, **93**, 2649 (1960); D. A. Bolon, *J. Amer. Chem. Soc.*, **88**, 3148 (1966); H. S. Blanchard, *J. Org. Chem.*, **25**, 264 (1960).

(3) A. S. Hay, U. S. Patent 3,210,384 (1965); *Chem. Abstr.*, **64**, 17494*b* (1966).

(4) A. S. Hay, *Advan. Polym. Sci.*, **4**, 496 (1967); G. F. Endres and J. Kwiatek, *J. Polym. Sci.*, **58**, 593 (1962).

(5) A. Rieche, B. Elschner, and M. Landbeck, *Angew. Chem.*, **72**, 385 (1960); H. Musso, *Angew. Chem. Intern. Ed. Engl.*, **2**, 723 (1963); W. A. Waters, "Mechanisms of Oxidation of Organic Compounds," Methuen Ltd., London, 1964.

(6) W. Brackman and E. Havinga, *Rec. Trav. Chim. Pays-Bas*, **74**, 937 (1955).

(7) H. Finkbeiner, A. S. Hay, H. S. Blanchard, and G. F. Endres, *J. Org. Chem.*, **31**, 549 (1966).

(8) H. S. Blanchard, H. Finkbeiner, and G. F. Endres, *Soc. Plastics Eng. Trans.*, **2**, 110 (1962).

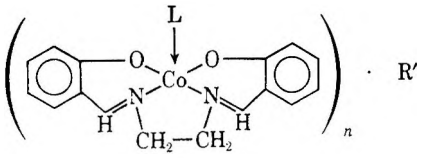
(9) H. M. van Dort, and H. J. Geursen, *Rec. Trav. Chim. Pays-Bas*, **86**, 520 (1967).

(10) Dynamit Nobel Aktiengesellschaft, Dutch Patent 6,609,843 (1967).

(11) The generic term salcomine has been applied to Schiff base coordination compounds consisting of salicylaldehyde, cobalt, and an amine. Salcomine (salco) is bis(salicylaldehyde)ethylenediiminecobalt(II). The bissalicylaldehyde Schiff base ligand is abbreviated as salen.

TABLE I

BIS(SALICYLALDEHYDE)ETHYLENEDIIMINECOBALT COMPLEXES



No.	n	Name	L	R′	Description	Ref
I	1	Salcomine (salco)	None	None	Red-brown crystals stable under vacuum or N_2; reacts at room temperature with O_2 to give (III) ($C_{16}H_{14}CoN_2O_2$; mol wt, 325.26)	12, *a*
II	1	Pyr–salco	Pyr	None	Red crystals stable in air; pyridine can be displaced thermally to give I; forms IV reversibly when exposed to O_2 in $CHCl_3$ solution ($C_{21}H_{19}CoN_3O_2$; mol wt, 404.33)	12, *a*
III	2	O_2–(salco)$_2$	None	O_2	O_2-bridged dimer; jet black crystals prepared from I plus O_2; O_2 can be displaced thermally to give I ($C_{32}H_{28}Co_2N_4O_6$; mol wt, 682.45)	12, *a*
IV	2	O_2–(salco–pyr)$_2$	Pyr	O_2	Brown solid, poorly characterized; soluble in $CHCl_3$ ($C_{42}H_{38}Co_2N_6O_6$; mol wt, 840.66)	*a*

[a] R. H. Bailes and M. Calvin, *J. Amer. Chem. Soc.*, 69, 1886 (1947); II was prepared as described on p 1887; III was obtained from II by heating at 160° (10^{-4} mm) for 2 hr.

ular oxygen.[12] However, not one bis(salicylaldehyde)-ethylenediimine complex containing a metal other than cobalt has been found to be a reversible oxygen carrier.

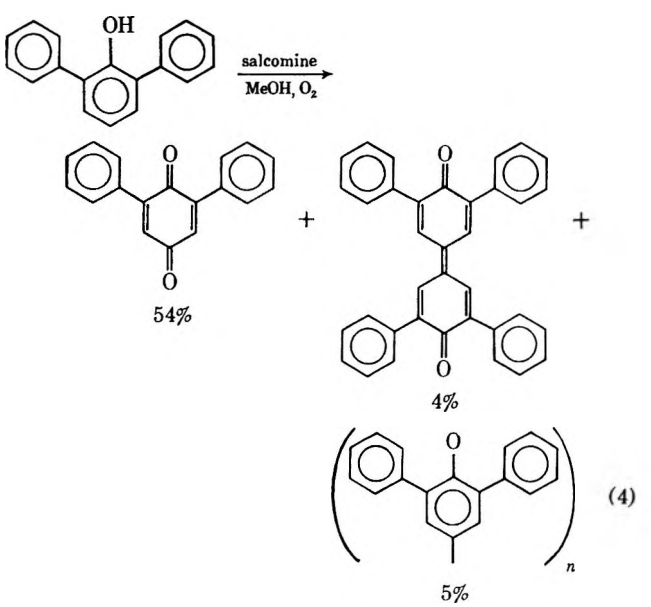


Table I gives some of the pertinent data that characterize the four compounds of interest. Hereafter, Roman numerals I–IV refer to the specific salcomine designated in Table I.

(12) L. H. Vogt, Jr., H. M. Faigenbaum, and S. E. Wiberley, *Chem. Rev.*, **63**, 269 (1963); A. E. Martell and M. Calvin, "Chemistry of the Metal Chelate Compounds," Prentice Hall, Englewood Cliffs, N. J., 1954, pp 337–352.

In the work of van Dort and Geursen,[9] it is not clear which catalyst was used (the formula given for their catalyst is I, but the reference cited for the method of preparation[13] is for an alleged aquo dimer of I).

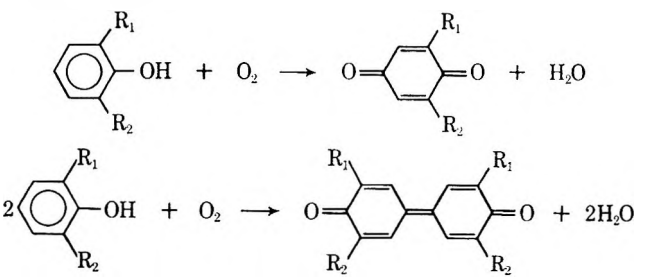
A number of questions arise concerning the behavior of the salcomines as catalysts in the oxidation of 2,6-substituted phenols, *viz.*, (1) do II and III lead to different products or product ratios; (2) what effect do concentration, temperature, solvent, etc., have on the oxidation; (3) do nonoxygen carrying bis(salicylaldehyde)ethylenediimine complexes containing metals like Fe, Mn, Cu, etc., show catalytic activity; and (4) can other reversible oxygen carriers such as Vaska's $Ir(CO)Cl[C_6H_5)_3P]_2$[14] complex catalyze phenol oxidations.

In order to answer these questions, a series of oxidations was carried out in which phenol, catalyst, solvent, temperature, catalyst concentration, and concentration of added amine were varied.

Results and Discussion

The only metal complexes that exhibited appreciable catalytic activity (50% or more of 2,6-dimethylphenol oxidized in 24 hr) were the cobalt complexes. Under the conditions described (Experimental Section), Cu^{II} (salen), Fe^{II} (salen), Mn^{II} (salen), Ni^{II} (salen), and $Ir^{I}(CO)[(C_6H_5)_3P]_2X$ (where X = Cl, Br, I) were all inactive as indicated by recovery of essentially all of the 2,6-dimethylphenol after 24 hr. About 10% of the phenol was oxidized by $V^{IV}O$ (salen) in the same time suggesting that the vanadium complex was acting stoichiometrically rather than catalytically.

The products of the oxidation of the 2,6-substituted phenols shown in Table II are predominantly the corresponding 2,6-disubstituted benzoquinones (BQ) or 3,3′,5,5′-diphenoquinones (DPQ).



Benzoquinone formation is not common in metal-catalyzed oxidations of phenols. For example, in the oxidation of 2,6-dimethylphenol with a copper catalyst (methanol green),[7] the DPQ is formed in the total absence of the BQ[15] (Table II, expt 17) although the same catalyst does give both BQ and DPQ when 2-methyl-6-benzylphenol is oxidized (expt 16). In general, for the same concentration of both salcomine catalysts (based on the gram-atoms of cobalt present), the pyr–salco catalyst gave higher BP/DPQ ratios for all of the phenols oxidized than the O_2–(salco)$_2$ catalyst, *e.g.*, expt 10, 22, 26, and 8 compared to 4, 21, 25, and 27, respectively. The BQ/DPQ ratio can be altered

(13) H. Diehl and C. C. Hach, *Inorg. Syn.*, **3**, 196 (1950).
(14) L. Vaska, *Science*, **140**, 809 (1963).
(15) G. F. Endres and H. Finkbeiner, unpublished results.

TABLE II

PRODUCTS OF THE CATALYTIC OXIDATION OF 2,6-SUBSTITUTED PHENOLS[b]

Expt no.	2,6-Phenol	Temp, °C	Solvent	Catalyst	Catalyst concn[a]	Conversion,[k] %	Amt, %[c] Benzo	Amt, %[c] Dipheno	BQ/DPQ
1	Me, Bz (benzyl)	50	$CHCl_3$	O_2–(salco)$_2$	10:1	100	26.9	57.6	0.47
2	Me, Bz	20	$CHCl_3$	O_2–(salco)$_2$	10:1	89	66.9	16.6	4.03
3	Me, Bz	20	$CHCl_3$	Diehl[d]	10:1	89	82.0	24.0	3.42
4	Me, Bz	20	$CHCl_3$	O_2–(salco)$_2$	20:1	73	58.1	41.9	1.39
5	Me, Bz	20	1.7$CHCl_3$[e]	O_2–(salco)$_2$	20:1	75	58.1	44.1	1.32
6	Me, Bz	20	$CHCl_3$–$MgSO_4$[f]	O_2–(salco)$_2$	20:1	70	63.6	40.6	1.57
7	Me, Bz	50	$CHCl_3$	Pyr–salco	10:1	76	63.5	25.6	2.48
8	Me, Bz	20	$CHCl_3$	Pyr–salco	10:1	71	73.3	9.3	7.88
9	Me, Bz	20	$CHCl_3$–H_2O[g]	Pyr–salco	20:1	71	79.3	8.6	9.24
10	Me, Bz	20	$CHCl_3$	Pyr–salco	20:1	59	76.8	22.0	3.50
11	Me, Bz	20	$CHCl_3$–$MgSO_4$[f]	Pyr–salco	20:1	64	72.6	12.7	5.72
12	Me, Bz	20	$CHCl_3$–$NaSO_4$[f]	Pyr–salco	20:1	62	73.7	14.6	5.05
13	Me, Bz	20	C_6H_6	Pyr–salco	20:1	67	84.8	3.9	21.7
14	Me, Bz	20	C_6H_6	O_2–(salco)$_2$	20:1	26	37.6	57.8	0.65
15	Me, Bz	20	CH_3OH	O_2–(salco)$_2$	20:1	86	43.3[i]	14.9[i]	2.91
16	Me, Bz	20	$CHCl_3$	Methanol green[h]	20:1	49	19.4	63.0	0.31
17	Me, Me	20	$CHCl_3$	Methanol green[h]	20:1	68	0.0	69.2[l]	0.00
18	Me, Me	20	$CHCl_3$	Salcomine[i]	20:1	93	56.0	53.7	1.04
19	Me, Me	20	$CHCl_3$	Diehl[d]	20:1	92	59.8	53.4	1.12
20	Me, Me	20	$CHCl_3$	O_2–(salco)$_2$	10:1	96	69.4	29.9	2.32
21	Me, Me	20	$CHCl_3$	O_2–(salco)$_2$	20:1	85	51.5	43.7	1.18
22	Me, Me	20	$CHCl_3$	Pyr–salco	20:1	78	81.4	22.5	3.62
23	Me, Me	20	$CHCl_3$	Pyr–salco	10:1	88	88.6	11.1	7.97
24	Me, Me	20	$CHCl_3$	O_2–(salco)$_2$	44:1	89	46.3	52.7	0.88
25	C_6H_5, C_6H_5	20	$CHCl_3$	O_2–(salco)$_2$	20:1	48	43.8	1.3	3.4
26	C_6H_5, C_6H_5	20	$CHCl_3$	Pyr–salco	20:1	48	39.6	0	
27	Me, C_6H_5	20	$CHCl_3$	O_2–(salco)$_2$	20:1	47	46.2	26.6	2.1
28	Me, C_6H_5	20	$CHCl_3$	Pyr–salco	20:1	38	85.6	17.3	4.95
29	Cl, Cl	20	$CHCl_3$	Pyr–salco or	20:1		No reaction		
30	H, H	20	$CHCl_3$	O_2–(salco)$_2$	20:1		No reaction		

[a] Moles of phenol/gram-atoms of metal in the catalyst. [b] The oxidations were stopped when the rate of O_2 absorption dropped to 0.01 ml/min. In most instances, this occurred about 700 min after the start of the oxidation. [c] Based on per cent conversion. Unless otherwise noted, only the unreacted phenols, BQ and DPQ, were detected. This does not preclude formation of somewhat higher molecular weight products that would not be detectable by glpc or tlc methods. However, the reaction mixture did not give a precipitate in CH_3OH indicating that high polymer ($[\eta] \gg 0.06$ dl/g) was not present. [d] Although the method used to make this complex alleges to give an aquo-bridged binuclear salcomine complex (see discussion), we assumed the product to be salcomine (I) itself, mol wt 325.26. [e] Used 1.7 times the standard volume (75 ml) of $CHCl_3$. [f] Drying agent (1 g, anhydrous $MgSO_4$ or Na_2SO_4) was added before the phenol was introduced. [g] Water (2 ml) was added before the phenol was introduced. [h] Methanol green is $Cu(OCH_3)(Cl)(pyr)$; see Experimental Section. [i] Active salcomine (I) was stored in N_2 and was weighed out rapidly to avoid O_2 absorption. [j] The remaining 42% is unidentified products, probably resulting from the oxidation of the CH_3OH solvent by the catalyst. [k] The difference between this value and 100 is the per cent of the recovered, unreacted phenol. [l] In addition, a mixture (19%) of the corresponding dimer and trimer was recovered.

by changing solvent, catalyst concentration (Figure 1), and temperature (Table II).

Inspection of Table II shows that high BP/DPQ ratios (BQ the major product) are favored by the pyr–salco catalyst in high concentration (Figure 1) in a nonpolar solvent (expt 13 *vs.* 10) and at low temperatures (expt 8 *vs.* 7). Low BQ/DPQ ratios (DPQ the major product) are obtained for the O_2–(salco)$_2$ catalyst in low concentration, at high temperatures and in a nonpolar solvent (expt 14 *vs.* 4). Changing the solvent volume by a factor of 1.7 (expt 5 *vs.* 4) made no significant change. Thus by suitable manipulation of these variables, the oxidation can be directed to give high yields of benzoquinone (expt 13) or diphenoquinone (expt 1, 14).

The effect of water on the reaction is not understood. Both the addition of water (expt 9) and drying agents (expt 11, 12) increased the BQ/DPQ ratios for 2-methyl-6-benzylphenol over the values obtained when neither was added (expt 10). Since the amount of water produced by the oxidations should be about the same for all of the phenols investigated (and is in solution), drying agents were not employed routinely in our studies.

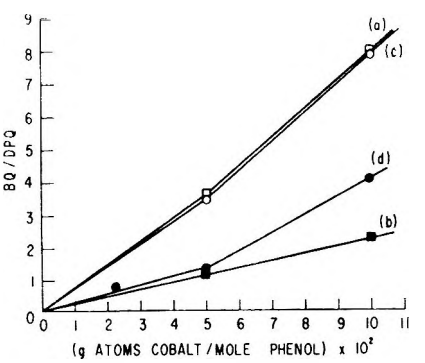
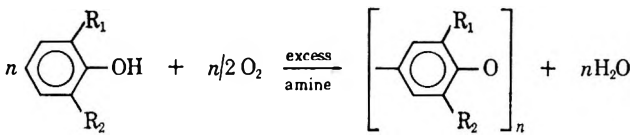


Figure 1.—A plot of BQ/DPQ *vs.* catalyst concentration for the oxidation of 2,6-dimethylphenol with (a) pyr–salco and (b) O_2–(salco)$_2$ and 2-methyl-6-benzylphenol with (c) pyr–salco and (d) O_2–(salco)$_2$. Reaction conditions are indicated in Table II: expt no. 23 and 24 for a, 20 and 21 for b, 8 and 10 for c, and 2 and 4 for d.

If N,N,N′,N′-tetramethylethylenediamine is added to any of the O_2–(salco)$_2$-catalyzed reaction mixtures

shown in Table II (except those containing dichlorophenol or phenol), a low molecular weight phenylene oxide polymer ([η] = 0.06 dl/g) is formed. In pyr–



salco-catalyzed oxidations, polymer formation was not detected. Other workers[10] have reported that low molecular weight polymers can be obtained by salcomine-catalyzed oxidation of substituted phenols containing 5 mol % of the corresponding sodium phenoxide in lieu of an amine.

The rate of oxygen absorption was always slower initially for the O_2–(salco)$_2$ catalyst than for the pyr–salco catalyst. However, the rates of oxygen absorption became approximately the same after about 50% of the stoichiometric amount had reacted (based on a 1:1 molar ratio of phenol to O_2). A typical set of rate curves for the oxidation of 2-methyl-6-benzylphenol is shown in Figure 2. These rate curves are difficult to interpret since the stoichiometry requires 1 mol of oxygen/mol of phenol for benzoquinone formation and 0.5 mol/mol of phenol for diphenoquinone formation. Table III gives the volumes of

TABLE III

O_2 ABSORBED 100 MIN AFTER INITIATION OF PHENOL OXIDATIONS

Phenol	—Volume of O_2 absorbed[a]— Pyr–salco	O_2–(salco)$_2$
2-Methyl-6-benzyl	81	55
2,6-Dimethyl	123	40
2-Methyl-6-phenyl	68	6
2,6-Diphenyl	42	12

[a] Stoichiometric O_2 for only DPQ formed is 120 ml and for only BQ formed, 240 ml.

O_2 absorbed in a period of 100 min for several phenols. The rate of oxygen absorption at 50° was slower for both catalysts than the rate at 20°. Similar temperature effects have been observed for the oxidation of 2,6-dimethylphenol using the methanol green catalyst.[7,15] The BQ/DPQ ratio did not change markedly during the course of the reaction (see Table IV).

TABLE IV

CHANGES IN THE BQ/DPQ RATIO DURING THE OXIDATION OF 2-METHYL-6-BENZYLPHENOL[a]

Minutes (days) from start of oxidation	Conversion, %	Amt, % BQ	Amt, % DPQ	BQ/DPQ
5	27	52.9	19.5	2.7
20	27	57.5	19.2	3.0
50	44	64.9	21.3	3.3
80	66	69.6	17.2	4.1
400	91	69.8	16.8	4.2
(7)	94	65.1	19.6	3.3[b]

[a] Reaction conditions: temp 20°, $CHCl_3$ solvent, O_2–(salen)$_2$ catalyst, 10:1 catalyst concentration (moles of phenol/gram-atoms of cobalt). [b] The decrease in this ratio is due to loss of BQ on standing rather than an increase in DPQ.

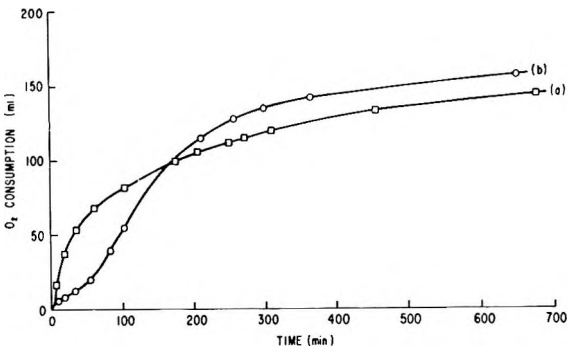


Figure 2.—Rate curves for oxidation of 2-methyl-6-benzylphenol catalyzed by (a) pyr–salco and (b) O_2–(salco)$_2$ complexes. Reaction conditions are indicated in Table II, expt no. 4 and 10.

These results along with those of van Dort and Geursen[9] show that salcomines are synthetically useful catalysts for the synthesis of *p*-benzoquinones and diphenoquinones and that copper catalysts are far superior for forming polyphenylene oxide polymers.

It is difficult even to attempt to draw analogies between the salcomine-catalyzed oxidations and the more extensively studied phenol oxidations which use organic peroxides. Different organic peroxides have been reported to give different BQ/DPQ ratios. Furthermore, the DPQ produced in some of these oxidations has frequently been reported in the "other products" category and was not determined quantitatively. Therefore, it is impossible to determine if the O_2 in O_2–(salco)$_2$ or O_2–(pyr–salco)$_2$ complexes is behaving like a "typical" peroxide oxygen. It is unlikely that the O_2 in these complexes is the only governing factor in the oxidations since the Vaska complexes are not oxidation catalysts even though the coordinated O_2 ligands vary in character (based on the O–O bond distance) from a superoxide (chloro complex) to a peroxide (iodo complex).

In solution, the apparent molecular weights of salcomines II and III show a dependence on concentration (Figure 3) indicating the existence of monomer–O_2-bridged dimer equilibria analogous to that reported for the salcomine in which R = γ,γ'-diaminodipropylamine.[16] These equilibria will also be affected by

$$O_2\text{–(pyr–salco)}_2 \rightleftharpoons 2\text{(pyr–salco)} + O_2$$

$$O_2\text{–(salco)}_2 \rightleftharpoons 2\text{(salco)} + O_2$$

changes in temperature and solvent. The quantities of DPQ and BQ appear to be correlated, respectively, with the amounts of mononuclear and O_2-bridged dimer present in the catalyst system (Figures 1 and 3). The hypothesis that mononuclear complexes give predominantly or exclusively DPQ and O_2-bridged dimer complexes BQ is currently being tested.

Experimental Section

I. Reagents.—2,6-Dimethylphenol was distilled before use. Reagent grade N,N,N′,N′-tetramethylethylenediamine, chloroform, methanol, phenol, benzene, Aldrich 2,6-dichlorophenol and bis(trimethylsilyl)acetamide, and Eastman White Label diphenyl ether were used as received. It was shown that the small amount of ethanol present in reagent grade chloroform did not affect

(16) H. P. Fritz and W. Gretner, *Inorg. Nucl. Chem. Lett.*, **3**, 14 (1967).

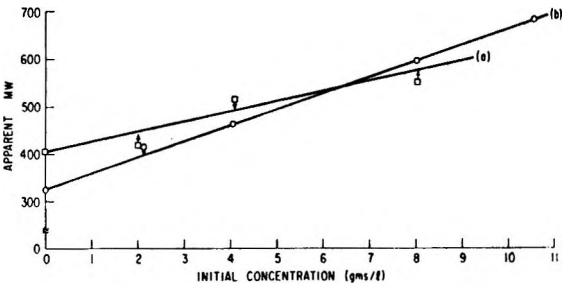


Figure 3.—Concentration *vs.* apparent molecular weight of (a) salco-pyr and (b) O_2–(salco)$_2$ in chloroform saturated with O_2. The abscissa gives the initial (not equilibrium) concentrations.

the reactions. Salcomine catalysts II and III were prepared by the method of Bailes and Calvin.[17] Methanol green [CuPyCl-(OCH_3)] was synthesized by Finkbeiner's method.[18] The following complexes were prepared by the method used for pyr–salco(II): [Cu^{II} (salen)],[19a] [Fe^{II}(salen)],[19b] [Mn^{II}(salen)],[19c] and [Ni^{II}(salen)].[19d] Billig and Bayer's[20] synthesis of [$V^{IV}O$-(salen)] was employed. Vaska's complexes—$Ir(CO)[(C_6H_5)_3P]_2$-X, where X = Cl, Br, I—were prepared by the following methods. For X = Cl,[21] 3 g of $IrCl_3 \cdot 3H_2O$ was made into a paste with 2 ml of water. Methylcarbitol (50 ml) was added followed by 20 g of triphenylphosphine. The reaction vessel was flushed with N_2 and heated to reflux. A reflux temperature of 190° was maintained by allowing water to boil off if the temperature was too low or by adding more water if it was too high. Reflux was continued for 3 hr after which the reaction mixture was cooled; the yellow crystals were filtered off, washed successively with methylcarbitol and petroleum ether, and dried at 60° under vacuum. A 75% yield (5 g) was obtained. The X = Br, I complexes were derived from the chloro complex by Halpern's method.[22] Literature methods are available for the preparation of 2-methyl-6-phenylphenol,[23] 2-methyl-6-benzylphenol,[24] and 2,6-diphenylphenol.[25]

II. Oxidations. A. Evaluation of Several Complexes as Oxidation Catalysts.—2,6-Dimethylphenol (1.22 g, 0.01 mol) was dissolved in 100 ml of $CHCl_3$ containing 0.005 mol of catalyst. Oxygen was bubbled through the solution for 24 hr, after which the reaction mixture was analyzed quantitatively for unreacted 2,6-dimethylphenol by glpc, and qualitatively for the oxidation products using analytical thin layer chromatography.

B. Oxidation of 2,6-Substituted Phenols.—Sufficient catalyst to contain 0.0005 g-atom of metal [*e.g.*, 0.00025 mol (0.170 g) of O_2–(salco)$_2$ or 0.0005 mol (0.202 g) of pyr–salco] was added to 75 ml of solvent (at 20 ± 2°). The reaction vessel was sealed under O_2 and vigorously stirred with a Vibromixer until the oxygen atmosphere was saturated with solvent vapor (about 0.5 hr). A solution of 0.01 mol of the phenol in 25 ml of solvent was added and the oxygen uptake was monitored. In all cases, after addition of the phenol, the solutions were homogeneous. After 12 hr, or when the rate of O_2 uptake was 0.01 ml/min, the reaction mixture was analyzed. At this stage, there are a few tenths of a gram of solid in the otherwise homogeneous system. The solid has a high Co content and is devoid of any phenol, benzoquinone, or diphenoquinone.

III. Analytical Methods.—The quantitative analysis of 2,6-dimethylphenol and its oxidation products was achieved by adding 0.340 g (2×10^{-5} mol) of diphenyl ether to the reaction mixture (as an internal standard) and diluting to 100 ml with $CHCl_3$. The benzo- and diphenoquinones were catalytically reduced with H_2 (50 mg of PtO_2) to the corresponding hydroquinones. Bis(trimethylsilyl)acetamide[26] (2 ml) was transferred to a 10-ml flask and diluted to the mark with the reduced reaction mixture. The resulting solution of silylated phenols was chromatographed [(F & M Model 700 gas–liquid partition chromatograph, 2 ft 10% silicone rubber UC-W98 column; temperature programmed 100–300° (10°/min)]. All of the components were well resolved and reproducible and quantitative data were obtained. If the reaction mixture were put through the glpc without first reducing and silylating, quantitative data could not be obtained since the benzo- and diphenoquinones decomposed.

All of the other phenols and their oxidation products were analyzed by preparative thin layer chromatography (Merck Preparative tlc–SiO_2 coated plates) using benzene as the eluent. The phenols and quinone bands were cut from the plates, extracted with acetone, and weighed. Both methods give results that are reproducible to about ±10% of the yields shown in Table II. Neither tlc nor glpc would necessarily detect higher molecular weight products than the diphenoquinone.

Eastman Kodak Type K301R chromatogram sheets (SiO_2 coated) were used for qualitative thin layer chromatography. Intrinsic viscosities were determined in $CHCl_3$ using a Ubbelohde viscometer.

IV. Polymerization.—The reaction conditions were identical with those described in part IIA of the Experimental Section except for the addition of 0.4 ml (0.004 mol) of N,N,N′,N′-tetramethylethylenediamine before the phenol was added. After 12 hr, the solution was poured into 1 l. of methanol containing 5 ml of acetic acid. The precipitated polymer was filtered and washed with methanol.

Registry No.—I, 14167-18-1; II, 18309-20-1; III, 18309-21-2; IV, 15878-97-4; 2-methyl-6-benzylphenol, 1208-45-3; 2-methyl-6-methylphenol, 576-26-1; 2-phenyl-6-phenylphenol, 2432-11-3; 2-methyl-6-phenylphenol, 17755-10-1.

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(17) See Table I, footnote *a*.

(18) H. L. Finkbeiner, A. S. Hay, H. S. Blanchard, and G. F. Endres, *J. Org. Chem.*, **31**, 554 (1966). Method B for the oxidation of Cu(I) chloride in methanol.

(19) $Co(OAc)_2 \cdot 4H_2O$ was replaced by (a) $Cu(OAc)_2 \cdot H_2O$, (b) $FeCl_2 \cdot 4H_2O$, (c) $MnCl_2 \cdot 4H_2O$, (d) $Ni(OAc)_2 \cdot 4H_2O$.

(20) H. J. Billig and E. Bayer, *Ann.*, **580**, 155b (1953).

(21) A. J. Chalk, this laboratory, private communication.

(22) J. Halpern, *J. Amer. Chem. Soc.*, **88**, 3512 (1966).

(23) J. C. Colbert and R. M. Lacy, *ibid.*, **68**, 270 (1946).

(24) P. Schorigin, *Ber.*, **58**, 2033 (1925).

(25) J. Plesek, *Chem. Listy*, **50**, 252 (1956).

(26) J. F. Klebe, H. Finkbeiner, and D. M. White, *J. Amer. Chem. Soc.*, **88**, 3390 (1966).

The Nature of the *ortho* Effect. I. Electrophilic Aromatic Substitution

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ortho, *meta*, and *para* partial rate factors for 19 sets of electrophilic aromatic substitution data were correlated with the extended Hammett equation $Q_X = \alpha\sigma_{I,X} + \beta,\sigma_{R,X} + h$. Significant correlations were obtained for 17 out of the 19 sets of *ortho* partial rate factors, 13 out of 15 sets of *meta*, and 17 out of 19 sets of *para*. We find that in the sets studied there is no significant steric effect. The results indicate that $\alpha_o = \alpha_p$ and $\beta_o = 0.77\beta_p$. The equality of α_o and α_p is accounted for in terms of the geometry of the transition state. The observation that the resonance effect for *ortho* substitution is smaller than that for *para* is in accord with the literature. The composition of the *ortho* electrical effect may be written $\epsilon_o = \beta_o/\alpha_p = 0.77\epsilon_p$. These results indicate that the *ortho*–*para* product ratio is given by $\log (p_o/2p_p) = \beta'\sigma_R + h'$. Thus the *ortho*–*para* product ratio is dependent solely upon the resonance effect of the substituent.

We have for some time been engaged in investigation of the effect of *ortho* substituents upon physical properties and chemical reactivity. In this paper we extend our studies to the effect of *ortho* substituents upon electrophilic aromatic substitution.[1] It has been suggested by de la Mare and Ridd[2] on the basis of a parallelism in the *para*–*meta* and *ortho*–*meta* product ratios that the *ortho* effect in nitration is primarily electronic in nature. They suggest, however, that halogenation of *ortho*-substituted benzenes is dependent at least in part on steric effects. We have two purposes in this work; the first is to determine the validity of the proposal of de la Mare and Ridd; the second is to investigate the magnitude and composition of the *ortho* electrical effect. To this end, we have examined the correlation of partial rate factors taken from the literature for 19 sets of aromatic substitution data with the extended Hammett equation. The reactions studied

$$Q_X = \sigma_{I,X} + \sigma_{R,X} + h \qquad (1)$$

include detritiation, nitration, chlorination, bromination, mercuration, and alkylation. The correlations were made by multiple linear regression analysis. The σ_I constants are taken from our collection;[3] the σ_R constants are from

$$\sigma_R = \sigma_p - \sigma_I \qquad (2)$$

The necessary σ_p values are from McDaniel and Brown[4] with the exception of that for the phenoxy group.[5] The data used in the correlations are presented in Table I.

Results

The results of the correlations are presented in Table II.

ortho **Partial Rate Factors.**—Sets 1, 6, 9, and 15 gave excellent correlation; the results obtained for set 8 were very good; set 13 gave good results; sets 10 and 14 gave fair results. For sets 3, 5, 7, 11, 12, 16, 18, and 19 poor but significant correlation was obtained. Exclusion of the value for X = I in set 3 gave good results. Exclusion of the value X = NHAc in set 5 gave excellent results. Sets 4 and 17 did not give significant correlation. The results for set 4 were improved by the exclusion of X = Ph (set 4A). The results for set 2 were not considered significant as α and β differed in sign.

meta **Partial Rate Factors.**—Excellent correlations were obtained for sets 1, 5, 6, 8, 12, 13, 14, and 15. Very good results were obtained for set 16, good results for sets 17 and 19. The results obtained for sets 3 and 7 were not significant. The results of sets 2 and 18 are considered to be not significant owing to the difference in sign between α and β. Exclusion of the value X = I gave fair results for set 2.

para **Partial Rate Factors.**—Excellent correlation was obtained for sets 1, 6, and 14; sets 8, 12, and 13 gave very good results. Exclusion of the value X = NHAc gave excellent results for set 8 (set 8A). Good results were obtained for sets 2, 15, and 16; exclusion of the value X = I from set 2 gave excellent results (set 2A). Sets 3, 5, 7, 9, 10, 11, 18, and 19 gave poor but significant correlation. Exclusion from set 5 of the values for X = NHAc and Ph resulted in an excellent correlation (set 5A). Sets 4 and 17 did not give a significant correlation; exclusion of the value X = Ph from set 4 gave some improvement but the correlation remained not significant (set 4A).

The results seem to show that partial rate factors are well correlated with eq 1. It is of particular interest to note that, of the *ortho*-substituted sets which gave poor but significant correlation, five had only four members. Of the *para*-substituted sets which gave poor but significant correlation, five out of seven had only four members. We believe that, had more data been available for these sets, the correlation would be much improved.

Discussion

The *ortho* Substituent Effect.—In addition to the localized and delocalized electrical effects characteristic of any substituent bonded to sp^2-hybridized carbon atoms, *ortho* substituents are also capable in some cases of proximity effects of various types. We may represent the effect of *ortho* substituents by an equation analogous to that proposed by Taft[6] (eq 3), where ζ is

$$Q_X = \alpha\sigma_{I,X} + \beta\sigma_{R,X} + \psi\zeta_X + h \qquad (3)$$

(1) L. M. Stock and H. C. Brown, *Advan. Phys. Org. Chem.*, **1**, 35 (1963).
(2) P. B. D. de la Mare and J. H. Ridd, "Aromatic Substitution," Butterworth and Co. (Publishers) Ltd., London, 1959, pp 82, 142.
(3) M. Charton, *J. Org. Chem.*, **29**, 1222 (1964).
(4) D. H. McDaniel and H. C. Brown, *ibid.*, **23**, 420 (1958).
(5) M. Charton, *J. Chem. Soc.*, 5884 (1964).
(6) R. W. Taft, Jr., in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley & Sons, Inc., New York, N. Y., 1956, p 565.

a parameter characteristic of the proximity effect of the X substituent and ψ is its coefficient. The proximity effect may consist of any combination of the following contributions: (1) intramolecular hydrogen bonding between substituent and reaction site; (2) intramolecular van der Waals and London forces between substituent and reaction site; (3) steric inhibition of resonance either between reaction site and skeletal group or substituent and skeletal group or both; (4) steric interference with solvation; (5) steric inhibition of the reagent. For our present purposes we shall make no attempt to dissect the proximity effect into contributions but simply consider the over-all proximity effect.

We may now consider a number of special cases of interest. (1) The proximity effect is zero. In this case eq 3 simplifies to

$$Q_X = \alpha\sigma_{I,X} + \beta\sigma_{R,X} + h \quad (1)$$

(2) ζ_X = constant. Equation 3 now simplifies to

$$Q_X = \alpha\sigma_{I,X} + \beta\sigma_{R,X} + h' \quad (4)$$

where $h' = h + \psi\zeta_X$. Equation 4 is equivalent to eq 1. (3A)

$$\zeta_X = m\sigma_{I,X} + c \quad (5)$$

Then

$$Q_X = (\alpha + m\psi)\sigma_{I,X} + \beta\sigma_{R,X} + h + \psi c \quad (6)$$

$$Q_X = \alpha'\sigma_{I,X} + \beta\sigma_{R,X} + h' \quad (7)$$

Equation 7 is equivalent to eq 1. (3B)

$$\zeta_X = m\sigma_{R,X} + c \quad (8)$$

Then

$$Q_X = \alpha\sigma_{I,X} + (\beta + m\psi)\sigma_{R,X} + h + \psi c \quad (9)$$

$$Q_X = \alpha\sigma_{I,X} + \beta'\sigma_{R,X} + h' \quad (10)$$

Equation 10 is equivalent to eq 1. (3C)

$$\zeta_X = m\sigma_{I,X} + n\sigma_{R,X} + c \quad (11)$$

Then

$$Q_X = (\alpha + m\psi)\sigma_{I,X} + (\beta + n\psi)\sigma_{R,X} + \psi c + h \quad (12)$$

$$Q_X = \alpha'\sigma_I + \beta'\sigma_R + h' \quad (13)$$

Equation 13 is again equivalent to eq 1. (4A) $\alpha\sigma_{I,X} \cong \beta\sigma_{R,X} \gg \psi\zeta_X$. Then

$$Q_X = \alpha\sigma_{I,X} + \beta\sigma_{R,X} + h \quad (1)$$

(4B) $\psi\zeta_X \cong \alpha\sigma_{I,X} = \beta\sigma_{R,X}$. In this case eq 3 applies. (4C) $\zeta_X \gg \alpha\sigma_{I,X} \cong \beta\sigma_{Y,X}$. Then

$$Q_X = \psi\zeta_X + h \quad (14)$$

(5A) $\sigma_{I,X} = 0$. Then

$$Q_X = \beta\sigma_{R,X} + \psi\zeta_X + h \quad (15)$$

(5B) $\sigma_{R,X} = 0$. Then

$$Q_X = \alpha\sigma_{I,X} + \psi\zeta_X + h \quad (16)$$

(5C) $\sigma_{I,X} = \sigma_{R,X} = 0$. Then

$$Q_X = \psi\zeta_X + h \quad (17)$$

(6A) $\sigma_{I,X}$ = constant.

$$Q_X = \beta\sigma_{R,X} + \psi\zeta_X + h' \quad (18)$$

where $h' = \alpha\sigma_{I,X} + h$. (6B) $\sigma_{Q,X}$ = constant.

$$Q_X = \alpha\sigma_I + \psi\zeta_X + h' \quad (19)$$

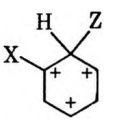
where $h' = \beta\sigma_{R,X} + h$. (6C) $\sigma_{I,X}$ = a constant, $\sigma_{R,X}$ = a constant. Then

$$Q_X = \psi\zeta_X + h' \quad (20)$$

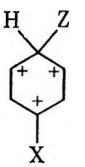
where $h' = \alpha\sigma_{I,X} + \beta\sigma_{R,X} + h$.

The results of the correlations have shown that the partial rate factors for *ortho* substitution are correlated successfully by eq 1. Then we may exclude cases 4B, 4C, 5A, 5B, 5C, 6A, 6B, and 6C. Thus the proximity effects must be either 0, constant, or a linear function of σ_I, σ_R, or both. Of the contributions to the proximity effect we have cited, only the van der Waals and possibly the London interactions between reaction site and substituent should lead to a relationship between ζ and σ_I or σ_R or both. We infer then that certainly all of the other contributions to the proximity effect are either constant or zero and that in accord with the suggestion of de la Mare and Ridd the effect of *ortho* substituents upon electrophilic aromatic substitution is primarily an electrical effect.

Localized *ortho* Electrical Effect.—To make possible a comparison of α_o with α_p we have carried out a correlation by means of simple regression analysis. The results of the correlation are given in Table III; they show that the α values are equal for *ortho* and *para* substitution. To account for this observation let us consider the intermediate in electrophilic aromatic substitution. In this intermediate (I) positive charges are located at carbons 2, 4, and 6. If we compare the *ortho*-substituted intermediate with the *para*-substituted intermediate (II) we see that the substituent



I



II

in each case is adjacent to one charge and about the same distance from the other two. Thus the localized effect of the substituent should be the same in the *ortho*- and in the *para*-substituted intermediates as the geometry is essentially the same. The transition-state structure will resemble to some extent the structure of the intermediate. Therefore it is not unreasonable to assume that the *ortho* and *para* transition states will have the same geometry and will exhibit the same localized effect.

The Delocalized Electrical Effect.—For purposes of comparison values of β_o have been correlated with values of β_p. The results of the correlation are presented in Table III. The results show that β_o is = $0.77\beta_p$; that is, the effect of resonance upon *ortho* substitution is somewhat less than that upon *para* substitution. This result is in accord with arguments presented by Norman and Radda[7] to the effect that the *para*-substituted intermediate is stabilized to a greater extent by resonance than is the *ortho*-substituted intermediate.

Composition of the *ortho* Electrical Effect.—We find it conventient to describe the composition of the elec-

(7) R. D. C. Norman and G. K. Radda, *J. Chem. Soc.*, 3610 (1961).

TABLE I

PARTIAL RATE FACTORS FOR ELECTROPHILIC AROMATIC SUBSTITUTION

Set	Reaction	Reagent	Solvent	Ref
1	Detritiation	H_2SO_4	CF_3CO_2H–H_2O	*a*
2	Nitration	HNO_3	$MeNO_2$	*a*
3	Nitration	NO_2BF_4	$C_4H_8SO_2$	*a*
4	Nitration	$AcONO_2$	Am_2O	*a*
5	Chlorination	Cl_2	AcOH	*a*
6	Chlorination	$Cl_2 + FeCl_3$	$MeNO_2$	*b*
7	Chlorination	$Cl_2 + AlCl_3$	$MeNO_2$	*b*
8	Bromination	Br_2	AcOH–H_2O	*a*
9	Bromination	Br_2(l) + $FeCl_3$	$MeNO_2$	*c*
10	Bromination	Br_2 in $MeNO_2$ + $FeCl_3$	$MeNO_2$	*c*
11	Bromination	(Br_2 + $FeCl_3$) in $MeNO_2$	$MeNO_2$	*c*
12	Mercuration	$Hg(OAc)_2$	AcOH	*a*, *d*
13	Mercuration	$Hg(OAc)_2$	AcOH	*a*
14	Mercuration	$Hg(O_2CCF_3)_2$	CF_3CO_2H	*e*
15	Benzylation	$PhCH_2Cl + AlCl_3$	$MeNO_2$	*a*
16	Ethylation	$EtBr + GaBr_3$	$C_2H_4Cl_2$	*a*
17	Isopropylation	$MeCH{=}CH_2 + AlCl_3$	$MeNO_2$	*f*
18	Isopropylation	*i*-PrBr + $AlCl_3$	$MeNO_2$	*f*
19	Isopropylation	*i*-PrBr + $FeCl_3$	$MeNO_2$	*f*

ortho partial rate factors

Set	X = F	Cl	Br	I	Me	Et	*i*-Pr	Ph	NHAc	OMe	OPh
01	0.13	0.035	0.027	0.043	541	133					
02		0.0277	0.030	0.253	38.9						
03	0.115	0.093	0.093	0.304	3.2						
04	0.037				46.5	31.4	14.8	41			117
05	0.22	0.097	0.084		617	450	218	190	6.1×10^5	6.1×10^6	
06	0.222	0.217	0.201		27.5	20.0					
07	0.254	0.236	0.197		34.7						
08					600	465	180	37.5		8.7×10^7	
09	0.217	0.213	0.212		4.46	4.02					
010	0.0851	0.0796	0.0780		15.1						
011	0.171	0.151	0.131		7.42						
012	0.53	0.081	0.068		3.51			0.221			
013	0.63	0.075	0.070		5.71			0.0813		186	
014	0.0983	0.0168	0.0126		3.62	1.96	0.533				
015	0.203	0.248	0.175	0.256	4.20	3.12					
016	0.364	0.271	0.096		2.84			0.905			
017	0.285	0.177	0.116		2.70						
018	0.343	0.200	0.171		2.84						
019	0.288	0.149	0.123		2.97						

meta partial rate factors

Set	X = F	Cl	Br	I	Me	Et	*i*-Pr	*t*-Bu	Ph	OMe
m1	0.002	0.002	0.001	0.003	9.2			32		
m2		0.00084	0.00098	0.0112	1.3			3.7		
m3		0.0029	0.0040		0.14			0.38		
m4										
m5	0.0056	0.0023	0.0032		4.95			6.0	0.74	
m6	0.0174	0.0158	0.0144		0.932	0.893				
m7	0.0245	0.0205	0.0135		1.10					
m8	0.0010	0.00056	0.00053		5.5			6.09	0.3	2.0
m12	0.109	0.058	0.062		1.70			2.58	0.681	
m13	0.040	0.060	0.054		2.23			3.41	0.773	1.2
m14	0.00687	0.00820	0.00954		2.55	2.37	2.18	1.97		
m15		0.0043	0.0038	0.0059	0.43	0.37				
m16	0.116	0.102	0.087		1.56				0.695	
m17	0.0145	0.0168	0.0181		0.888					
m18	0.0131	0.0237	0.0271		0.895					
m19	0.0235	0.0316	0.0383		1.03					

para partial rate factors

Set	X = F	Cl	Br	I	Me	Et	*i*-Pr	*t*-Bu	Ph	NHAc	OPh	OMe	OH
p1	1.73	0.127	0.072	0.0865	702			863	143				
p2	0.77	0.130	0.103	0.776	45.8			71.6					
p3	2.47	0.643	0.526	1.07	3.2			5.3					
p4	0.77				48.5			57.7	38		2.30		
p5	3.93	0.406	0.310		820	840	650	401	590	2.52×10^6		4.6×10^7	
p6	1.26	0.555	0.470		24.2	29.6							
p7	1.48	0.627	0.480		38.2								

Table I (*Continued*)

		para partial rate factors											
Set	X = F	Cl	Br	I	Me	Et	*i*-Pr	*t*-Bu	Ph	NHAc	OPh	OMe	OH
p8	4.62	0.145	0.0618		2420	1800	1200	806	2920	1.2×10^9	1×10^8	1.1×10^{10}	3.7×10^{12}
p9	3.71	1.67	1.38		4.64	6.13							
p10	1.45	0.561	0.444		11.6								
p11	2.54	0.899	0.699		6.37								
p12	1.87	0.26	0.22		11.2			9.61	4.02		1.94	2310	
p13	2.98	0.36	0.27		23.0			17.2	6.42	277			
p14	1.51	0.232	0.194		46.9	42.8	39.0	32.3					
p15		0.955	0.721	1.15	10.0	7.7							
p16	0.738	0.588	0.433		6.02				2.23				
p17	0.778	0.271	0.151		4.56								
p18	0.777	0.254	0.179		4.70								
p19	0.948	0.315	0.242		5.26								

[a] Reference 1. [b] G. A. Olah, S. J. Kuhn, and B. A. Hardie, *J. Amer. Chem. Soc.*, **86**, 1055 (1964). [c] G. A. Olah, S. J. Kuhn, S. H. Flood, and B. A. Hardie, *ibid.*, **86**, 1039, 1044 (1964). [d] At 90°. [e] H. C. Brown and R. A. Wirkkala, *ibid.*, **88**, 1456 (1966). [f] G. A. Olah, S. H. Flood, and M. E. Moffat, *ibid.*, **86**, 1065 (1964); G. A. Olah, S. H. Flood, S. J. Kuhn, M. E. Moffat, and N. A. Overchuck, *ibid.*, **86**, 1046 (1964).

Table II

Results of Correlations with Eq 1

	ortho partial rate factors								
Set	$-\alpha$	$-\beta$	h	R^a	F^b	r^c	$s_{estd}{}^d$	$s_\alpha{}^d$	$s_\beta{}^d$
01	9.93	4.75	2.04	0.987	56.59	0.675	0.406	1.06	1.84
02	5.00	−5.20	1.96	0.999	222.8	0.680	0.121	0.388	1.49
03	2.82	0.174	0.360	0.975	18.93	0.612	0.207	0.566	0.944
03A	3.29	1.27	0.188	0.9998	1041	0.729	0.0286	0.0906	0.169
04	9.68	8.91	0.379	0.772	2.214	0.934	1.04	5.26	6.58
04A	1.67	1.86	−1.31	0.999	186.3	0.952	0.144	0.919	1.21
05	12.3	15.5	1.11	0.794	5.121	0.649	1.98	3.96	5.91
05A	12.7	15.1	0.838	0.922	14.16	0.646	1.22	2.44	3.63
06	4.33	1.30	1.01	0.999	462.1	0.805	0.0736	0.213	0.433
07	4.66	1.55	1.12	0.999	180.0	0.729	0.0996	0.315	0.586
08	6.71	18.0	−1.75	0.996	125.1	0.875	0.322	2.54	1.83
09	2.73	0.769	0.405	0.9997	1545	0.805	0.0255	0.0739	0.150
010	4.78	1.41	0.770	0.9996	662.5	0.729	0.0540	0.171	0.318
011	3.67	1.35	0.524	0.999	183.6	0.729	0.0766	0.242	0.451
012	4.19	5.42	−0.525	0.959	11.54	0.784	0.279	0.879	1.60
013	5.33	8.21	−0.829	0.957	16.19	0.511	0.518	1.17	1.56
014	5.66	5.16	−0.426	0.998	230.3	0.805	0.106	0.308	0.626
015	2.62	0.731	0.346	0.994	120.2	0.687	0.0909	0.211	0.413
016	2.95	2.43	−0.00169	0.956	10.52	0.784	0.232	0.729	1.32
017	2.95	2.10	0.0283	0.991	26.40	0.729	0.144	0.455	0.846
018	2.73	1.90	0.0877	0.998	131.6	0.729	0.0601	0.190	0.354
019	3.12	2.26	0.0444	0.998	119.4	0.729	0.0711	0.225	0.419

Set	$s_h{}^d$	n^e	C.L.$_{reg}{}^f$	$t_\alpha{}^g$	C.L.$_\alpha{}^f$	$t_\beta{}^g$	C.L.$_\beta{}^f$	$t_h{}^g$	C.L.$_h{}^f$
01	0.339	6	99.5	9.368	99.0	2.582	90.0	6.017	99.0
02	0.208	4	...[h]	12.89	95.0	3.490	80.0	9.420	90.0
03	0.208	5	90.0	4.982	95.0	0.1843	20.0	1.731	50.0
03A	0.0332	4	97.5	36.31	98.0	7.515	90.0	5.662	80.0
04	0.997	6	90.0	1.840	80.0	1.354	50.0	3.801	95.0
04A	0.211	4	90.0	1.817	50.0	1.537	50.0	6.209	80.0
05	1.27	9	90.0	3.106	95.0	2.623	95.0	0.8740	50.0
05A	0.785	8	99.5	5.205	99.0	4.160	99.0	1.068	50.0
06	0.0708	5	99.5	20.33	99.0	3.002	90.0	14.27	99.9
07	1.16	4	90.0	14.79	95.0	2.645	50.0	0.9655	20.0
08	0.299	5	99.0	2.642	80.0	9.836	98.0	5.853	95.0
09	0.0246	5	99.9	36.94	99.9	5.127	95.0	16.46	99.0
010	0.0627	4	95.0	27.95	95.0	4.434	80.0	12.28	90.0
011	0.0889	4	90.0	15.17	95.0	2.993	50.0	5.894	80.0
012	0.261	5	90.0	4.767	95.0	3.388	90.0	2.011	80.0
013	0.445	6	97.5	4.556	98.0	5.263	98.0	1.863	80.0
014	0.102	4	95.0	18.38	95.0	8.243	90.0	4.176	80.0
015	0.0732	6	99.5	12.42	99.0	1.770	80.0	5.726	98.0
016	0.216	5	90.0	4.046	90.0	1.841	50.0	0.0078	20.0
017	0.167	4	90.0	6.484	90.0	2.482	50.0	0.0169	20.0
018	0.0697	4	90.0	14.37	95.0	5.363	80.0	1.258	50.0
019	0.0826	4	90.0	13.87	95.0	4.394	80.0	0.5375	20.0

TABLE II (*Continued*)

meta partial rate factors

Set	$-\alpha$	$-\beta$	h	R^a	F^b	r^c	$s_{estd}{}^d$	$s_\alpha{}^d$	$s_\beta{}^d$	$s_h{}^d$
m1	8.41	2.84	0.378	0.997	216.0	0.649	0.221	0.480	0.990	0.185
m2	5.27	−6.03	0.784	0.996	118.8	0.712	0.222	0.578	2.68	0.374
m2A	9.00	12.3	−1.73	0.9991	284.1	0.990	0.142	1.93	9.48	1.30
m3	5.32	8.84	−2.06	0.993	33.62	0.490	0.225	3.05	15.0	2.06
m5	6.91	2.69	0.0549	0.997	289.0	0.793	0.151	0.405	0.836	0.133
m6	3.79	1.28	−0.371	0.9994	897.6	0.805	0.0455	0.132	0.268	0.0438
m7	3.96	1.81	−0.377	0.995	46.40	0.729	0.159	0.503	0.936	0.185
m8	9.15	5.18	−0.324	0.995	199.9	0.586	0.234	0.472	0.705	0.172
m12	3.37	1.91	−0.0985	0.998	441.9	0.793	0.0555	0.149	0.307	0.0489
m13	3.80	1.58	0.0657	0.989	88.97	0.586	0.151	0.305	0.455	0.111
m14	4.83	0.661	0.0313	0.998	540.9	0.834	0.0972	0.253	0.564	0.0868
m15	4.22	1.37	−0.761	0.9992	638.2	0.777	0.0596	0.176	0.730	0.0918
m16	2.64	1.04	−0.0417	0.997	188.9	0.784	0.0585	0.184	0.334	0.0547
m17	3.47	0.561	−0.293	0.99993	3,396	0.729	0.0182	0.0577	0.107	0.0212
m18	2.93	−0.479	−0.137	0.99999	20,325	0.729	0.00716	0.0227	0.0422	0.00831
m19	2.89	−0.00709	−0.132	0.99990	2,627	0.729	0.0184	0.0582	0.108	0.0213

Set	n^e	C.L.$_{reg}{}^f$	$t_\alpha{}^g$	C.L.$_\alpha{}^f$	$t_\beta{}^g$	C.L.$_\beta{}^f$	$t_h{}^g$	C.L.$_h{}^f$
m1	6	99.9	17.52	99.9	2.868	90.0	2.043	80.0
m2	5	n.s.[h]	9.117	98.0	2.250	80.0	2.096	80.0
m2A	4	95.0	4.663	80.0	1.297	50.0	1.331	50.0
m3	4	90.0	1.744	50.0	0.5893	20.0	1.000	50.0
m5	6	99.9	13.96	99.9	3.218	95.0	0.4128	20.0
m6	5	99.5	28.71	99.9	4.776	95.0	8.470	98.0
m7	4	90.0	7.872	90.0	1.934	50.0	2.038	50.0
m8	7	99.9	19.39	99.9	7.347	99.0	1.884	80.0
m12	6	99.9	22.62	99.9	6.221	99.0	2.014	80.0
m13	7	99.9	12.46	99.9	3.473	95.0	0.5919	20.0
m14	7	99.9	19.09	99.9	1.172	50.0	0.3606	20.0
m15	5	99.5	23.98	99.0	1.876	50.0	8.290	98.0
m16	5	99.0	14.35	99.0	3.114	90.0	0.7623	20.0
m17	4	97.5	60.13	98.0	5.243	80.0	13.82	95.0
m18	4	n.s.[h]	129.1	99.0	11.35	90.0	16.48	95.0
m19	4	97.5	49.65	98.0	0.0756	20.0	6.197	80.0

para partial rate factors

Set	$-\alpha$	$-\beta$	h	R^a	F^b	r^c	$s_{estd}{}^d$	$s_\alpha{}^d$	$s_\beta{}^d$	$s_h{}^d$
p1	9.02	6.81	1.70	0.987	73.48	0.678	0.373	0.807	1.64	0.280
p2	5.18	2.75	1.12	0.970	23.93	0.649	0.388	0.842	1.74	0.325
p2A	6.24	5.24	0.728	0.9995	996.6	0.780	0.0613	0.165	0.358	0.0630
p3	1.81	2.16	0.248	0.923	8.661	0.649	0.201	0.436	0.899	0.168
p3A	2.33	3.39	0.0525	0.992	64.93	0.780	0.0771	0.208	0.450	0.0792
p4	6.61	6.84	0.785	0.780	1.555	0.417	0.821	3.89	4.98	0.846
p4A	11.2	14.0	−0.693	0.994	39.89	0.951	0.206	1.28	1.79	0.341
p5	10.9	16.7	−0.0348	0.782	5.512	0.672	1.86	3.54	5.56	1.13
p5A	11.7	17.6	−0.677	0.939	18.69	0.665	1.06	2.03	3.29	0.711
p6	4.00	2.72	0.926	0.998	209.7	0.805	0.0863	0.250	0.508	0.0831
p7	4.26	3.01	0.101	0.998	114.6	0.729	0.0999	0.316	0.588	0.116
p8	14.7	24.7	0.505	0.862	13.06	0.608	2.46	4.21	4.86	1.32
p8A	16.2	25.8	−0.0545	0.953	39.41	0.613	1.48	2.55	2.94	0.804
p9	1.54	2.05	0.423	0.975	19.18	0.805	0.0889	0.259	0.524	0.856
p10	3.30	2.90	0.550	0.998	103.0	0.729	0.0777	0.246	0.458	0.0902
p11	2.39	2.84	0.342	0.996	57.41	0.729	0.0710	0.225	0.418	0.0824
p12	4.05	4.41	0.295	0.983	42.62	0.793	0.179	0.479	0.989	0.157
p13	5.57	8.08	0.324	0.890	11.38	0.603	0.696	1.39	1.81	0.480
p13A	5.75	8.28	0.133	0.973	45.22	0.604	0.358	0.715	0.930	0.251
p14	5.49	4.92	0.743	0.993	144.3	0.834	0.158	0.410	0.916	0.141
p15	2.07	3.56	0.801	0.992	61.56	0.777	0.0968	0.287	1.19	0.149
p15A	3.77	7.49	−0.0701	0.9992	295.8	0.989	0.0424	0.567	2.38	0.291
p16	2.39	1.44	0.463	0.992	65.06	0.784	0.0825	0.260	0.471	0.0771
p17	3.40	3.48	0.0672	0.987	19.31	0.729	0.179	0.566	1.05	0.208
p18	3.35	3.35	0.100	0.995	52.22	0.729	0.108	0.341	0.635	0.125
p19	3.19	3.18	0.178	0.997	81.32	0.729	0.0822	0.260	0.484	0.0955

X

Set	n^e	C.L.$_{reg}{}^f$	$t_\alpha{}^g$	C.L.$_\alpha{}^f$	$t_\beta{}^g$	C.L.$_\beta{}^f$	t_h	C.L.$_h{}^f$
p1	7	99.9	11.18	99.9	4.152	98.0	6.071	99.0
p2	6	97.5	6.152	99.0	1.580	50.0	3.446	95.0
p2A	5	99.5	37.82	99.9	14.64	99.0	11.56	99.0
p3	6	90.0	4.151	95.0	2.403	90.0	1.476	50.0

TABLE II (*Continued*)

Set	X							
	n^e	C.L.$_{reg}{}^f$	$t_\alpha{}^g$	C.L.$_\alpha{}^f$	$t_\beta{}^g$	C.L.$_\beta{}^f$	t_h	C.L.$_h{}^f$
p3A	5	97.5	11.20	99.0	7.533	98.0	0.6629	20.0
p4	5	90.0	1.699	50.0	1.373	50.0	0.9279	50.0
p4A	4	90.0	8.750	90.0	7.821	90.0	2.032	50.0
p5	10	90.0	3.079	98.0	3.003	98.0	0.0308	20.0
p5A	8	99.5	5.764	99.0	5.350	99.0	0.9521	50.0
p6	5	99.5	16.00	99.0	5.354	95.0	11.14	99.0
p7	4	90.0	13.48	95.0	5.119	80.0	8.707	90.0
p8	12	99.0	3.492	99.0	5.082	99.9	0.3826	20.0
p8A	11	99.9	6.352	99.9	8.775	99.9	0.0068	20.0
p9	5	95.0	5.946	95.0	3.912	90.0	4.942	90.0
p10	4	90.0	13.41	95.0	6.332	90.0	6.098	80.0
p11	4	90.0	10.62	90.0	6.794	90.0	4.150	80.0
p12	6	99.0	8.455	99.0	4.459	95.0	1.879	80.0
p13	9	99.9	4.007	99.0	5.464	99.0	0.6750	20.0
p13A	8	99.9	8.042	99.9	8.903	99.9	0.5299	20.0
p14	7	99.9	13.39	99.9	5.371	99.0	5.270	99.0
p15	5	97.5	7.213	99.0	2.992	90.0	5.376	98.0
p15A	4	95.0	6.649	90.0	3.147	80.0	0.2401	20.0
p16	5	97.5	9.192	98.0	3.057	90.0	6.005	95.0
p17	4	90.0	6.007	80.0	3.314	80.0	0.3231	80.0
p18	4	90.0	9.824	90.0	5.275	80.0	0.800	20.0
p19	4	90.0	12.27	90.0	6.570	90.0	1.864	50.0

[a] Multiple correlation coefficient. [b] F test for significance of regression. [c] Partial correlation coefficient of σ_I on σ_R. [d] Standard errors of the estimate, α, β, and h. [e] Number of points in set. [f] Confidence levels for regression, α, β, and h. [g] "t" test for significance of α, β, and h. [h] Not significant owing to difference in sign of α and β.

trical effect in terms of the ratio of β to α. Thus

$$\epsilon = \beta/\alpha \tag{21}$$

Then, for *ortho* substitution we may write

$$\epsilon_o = \beta_o/\alpha_o \tag{22}$$

From the correlation of α_o with α_p we obtain $\alpha_o = \alpha_p$. From the correlation of β_o with β_p we obtain $\beta_o = 0.77\beta_p$. Then

$$\epsilon_0 = \frac{0.77\beta_p}{\alpha_p} = 0.77\epsilon_p \tag{23}$$

For those sets of *para* partial rate factors studied here in which β was significant we find an average value ϵ_p of 1.15. Exclusion of those sets in which the value

Table III

CORRELATION OF α_o WITH α_p AND β_o WITH β_p

	m^a	c^b	r^c	s^d	$s_m{}^d$	t^e	C.L.^{f}	n^g
A	1.00	0.515	0.976	0.643	0.0620	16.17	99.9	15
B	0.767	−0.139	0.967	1.37	0.0543	14.13	99.9	16

[a] Slope. [b] Intercept. [c] Correlation coefficient. [d] Standard error of the estimate and of m. [e] "t" test for significance of m (and of regression). [f] Confidence level for significance of regression. [g] Number of points in the set.

TABLE IV[a]

VALUES OF THE RATIO $p_o/2p_p$

Set	F	Cl	Br	I	Me	Et	*i*-Pr	Ph	NHAc	OMe	NO_2	CN	CHO	CF_3
R2	0.0476	0.213	0.292	0.321	0.848					0.407	10.7[d]	4.28[d]	1.06[d]	
R3	0.0464	0.144	0.176	0.285	1.03									
R4	0.0476				0.934	0.452	0.207			0.500				
R5	0.0612	0.240	0.414		0.753	0.531	0.333	0.564	0.241	0.133				
R6	0.176	0.391	0.427		1.13	0.673								
R7	0.171	0.376	0.410		0.908									
R8					0.246	0.255	0.149	0.0128		0.00813				
R9	0.0556	0.127	0.154		0.961	0.655								
R10	0.0556	0.142	0.176		1.30									
R11	0.0675	0.168	0.187		1.16									
R12	0.284	0.310	0.307		0.314			0.0551						
R14	0.0649	0.0723	0.0651		0.0772	0.0457	0.0137							
R15	0.0864	0.248	0.293	0.183	0.418	0.403								
R16	0.499	0.504	0.221		0.473			0.405						
R17	0.366	0.657	0.769		0.594									
R18	0.371	0.589	0.689		0.605									
R19	0.362	0.635	0.708		0.564									
R20[b]		0.292	0.349		1.62					0.268	5.87	4.00	2.65	1.96
R21[c]	0.0618	0.141			0.269									

[a] Set numbers refer to Table I unless otherwise noted. Data are from Table I unless otherwise noted. [b] $Cl_2/CCl_4/HClO_4/AgClO_4$/ 25° (ref 7). [c] $(3\text{-}O_2NC_6H_4SO_2O)_2$ in PhX at room temperature: R. L. Dannley and G. E. Corbett, *J. Org. Chem.*, **31**, 153 (1966). [d] Reference 7.

TABLE V

RESULTS OF CORRELATIONS WITH EQ 29

Set	β'	h	r	t	s	n	n	C.L.
R2	2.48	0.191	0.800	3.528	0.453	0.702	9	99.0
R2A	4.02	0.359	0.968	8.605	0.222	0.468	7	99.9
R3	3.13	0.0344	0.891	3.392	0.257	0.924	5	95.0
R4	1.25	−0.142	0.498	1.148	0.485	1.09	6	50.0
R4A	3.40	0.254	0.955	4.535	0.228	0.751	4	95.0
R5	1.96	−0.0639	0.894	5.276	0.164	0.372	9	99.0
R5A	2.10	−0.00656	0.917	5.614	0.158	0.374	8	99.0
R6	1.96	0.116	0.935	4.584	0.122	0.427	5	98.0
R7	2.01	0.116	0.970	5.602	0.0889	0.358	4	95.0
R8	2.71	−0.677	0.677	1.593	0.620	1.70	5	50.0
R8A	3.63	−0.203	0.9995	30.14	0.403	0.120	3	95.0
R9	3.29	0.117	0.911	3.837	0.246	0.857	5	95.0
R10	3.57	0.242	0.888	2.732	0.324	1.31	4	80.0
R11	3.22	0.186	0.893	2.800	0.286	1.15	4	80.0
R12	−1.01	−0.899	0.431	0.827	0.346	1.23	5	50.0
R12A	0.122	−0.483	0.973	5.910	0.00560	0.0226	4	95.0
R14	−0.786	−1.47	0.375	0.808	0.295	0.973	6	50.0
R15	1.59	−0.298	0.855	3.300	0.146	0.483	6	95.0
R15A	1.92	−0.173	0.996	18.36	0.0300	0.105	5	99.9
R16	−0.201	−0.442	0.189	0.333	0.170	0.603	5	20.0
R17	0.770	−0.0397	0.794	1.844	0.104	0.417	4	50.0
R18	0.722	−0.0723	0.881	2.635	0.0680	0.274	4	80.0
R19	0.706	−0.0757	0.791	1.831	0.0957	0.386	4	50.0
R20	2.10	0.280	0.889	4.760	0.265	0.440	8	99.0
R20A	3.30	0.345	0.958	6.644	0.177	0.497	6	99.0
R21	1.85	−0.372	0.995	10.16	0.0443	0.182	3	90.0

of h was significant gives an average value of ϵ_p of 1.27.

The *ortho–para* Ratio in Electrophilic Aromatic Substitution.—From the definition of partial rate factors we may write

$$f_{X^o} = \frac{k_{PhX} \times 6 \times p_o}{k_{PhH} \times 2 \times 100} \quad (24)$$

where p_o is per cent *ortho* substitution and k_{PhX} and k_{PhH} are rate constants for the substituted benzene and benzene itself. Similarly

$$f_{X^p} = \frac{k_{PhX} \times 6 \times p_p}{k_{PhH} \times 100} \quad (25)$$

From eq 1 we may write

$$\log f_{X^o} = \alpha_o\sigma_{I,X} + \beta_o\sigma_{R,X} + h_o \quad (26)$$

$$\log f_{X^p} = \alpha_p\sigma_{I,X} + \beta_p\sigma_{R,X} + h_p \quad (27)$$

Then

$$\log\left(\frac{f_{X^o}}{f_{X^p}}\right) = \log\left(\frac{p_o}{2p_p}\right)_X = (\alpha_o - \alpha_p)\sigma_{I,X} + (\beta_o - \beta_p)\sigma_{R,X} + (h_o - h_p) \quad (28)$$

Now as $\alpha_o = \alpha_p$ and $\beta_o = 0.77\beta_p$ we write

$$\log\left(\frac{p_o}{2p_p}\right)_X = -0.23\beta_p\sigma_{R,X} + h' = \beta'\sigma_{R,X} + h' \quad (29)$$

where $h' = h_0 - h_p$. In the general case h' will equal zero.

To provide a test of eq 29 we have correlated it with all of the available data. The data used are set forth in Table IV. The results of these correlations are given in Table V. The results for set R2 were significantly improved by the exclusion of the value for X = OMe and CHO (set R2A). Significant correlation was obtained for set R4 on the exclusion of X = OPh and *i*-Pr (set R4A) and set R8 on the exclusion of X = Ph and *i*-Pr (set R8A). As set 8A has only three points, two of which are alkyl groups, its value is doubtful. Exclusion of the point for X = Ph (set R12A) gave a significant correlation for set 12. Exclusion of the value for X = I from set R15 gave an excellent correlation (set R15A). Elimination of the points for X = CF_3 and X = OMe (set R20A) gave some improvement in the correlation for the set R20. It is noteworthy that the values of h' are not significantly different from zero.

Of 19 sets studied 12 gave significant correlation. All of the sets with eight or more members gave excellent correlation. We believe that, although the results are not absolutely certain, they do tend to support the validity of eq 29.

Steric Effects of *ortho* Substituents.—For most of the substituents studied, the substituent effect can be accounted for in terms of electrical effects as noted above. Certain substituents consistently (or often) show deviations suggestive of steric effects. These substituents include *t*-Bu, *i*-Pr, CF_3, I, and occasionally Ph.

Preformed Substituting Reagents.—Of the 19 sets studied in this paper eight are based on the work of Olah, *et al.*,[8] who have used the so-called preformed substitution reagents. A referee has pointed out that this work has been criticized as the relative rates

(8) Table I, footnotes *b*, *c*, and *f*.

and thus the partial rate factors may be controlled by the rate of mixing and diffusion of the reagents. If this were indeed the case we would expect no correlations for Olah's data or at the very least entirely different behavior for these sets. This is apparently not the case. There seems to be no difference in behavior between Olah's data and the other sets studied.

Variation of *ortho* Substitution with Reagent.—Equation 29 predicts that for a constant substrate, *e.g.*, toluene

$$\log \left(\frac{p_o}{2p_p}\right)^X = m'\beta_p + h' \qquad (30)$$

where

$$m' = -0.23\sigma_{R,X} \qquad (31)$$

Thus the variation of the *ortho–para* ratio with reagent should be a linear function of β_p for any given substrate. Equation 30 does not seem to be obeyed. We may perhaps account for this at least in part in terms of a steric effect of the reagent which is constant throughout a set of substituted benzenes but varies from one reagent to another. The small value of m' expected for most substituents suggests that the predominant effect of the reagent may well be steric.

Cyclopropylcarbinyl 3,5-Dinitrobenzoate Solvolysis. 1-Ring Substituent Effect Study

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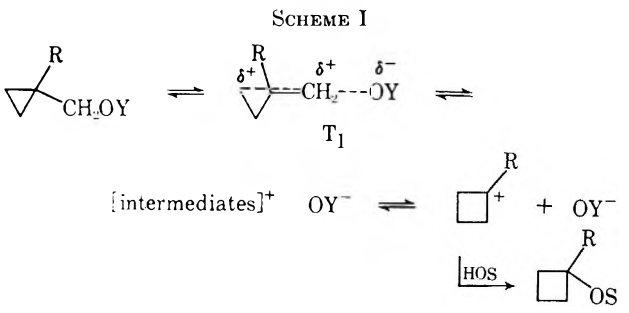
The solvolysis rates of the 3,5-dinitrobenzoate derivatives of cyclopropylcarbinol (**3**-H), 1-methylcyclopropylcarbinol (**3**-Me), 1-phenylcyclopropylcarbinol (**3**-Ph), 1-*p*-anisylcyclopropylcarbinol (**3**-An), cyclobutanol (**4**-H), 1-methylcyclobutanol (**4**-Me), and 1-phenylcyclobutanol (**4**-Ph) have been determined in 50 vol % aqueous dioxane. The relative first-order rates were found to parallel closely those for the acetolysis of the corresponding tosylate derivatives. The implications of this solvolytic behavior are discussed in terms of transition-state geometry and charge distribution.

In a recent paper,[1] a rationale was advanced explaining the insensitivity of the rate of solvolysis of cyclopropylcarbinyl tosylate to 1-ring substituents, in terms of a molecular reorganization mechanism (Scheme I) paralleling the solvolysis mechanism of similarly substituted allylcarbinyl tosylates. The lack of substituent effect upon solvolysis rate was attributed to a homoallyllike transition state, T_1, while the exclusive formation of ring expanded products was accommodated by a subsequent but greater structure reorganization, leading to a tertiarylike carbonium ion eventually captured by solvent.

SCHEME I



That a poorer leaving group in a solvolysis reaction will generate a transition state with less charge development but with greater orbital reorganization is a generally accepted postulate.[2] Furthermore, it is well established by the extensive work in the linear free-energy field[3] that substituent effects respond to variable charge development in classical SN1-type reactions. On the other hand, there is increasing evidence[4] against a simple extension of substituent effects in classical ion formation to nonclassical ion formation. Accordingly, based upon the slight influence of γ substituents upon the reactivity of allylcarbinyl substrates,[4d] one would predict little substituent effect dependency upon leaving group in the solvolysis of 1-ring-substituted cyclopropylcarbinyl derivatives.

As a test of this thinking, the solvolytic behavior of seven cyclopropylcarbinyl 3,5-dinitrobenzoate derivatives was studied. The selection of leaving group was dictated by several considerations: (a) relative to tosylates, much more slowly ionizing 3,5-dinitrobenzoates would afford a more rigorous test of the proposed insensitivity of the transition state to 1-ring substituents; (b) high-purity substrates could be prepared with good room-temperature stability; and (c) *t*-cyclobutyl derivatives could be synthesized which would permit an assessment of the substituent effect upon the proposed intermediate capture by solvent.

Results and Discussion

The kinetic data are summarized in Table I. Each of the esters was allowed to solvolyze in 50 vol % aque-

(1) D. D. Roberts, *J. Org. Chem.*, **33**, 2712 (1968).

(2) (a) A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp 67, 72; (b) H. M. R. Hoffman, *J. Chem. Soc.*, 6762 (1965); (c) E. R. Thornton, *J. Amer. Chem. Soc.*, **89**, 2915 (1967); and (d) C. J. Frisone and E. R. Thornton, *ibid.*, **90**, 1211 (1968).

(3) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," John Wiley & Sons, Inc., New York, N. Y., 1963, Chapter 7.

(4) (a) R. A. Sneen, *J. Amer. Chem. Soc.*, **80**, 3982 (1958); (b) E. J. Corey and H. Vda, *ibid.*, **85**, 1788 (1963); (c) H. C. Brown, F. J. Chloupek, and M. H. Rei, *ibid.*, **86**, 1246 (1964); (d) K. L. Servis and J. D. Roberts, *ibid.*, **87**, 1331 (1965); and (e) M. Nikoletic, S. Borcic, and D. E. Sunko, *Tetrahedron*, **23**, 649 (1967).

TABLE I

SUMMARY OF SOLVOLYSIS RATES FOR ORGANIC 3,5-DINITROBENZOATES IN 50 VOL % DIOXANE

Compound	Temp, °C	k_1,[a] 10^7 sec^{-1}	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu
H—CH$_2$ODNB (3-H)	70.0	0.44	26.9	−14
	80.0	1.50		
	90.0	4.45		
	100.0	11.1		
Ph—CH$_2$ODNB (3-Ph)	70.0	2.58	25.4	−15
	80.0	7.50		
	90.0	21.4		
	100.0	55.5		
Me—CH$_2$ODNB (3-Me)	70.0	0.61	23.2	−24
	80.0	1.50		
	90.0	4.44		
	100.0	9.73		
p-An—CH$_2$ODNB (3-An)	70.0	0.86	24.2	−20
	80.0	2.42		
	90.0	6.66		
	100.0	15.82		
H—ODNB (4-H)	90.0	1.39		
Me—ODNB (4-Me)	70.0	1.97	24.3	−17
	80.0	5.28		
	90.0	14.15		
	100.0	37.50		
Ph—ODNB (4-Ph)	60.0	700	22.4	−11
	70.0	1,860		
	80.0	5,400		
	90.0	12,100		
$(CH_3)_2CCH_2ODNB$ (5)	90.0	0.36		
$(CH_3)_3CODNB$ (6)	70.0	75	28.7	2
	80.0	270		
	90.0	810		

[a] The uncertainties varied from 0.5 to 1.8 standard deviation units from the mean.

ous dioxane and the course of reaction was followed by titrating the liberated 3,5-dinitrobenzoic acid. The reactions followed strictly first-order kinetic law up to at least 75% conversion and most furnished, within experimental error,[5] 100% of the theoretical amount of acid present. That cyclopropylcarbinyl 3,5-dinitrobenzoate derivatives hydrolyze by an uncatalyzed, alkyl-oxygen fission reaction has been established by Schleyer's work.[6] Additional support for this conclusion is evidenced in this work by the strict adherence of the rates to first-order kinetics, and the enhanced reactivity of the tertiary substrates.[7]

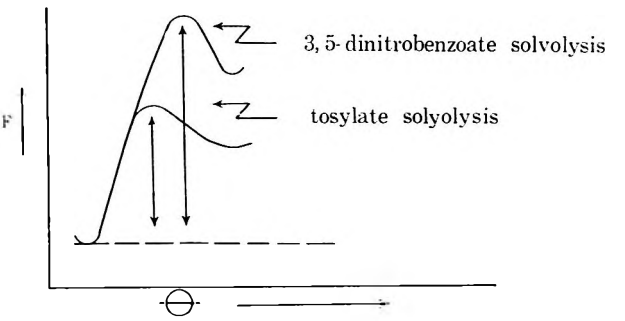
In Table II, the relative rates of selected 3,5-dinitrobenzoate and tosylate derivatives are listed. It is readily apparent that the 1-ring substituent effect is nearly insensitive to leaving group. This finding is even more marked when one notes that the ~500,000-fold difference in reactivity between the 3,5-dinitrobenzoate series and the tosylate series is equivalent to an approximately 9 kcal/mol difference in $\Delta\Delta F^{\ddagger}$. As shown diagrammatically in Scheme II, a $\Delta\Delta F^{\ddagger}$ value of this magnitude would reflect greater orbital

(5) The more slowly reacting cyclobutyl and isobutyl 3,5-dinitrobenzoates were followed only up to 20 and 10% reaction, respectively.

(6) P. von R. Schleyer and G. W. Van Dine, *J. Amer. Chem. Soc.*, **88**, 2321 (1966).

(7) The relative rates are **4**-Ph, 450,000; **6**, 3000; **4**-H, 5.2; **5**, 1.0.

SCHEME II



change for the 3,5-dinitrobenzoate series and, therefore, to the extent that the substituent effect is dependent upon orbital type and/or geometry, a significant change in the relative rate values listed in Table II would be expected. The fact that this is not the case is consistent with mechanism proposed in Scheme I.

TABLE II

RELATIVE SOLVOLYSIS RATES OF CYCLOPROPYLCARBINYL AND CYCLOBUTYL DERIVATIVES

Compound	k_{rel}[a] (X = ODNB)	k_{rel}[b,c] (X = OTS)
H—CH$_2$X (3-H)	1.0	1.0
Me—CH$_2$X (3-Me)	4.9	4.9
Ph—CH$_2$X (3-Ph)	1.0	2.0
p-An—CH$_2$X (3-An)	1.5	3.1
H—X (4-H)	0.31	0.008[d]
Me—X (4-Me)	3.2	
Ph—X (4-Ph)	27,000	
$(CH_3)_2CHCH_2X$ (5)	0.06	
$(CH_3)_3C$ (6)	180	

[a] Relative rates in 50 vol % aqueous dioxane at 90°. [b] Relative rates in acetic acid at 30°. [c] Taken from data of ref 1. [d] Relative rate in acetic acid at 90°, taken from data of H. C. Brown and G. Ham, *J. Amer. Chem. Soc.*, **78**, 2735 (1956).

Examination of the relative rate data for the substituted cyclobutyl compounds is also instructive. Although a methyl group produces only a small rate acceleration, the response to the 1-phenyl substituent reveals the greater stability of the benzyllike cation compared to the nonclassical carbonium ion proposed[8] for the four-membered ring. This result clearly demonstrates that the transition state for the solvolysis of **3**-Ph has little resemblance to the 1-phenylcyclobutyl cation.

Interpretation of activation parameters in a mixed solvent system is difficult;[9] however, the limited struc-

(8) R. H. Mazur, W. N. White, D. A. Semenow, C. C. Lee, M. S. Silver, and J. D. Roberts, *ibid.*, **81**, 4390 (1959).

(9) See ref 3, p 397 ff.

tural difference between isomeric substrates minimizes solvation differences. The kinetic data reveal that the ionization of **4**-Me is moderately influenced by methyl group assistance. Roberts has speculated[10] that the ionization of 1-methylcyclobutyl chloride is accompanied by significant but not complete reduction of bicyclobutonium ion character. In view of this reduced molecular reorganization, it is not unexpected that the partitioning of the free energy of activation for **4**-Me is similar to that for **3**-Me (see Table I).

On the other hand, the kinetic data reveal that the ionization of **4**-Ph is greatly influenced by phenyl group assistance, suggesting a transition state with appreciable benzyl ion character, while the ionization of **3**-Ph is unassisted by the phenyl group, supporting a transition state with considerable homoallylic ion character. It is, therefore, to be expected that **3**-Ph would ionize with a greater decrease in $\Delta S^{\pm}$ than **4**-Ph. The entropy values reported in Table I for the hydrolysis of **3**-Ph and **4**-Ph are in accord with these suggested differences in transition-state structure.

Experimental Section

Melting points were not corrected for stem exposure and were taken on a Mel-Temp apparatus. Spectra were determined on a Varian A-60A spectrophotometer. All microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Cyclopropylcarbinyl 3,5-Dinitrobenzoate (3-H).—Recrystallized 3,5-dinitrobenzoyl chloride (4.62 g, 20 mmol) was added in 10 min to a solution of cyclopropylcarbinol (1.48 g, 20 mmol) in 15 ml of pyridine (Baker Analyzed Reagent) maintained at 0°. After standing 2 hr at room temperature, the yellow mixture was poured, with vigorous stirring, into 70 ml of ice water. The resulting ester was collected by filtration, stirred 20 min with 100 ml of 10% sodium carbonate solution, recollected by filtration, and air dried to yield 2.8 g (53%) of crude ester (mp 99–102°). Three recrystallizations from 4:1 petroleum ether (bp 30–60°)–benzene gave the ester **3**-H: mp 100–101° (lit.[11] mp 101.2–101.4°); nmr (CCl_4) δ 0.6 (complex multiplet, 5 cyclopropyl H), 4.3 (d, J = 8 Hz, 2 methylene H), and 9.1 ppm (m, 3 aryl H).

1-Methylcyclopropylcarbinyl 3,5-dinitrobenzoate (3-Me) was prepared from 1-methylcyclopropylcarbinol[12] as described above in 57% yield: mp [after three recrystallizations from 4:1 petroleum ether (bp 30–60°)–benzene] 85–86° (lit.[13] mp 85.5–85.7°); nmr (CCl_4) δ 0.58 (m, 4 cyclopropyl H), 1.38 (s, 3 methyl H), 4.27 (s, 2 methylene H), and 9.1 ppm (m, 3 aryl H).

1-Phenylcyclopropylcarbinyl 3,5-dinitrobenzoate (3-Ph) was prepared from 1-phenylcyclopropylcarbinol[14] as described above in 68% yield: mp [after three recrystallizations from 2.3:1 petroleum ether (bp 30–60°)–benzene] 106–107°; nmr (C_6H_6) δ 0.97 (s, 4 cyclopropyl H) and 4.38 ppm (s, 2 methylene H).

Anal. Calcd for $C_{17}H_{14}N_2O_6$: C, 59.65; H, 4.12; N, 8.18. Found: C, 59.83; H, 4.02; N, 8.19.

1-*p*-Anisylcyclopropylcarbinyl 3,5-dinitrobenzoate (3-An) was prepared from 1-*p*-anisylcyclopropylcarbinol[1] as described above in 73% yield: mp [after three recrystallizations from 2.3:1 petroleum ether (bp 30–60°)–benzene] 89–90°; nmr (C_6H_6) δ 0.88 (s, 4 cyclopropyl H), 3.57 (s, 3 methoxyl H), and 4.28 ppm (s, 2 methylene H).

Anal. Calcd for $C_{18}H_{16}N_2O_7$: C, 58.00; H, 4.32; N, 7.56. Found: C, 58.21; H, 4.29; N, 7.40.

Cyclobutyl 3,5-Dinitrobenzoate (4-H).—Cyclobutanol (1.45 g, 20 mmol) was added rapidly to a solution of 3,5-dinitrobenzoic acid (4.24 g, 20 mmol) and *p*-toluenesulfonyl chloride (7.63 g, 40 mmol) in 130 ml of pyridine (Baker Analytical Reagent grade) cooled in an ice–water bath. After 1 hr at ice–water bath temperature, the mixture was hydrolyzed by addition to 400 ml of ice–water with vigorous stirring. The resulting ester was separated by filtration, stirred 20 min with 100 ml of 10% sodium carbonate solution, reseparated by filtration, air dried, and recrystallized from 2.5:1 petroleum ether (bp 30–60°)–benzene to yield 3.0 g (56%) of the ester (mp 105–107°). Three additional recrystallizations yielded the analytical sample of **4**-H (mp 108–109°).

Anal. Calcd for $C_{11}H_{10}H_2O_6$: C, 49.63; H, 3.78; N, 10.52. Found: C, 49.81; H, 3.81; N, 10.50.

1-Methylcyclobutyl 3,5-dinitrobenzoate (4-Me) was prepared from 1-methylcyclobutanol[12] as described above for **4**-H in 82% yield: mp [after three recrystallizations from 2.5:1 petroleum ether (bp 30–60°)–benzene] 133.0–133.5°; nmr ($CHCl_3$) δ 1.72 (s, 3 methyl H), and 2.0 and 2.4 (m, 6 cyclobutyl H), and 9.1 ppm (m, 3 aryl H).

Anal. Calcd for $C_{12}H_{12}N_2O_6$: C, 51.43; H, 4.31; N, 9.99. Found: C, 51.42; H, 4.50; N, 9.79.

1-Phenylcyclobutyl 3,5-dinitrobenzoate (4-Ph) was prepared from 1-phenylcyclobutanol[12] as described previously for **3**-H in 50% yield: mp [after three recrystallizations from 3:1 petroleum ether (bp 30–60°)–benzene] 107–108°; nmr (C_6H_6) δ 1.6 (complex multiplet) and 2.6 ppm (complex multiplet).

Anal. Calcd for $C_{17}H_{14}N_2O_6$: C, 59.65; H, 4.12; N, 8.18. Found: C, 59.85; H, 4.09; N, 8.18.

Isobutyl 3,5-dinitrobenzoate (5) was prepared from isobutyl alcohol as described previously for **3**-H in 86% yield: mp [after recrystallization from 6:1 petroleum ether (bp 30–60°)–benzene] 85.5–86° (lit.[15] mp 86°).

***t*-Butyl 3,5-dinitrobenzoate (6)** was prepared from *t*-butyl alcohol as described previously for **4**-H in 55% yield: mp [after recrystallization 6:1 petroleum ether (bp 30–60°)–benzene] 142–143° (lit.[16] mp 142°).

Rate measurements were accomplished by the ampoule technique. The titrating solution was 0.020 N sodium hydroxide and the indicator was bromothymol blue.

Solvent.—Dioxane was purified according to method of Fieser.[17]

Treatment of Kinetic Data.—The activation parameters were obtained by IBM 1620 computer regresson analysis of ln k/T *vs.* $1/T$.

Registry No.—**3**-H, 10364-97-3; **3**-Me, 10364-98-4; **3**-Ph, 18592-76-2; **3**-An, 18592-77-3; **4**-H, 18592-78-4; **4**-Me, 18592-79-5; **4**-Ph, 18592-80-8; **5**, 10478-01-0; **6**, 5342-97-2.

Acknowledgment.—This work was supported in part by the Petroleum Research Fund of the American Chemical Society. This support is gratefully acknowledged.

(10) E. F. Cox, M. C. Caserio, M. S. Silver, and J. D. Roberts, *J. Amer. Chem. Soc.*, **83**, 2719 (1961).
(11) J. D. Roberts, and R. H. Mazur, *ibid.*, **73**, 2509 (1951).
(12) D. D. Roberts, *J. Org. Chem.*, **31**, 2000 (1966).
(13) S. Siegel and C. G. Bergstrom, *J. Amer. Chem. Soc.*, **72**, 3815 (1950).
(14) J. W. Wilt and D. D. Roberts, *J. Org. Chem.*, **27**, 3430 (1962).
(15) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th ed, John Wiley & Sons, Inc., New York, N. Y., 1956, p 280.
(16) J. H. Brewster and C. J. Ciotti, *J. Amer. Chem. Soc.*, **77**, 6214 (1955).
(17) L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed, D. C. Heath and Co., Boston, Mass., 1957, p 285.

Lead Tetraacetate. VI. Stereochemical Studies on the Formation of Bicyclic Ethers from Alicyclic Primary Alcohols[1]

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Received June 24, 1968

The reactions of lead tetraacetate with 2-cyclohexylethanol, 3-cyclohexylpropanol, 2-cyclopentylethanol, and 3-cyclopentylpropanol were studied to determine the stereochemistry of the tetrahydrofurans formed. The oxidation of 2-cyclohexylethanol yielded both *cis*- and *trans*-7-oxabicyclo[4.3.0]nonanes, while 2-cyclopentylethanol yielded only the *cis* isomer of 2-oxabicyclo[3.3.0]octane. The oxidation of 3-cyclohexylpropanol yielded an oxaspiran, 1-oxaspiro[4.5]decane, in low yield, while the oxidation of 3-cyclopentylpropanol yielded a saturated oxaspiran, 1-oxaspiro[4.4]nonane, and an unsaturated oxaspiran, 1-oxaspiro[4.4]non-6-ene. The oxymercuration–demercuration of 2-(2-cyclohexenyl)ethanol (**18**) and 2-(2-cyclopentenyl)ethanol (**19**) yielded isomerically pure *cis*-7-oxabicyclo[4.3.0]nonane (**2**) and *cis*-2-oxabicyclo[3.3.0]octane (**9**).

In 1959 Jeger and his coworkers[3] treated pregnane-3β,20β-diol-3-acetate with lead tetraacetate and obtained a cyclic ether. Various steroids were subsequently treated with lead tetraacetate (LTA), yielding tetrahydrofurans in up to 50% yield.[4]

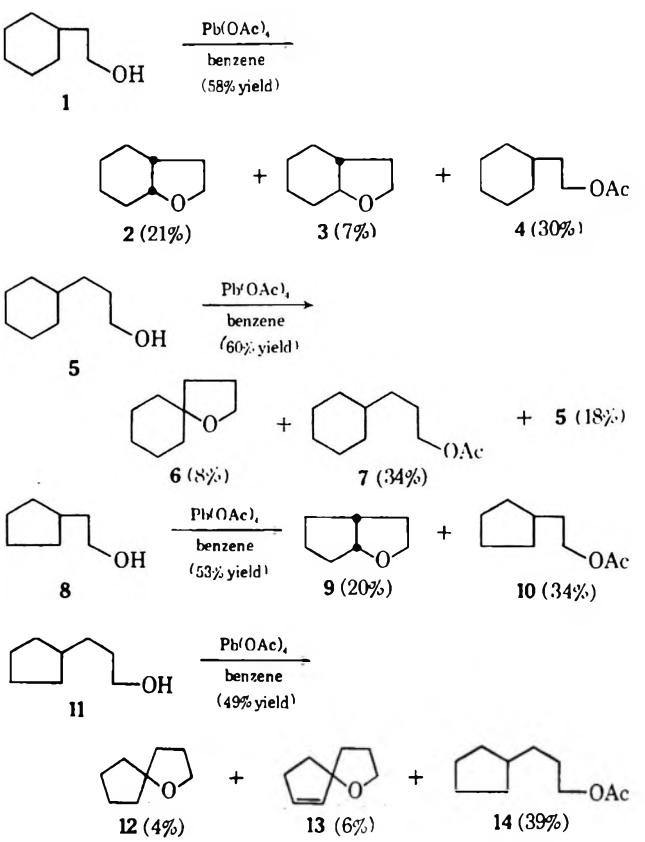
Micovic, *et al.*,[5] later discovered that treatment of saturated aliphatic alcohols with lead tetraacetate yielded tetrahydrofurans in up to 50% yield, accompanied by minute amounts of tetrahydropyrans. The oxidation of optically active (4*R*)-4,8-dimethylnonanol by Jeger and his coworkers[6] led to racemized tetrahydrofurans, indicating that the reaction involved either a free-radical or carbonium-ion intermediate. The ion or free-radical character of this intermediate has not as yet been conclusively established.

While the work by Jeger's[6] group indicated that the reaction proceeds through an intermediate capable of inversion, no attempt to correlate ring strain and product formation has been made previously. The systems we have chosen afford the opportunity to determine the stereochemistry of tetrahydrofuran ring formation and to study the reaction in relation to the geometry of the starting materials.

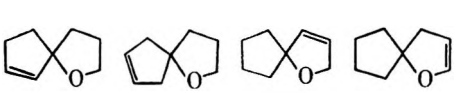
Results

The alcohols were treated with lead tetraacetate from a 1:1 to a 1:2 (ROH:LTA) molar ratio in refluxing benzene from 11 hr to 2 days. The composition of the products was determined by gas chromatography and products were identified by comparison of their ir and nmr spectra and retention times on a gas chromatograph with those of authentic samples. The results are summarized in Scheme I.

SCHEME I



The structure **13** was assigned on the basis of elemental analysis, spectroscopic evidence, and hydrogenation data. The infrared (ir) spectrum indicated unsaturation and an ether group. The nuclear magnetic resonance (nmr) spectrum of **13** showed a multiplet at τ 4.3 (2 H), a triplet at 6.25 (2 H), a multiplet at 7.7 (2 H), and a multiplet at 7.9–8.3 (6 H). Hydrogenation of **13** generated **12**. Assuming that the double bond is disubstituted, as indicated by nmr, there are only four places where a double bond can be placed



(1) (a) Part V: S. Moon and P. R. Clifford, *J. Org. Chem.*, **32**, 4017 (1967). (b) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

(2) NASA Trainee, 1964–1967.

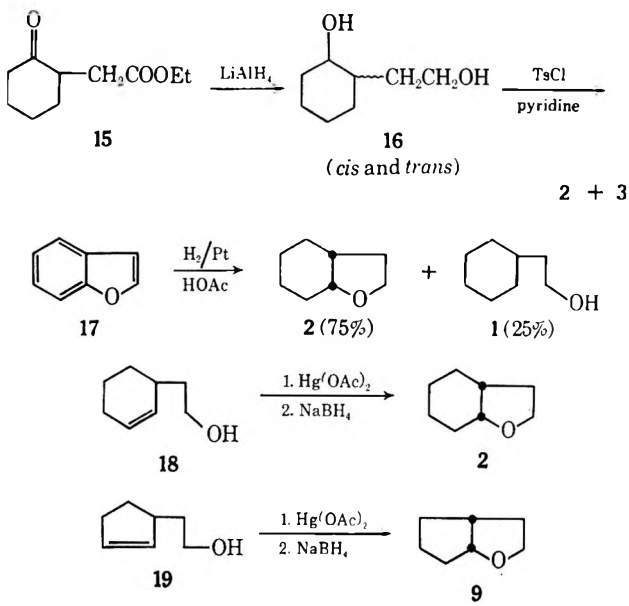
(3) G. Gainelli, M. L. Mihailovic, D. Arigoni, and O. Jeger, *Helv. Chim. Acta*, **42**, 1124 (1959).

(4) For leading references, see R. Criegee, "Oxidation in Organic Chemistry," part A, K. B. Wiberg, Ed., Academic Press, New York, N. Y., 1965, pp 278–366.

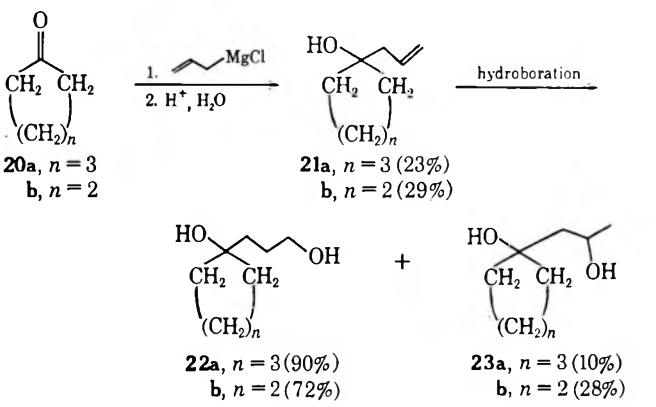
(5) V. M. Micovic, R. I. Mamuzic, D. Jeremic, and M. L. Mihailovic, *Tetrahedron*, **20**, 2279 (1964).

(6) D. Hauser, K. Schaffner, and O. Jeger, *Helv. Chim. Acta*, **47**, 1883 (1964).

SCHEME II



SCHEME III



in **12**, namely, **13**, **13a**, **13b**, and **13c**. Only **13** is consistent with the nmr spectrum.[7]

Synthesis and Stereochemistry of Products.—The synthesis of compounds **2**, **3**, and **9** is outlined in Scheme II.

Treatment of a mixture of *cis*- and *trans*-2-(2-hydroxycyclohexyl)ethanol with tosyl chloride in pyridine afforded a mixture of **2** and **3**. Hydrogenation of benzofuran yielded 75% **2** and 25% hydrogenolysis product, the alcohol **1**. The bicyclic ether **2** was therefore characterized as the *cis* isomer and **3** was accepted to be the *trans* isomer.

Treatment of 2-(2-cyclohexenyl)ethanol (**18**) with mercuric acetate yielded **2** in 100% isomeric purity. On the premise that the cyclopentenyl system would react analogously, 2-(2-cyclopentenyl)ethanol (**19**) was treated with mercuric acetate, and **9** was obtained, pure. On the basis of the stereoselectivity of the mercuric acetate oxidation of the cyclohexenyl alcohol, **9** was concluded to be the *cis* isomer. Since the mercuric acetate oxidation of **18** and **19** was shown to yield **2** and **9** in 67% and 75% yield and with 100% isomeric purity, the treatment of the olefinic alchols **18** and **19** with mercuric acetate is an excellent preparative method for the pure ethers **2** and **9**.

The synthesis of compounds **6** and **12** is outlined in Scheme III. Hydroboration of **21a** yielded two diols, **22a** and **23a**, in a 9:1 ratio. Diol **23a** was identified by its nmr as 1-(1-hydroxycyclohexyl)-2-propanol. It was independently synthesized by the mercuric acetate oxidation of **21a**. Diol **22a** was treated with tosyl chloride in pyridine, forming **6**.

Hydroboration of the alcohol **21b** yielded the diols **22b** and **23b** in a 3:1 ratio. The diols were characterized by their ir and nmr spectra. Treatment of the mixture of **22b** and **23b** with tosyl chloride in pyridine yielded **12** and unchanged **23b**.

(7) One of the referees has suggested that the nmr spectrum is also compatible with **13a**. It was pointed out that the two allylic protons *cis* to the oxygen may be shielded and hence submerged in the rest of the ring protons with values of approximately τ 8.3. However, a study of some models shows that the analogous protons of the saturated system are positioned exactly as the two protons questioned above. In the saturated system there is no observed absorption of two protons upfield as expected from such shielding. We submit, therefore, that such shielding does not exist in either case, and that the nmr spectrum is compatible only with **13**.

Discussion

The lead tetraacetate oxidation of 2-cyclohexylethanol (**1**) yielded the ethers **2** and **3** in a 3:1 ratio. The presence of both isomers indicates that the reaction is less stereospecific than the analogous mercuric acetate oxidation of 2-(2-cyclohexenyl)ethanol (**18**). The predominance of the *cis* isomer is an indication of a preference for formation of the less strained system. A variation of the alcohol to lead tetraacetate ratio did not materially change the distribution of the *cis* and *trans* isomers. (See Table I.)

TABLE I
RELATIVE YIELDS OF MAJOR PRODUCTS FROM THE LTA OXIDATION OF 2-CYCLOHEXYLETHANOL (1)

Molar ratio of alcohol to LTA	Solvent	Products, % 2	3	1	4
1:1	Benzene[a]	42	12	29	17
1:2	Benzene[b]	51	17	0	32
1:1.5	Benzene[c]	36	12	0	52

[a] Alcohol (2 g) in benzene (50 ml). [b] Alcohol (2 g) in benzene (70 ml). [c] Alcohol (10 g) in benzene (100 ml).

The lead tetraacetate oxidation of 2-cyclopentylethanol (**8**) yielded only the *cis* isomer of 2-oxabicyclo[3.3.0]octane. The lack of the *trans* isomer is probably due to the prohibitive strain of the system.

The lead tetraacetate oxidation of 3-cyclohexylpropanol produced the oxaspiran **6** in low yield. Variation of the conditions did not significantly change the amount of oxaspiran formed. Unlike the other reactions, addition of excess lead tetraacetate did not result in total consumption of starting material (see Table II). When the reaction was carried out in cyclohexane, cyclohexyl acetate was formed, which strongly suggests that a free-radical intermediate is produced in the reaction.

When cyclohexene was used as the solvent, in the presence of anhydrous calcium carbonate, 60% of the alcohol **5** was converted to the acetate **7** with just trace amounts of the ether being formed. Also found

TABLE II

RELATIVE YIELDS OF MAJOR PRODUCTS FROM THE LTA OXIDATION OF 3-CYCLOHEXYLPROPANOL (5)

Molar ratio of alcohol to LTA	Solvent	Products, % OAc	6	5	7
1:1	Cyclohexane[a]	5	14	41	40
1:1.5	Cyclohexane[a]	5	11	25	59
1:1.5	Cyclohexane[b]	5	11	37	46
1:1.5	Cyclohexane[c]	7	17	19	58
1:1	Benzene[a]		10	52	38
1:2	Benzene[a]		13	30	43

[a] Run in 25 ml of solvent. [b] Run in 200 ml of solvent. [c] Solvent (25 ml) with anhydrous calcium carbonate (2.11 g). [d] Yields were determined by integration of vapor phase chromatographic curves.

were 2-cyclohexen-1-ol, 2-cyclohexen-1-one, and 2-cyclohexen-1-yl acetate in a 1:1:2 ratio. The lead tetraacetate oxidation of neat cyclohexene yielded[8] 1.4% 2-cyclohexan-1-ol, 6.7% 2-cyclohexan-1-one, 80.4% 2-cyclohexen-1-yl acetate, 7.3% 1,2-cyclohexane diacetates, and 4% unknown mixture.

The observation that 60% of the alcohol was consumed when 1 g of **5** was treated with 4.5 g of lead tetraacetate in 200 ml of cyclohexene affords valuable information as to the relative reactivity of the double bond and the alcohol group. The 80.4% yield of 2-cyclohexen-1-yl acetate from the lead tetraacetate oxidation of neat cyclohexene demonstrates that this is a convenient procedure for the preparation of 2-cyclohexen-1-yl acetate from cyclohexene.

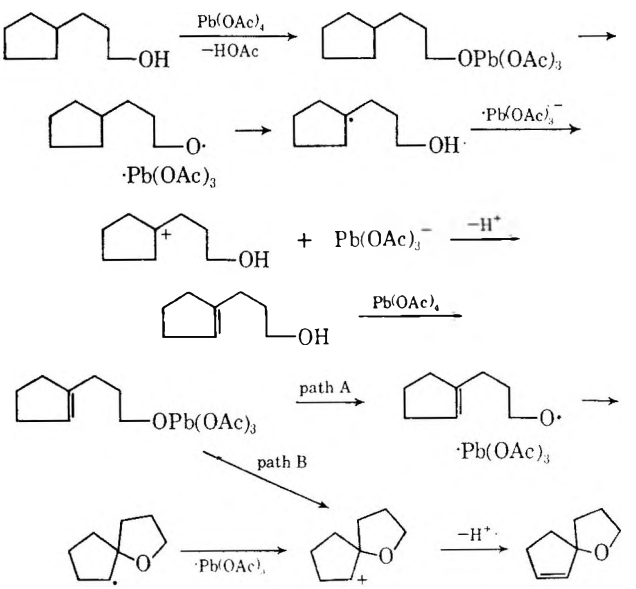
The lead tetraacetate oxidation of 3-cyclopentylpropanol (**11**) yielded **12** and **13**. The presence of **13** suggests that the process of tetrahydrofuran ring formation not only proceeds with inversion[6] and isomerization,[1] but also with elimination. The presence of **13** indicates that an intermediate with substantial carbonium-ion character may exist (see Scheme IV).

Heusler[9] was the first to suggest the oxidation of the carbon free radical to the carbonium ion as a plausible route to ring formation. Heusler proposed the lead tetraacetate free radical (generated from alcohol–lead bond homolysis) as the oxidizing agent for the conversion of the carbon radical into the carbonium ion. Recent work by Heiba,[10] however, suggests that lead tetraacetate itself is capable of oxidizing the carbon free radical to the carbonium ion.

Experimental Section[11]

Reaction of 2-Cyclohexylethanol with LTA.—A mixture of 10 g of 2-cyclohexylethanol and 60 g of LTA was refluxed in 100 ml of benzene for 19 hr. The mixture was cooled to room temperature and filtered. The precipitate was washed with benzene and the washings were added to the filtrate. The combined organic layer was washed with water, 10% sodium bicarbonate solution, and water, dried ($MgSO_4$), concentrated, and distilled, yielding 6.19 g (62% yield), bp 39–62° (1.5 mm). The fractions were analyzed by gas chromatography [ethylene glycol adipate (EGA) (programmed from 50 to 150°)] and showed five components, three of which were identified[12] as *cis*-7-oxabicyclo[4.3.0]nonane (**2**, 21%), *trans*-7-oxabicyclo[4.3.0]octane (**3**, 7%), and 2-cyclohexylethyl acetate (**4**, 30%). No starting alcohol was found in the reaction mixture.

SCHEME IV



Reaction of 3-Cyclohexylpropanol with LTA. A. In Benzene.—3-Cyclohexylpropanol (5 g) was treated with 20 g of LTA in 100 ml of refluxing benzene for 2 days. The mixture was cooled to room temperature and treated with 10 ml of ethylene glycol to remove any unchanged LTA. The ethylene glycol was removed and the benzene layer was washed with 10% sodium carbonate solution and water, dried ($MgSO_4$), concentrated, and distilled through a short-path distillation column, yielding 2.99 g (60% yield), bp 55° (40 mm) to 85° (0.7 mm). Gas chromatography showed three major products which were identified[12] as 1-oxaspiro[4.5]decane (**6**, 8%), 3-cyclohexylpropanol (**5**, 18%), and 3-cyclohexylpropyl acetate (**7**, 34%).

B. In Cyclohexane.—3-Cyclohexylpropanol (1 g) was treated with 4.7 g of LTA in 200 ml of refluxing cyclohexane for 18 hr. The product was isolated as above. Gas chromatography of the crude product mixture indicated four components which were identified[13] as cyclohexyl acetate (5%), **6** (11%), **5** (37%), and **7** (46%).

C. In Cyclohexene.—3-Cyclohexylpropanol (1 g) was treated with 4.7 g of LTA and 1.0 g of calcium carbonate in 200 ml of refluxing cyclohexene for 18 hr. The products were isolated as described above. Gas chromatography indicated that the alcohol to acetate ratio was almost 1:2 with just trace amounts of the ether being formed. Integration of peak areas indicated that the alcohol had been at least 60% consumed during the reaction. Gas chromatography also indicated the presence of three additional peaks which were identified[12] as 2-cyclohexen-1-ol, 2-cyclohexen-2-one, and 2-cyclohexen-1-yl acetate in a 1:1:2 ratio. The oxidation products of 3-cyclohexylpropanol and cyclohexene were found in about a 1:1 ratio.

Reaction of 2-Cyclopentylethanol (8) with LTA.—Cyclopentylethanol (**8**, 1 g) was treated with 6 g of LTA in 25 ml of refluxing benzene for 11 hr. The product was isolated as above.

(8) Based on lead tetraacetate.

(9) K. Heusler and J. Kalvoda, *Angew. Chem. Intern. Ed. Engl.*, 525 (1964).

(10) E. I. Heiba, R. M. Dessau, and W. J. Koehl, Jr., *J. Amer. Chem. Soc.*, **90**, 2706 (1968).

(11) For gas chromatography analysis, an F & M Model 720 thermal conductivity gas chromatograph was used. Ir spectra were recorded with a Perkin-Elmer Infracord, Model 337, and a Varian A-60 spectrometer was used to record the nmr spectra. The chemical shifts are shown in τ values from tetramethylsilane (TMS).

(12) The products were isolated by gas chromatography and identified by comparison of their ir spectra, nmr spectra, and retention times on gas chromatography with those of authentic samples.

(13) Product ratios were obtained by integration of peak areas. The products were identified by comparison of their ir spectra with those of authentic samples.

The product was distilled through a short-path distillation column yielding 0.56 g (56%), bp 40° (65 mm) to 75° (6 mm). Gas chromatography of the distillate showed two products which were identified[12] as 2-oxabicyclo[3.3.0]octane (**9**, 22%) and 2-cyclopentylethyl acetate (**10**, 34%).

Reaction of 3-Cyclopentylpropanol (11) with LTA.—3-Cyclopentylpropanol (10 g) was treated with 80 g of LTA in 250 ml of refluxing benzene for 17 hr. The product was isolated as above. The product was distilled through a short-path distillation column and collected, yielding 6.25 g (63% yield), bp 50° (15 mm) to 100° (0.4 mm). Gas chromatography of the product mixture showed three major peaks which were identified[11] as 1-oxaspiro-[4.4]nonane (**12**, 4%), 1-oxaspiro[4.4]non-6-ene (**13**, 6%), and 3-cyclopentylpropyl acetate (**14**, 39%).

Anal. Calcd for $C_8H_{12}O_1$ (**13**): C, 77.37; H, 9.85. Found: C, 77.07; H, 9.86.

13 (50 mg) was isolated by gas chromatography and hydrogenated at room temperature and atmospheric pressure in 10 ml of anhydrous ethanol in the presence of 0.1 g of platinum oxide. After 15 hr, 60% of **13** had been converted into **12** and a small quantity of higher boiling material.

3-Cyclopentylpropanol.—β-Cyclopentylpropionic acid (20 g) was treated with 4 g of lithium aluminum hydride in 100 ml of anhydrous ether, yielding 7.25 g (41%) of 3-cyclopentylpropanol, bp 63° (1.0 mm).

Reaction of LTA in Neat Cyclohexene.—LTA (10 g) was refluxed in 100 ml of cyclohexene for 2 days. The reaction mixture was concentrated by distillation of excess cyclohexene. Gas chromatography (silicone rubber) showed five products which were identified[11] as 2-cyclohexen-1-ol (1.4%), 2-cyclohexen-1-yl acetate (80%), 2-cyclohexen-1-one (7%), an unknown mixture (4%), and diacetates (7%).[14]

1-Cyclohexen-1-ylmorpholine.—Cyclohexanone (98 g, 1 mol) and morpholine (87 g, 1 mol) were refluxed in 220 ml of benzene for 18 hr. Water (25 ml) was collected in a Dean–Stark trap. The benzene was removed by distillation, and the residue was distilled, yielding 125 g (75%) of 1-cyclohexen-1-ylmorpholine, bp 78–81° (0.3–0.15 mm).

Ethyl (2-Oxocyclohexyl)acetate (15).—1-Cyclohexen-1-ylmorpholine (40 g) and 55 g of ethyl bromoacetate were stirred overnight in 160 ml of benzene at 50°. The mixture was cooled to room temperature and concentrated under reduced pressure. The crude product was diluted with 100 ml of methanol and treated with 50 ml of water at refluxing temperature for 15 hr. The product was condensed *in vacuo*, treated with 100 ml of 1.0 *M* hydrochloric acid for 10 min, and extracted with ether. The ethereal extract was washed with water, 10% sodium carbonate, and water, dried ($MgSO_4$), concentrated, and distilled, giving 3 g of the acetoxy ketone **15**: bp 73–74° (0.34–0.40 mm) [lit.[15] bp 131–134° (13 mm)]; ir (CS_2) 1710 (C=O), 1740 cm^{-1} (ester C=O). Gas chromatography (silicone rubber at 200°) showed the product to be homogeneous.

2-(2-Hydroxycyclohexyl)ethanol (16).—The acetate **15** was treated with 5 g of lithium aluminum hydride in 25 ml of refluxing ether for 22 hr. The mixture was cooled to room temperature and treated with 5 ml of water, 5 ml of 10% sodium hydroxide, and 15 ml of ether. The product was filtered and the precipitate was washed with ether. The washings were added to the filtrate and the ethereal layer was dried ($MgSO_4$) and concentrated. Gas chromatography (silicone rubber) of the crude product showed only one peak. The ir spectrum (CS_2) showed a strong band for associated hydroxyl group but little free absorption. The product is assumed to be a mixture of the *cis* and *trans* isomers.

***cis*- and *trans*-7-Oxabicyclo[4.3.0]nonanes (2 and 3).**—Compound **16** (1 g, crude mixture) was treated with 0.7 g of tosyl chloride in 15 ml of pyridine for 24 hr at 35–40°. The product was poured onto cracked ice and extracted with ether. The ethereal layer was washed with 10% sodium carbonate, water, 3 *M* hydrochloric acid, and water, dried ($MgSO_4$), and concentrated. Gas chromatography of the crude product (EGA) showed two peaks.

The first peak was identified as **2** (29%), and the second peak was identified as **3** (71%). The ir spectrum (CS_2) of **2** showed 1180, 1155, 1120, 1080, 1045, 1020, 985, 930, 880, 200 cm^{-1}; that (CS_2) of **3** showed 1190, 1150, 1142, 1070, 985, 935, 860 cm^{-1}. Cantor and Tarbell[16] give 1184, 1160, 1142, 1090 cm^{-1} as characteristic absorption peaks for **3**.

***cis*-7-Oxabicyclo[4.3.0]nonane (2).**—Benzofuran (**17**, 0.5 g) was hydrogenated at room temperature and atmospheric pressure in 50 ml of glacial acetic acid in the presence of 0.11 g of platinum oxide. After 4.5 hr, 575 ml of hydrogen[17] was taken up and the reaction was stopped.

The catalyst was removed by filtration and the product was diluted with water and extracted with ether. The ethereal extract was washed with water, 10% sodium carbonate solution, and water, dried ($MgSO_4$), and concentrated. Gas chromatography (silicone rubber and EGA) showed that the benzofuran was totally consumed in the reaction. Two products were found which were identified[13] as **2** (75%) and **1** (25%). None of the *trans* isomer **3** was found.

***cis*-7-Oxabicyclo[4.3.0]nonane (2).**—Mercuric acetate (12.8 g) was dissolved in 40 ml of water. Tetrahydrofuran (40 ml) was added, producing a yellow suspension. 2-(β-Cyclohexenyl)-ethanol was added rapidly (no heat developing), and the yellow color cleared within a minute. The solution was stirred for 45 min at room temperature after which time the solution gave a negative test for mercuric ion.[18] The solution was treated with 40 ml of 3 *M* sodium hydroxide, followed by 2 g of sodium borohydride in 40 ml of 3 *M* sodium hydroxide. The reaction, which was strongly exothermic, produced a black precipitate immediately upon the introduction of the sodium borohydride solution, which upon stirring settled into a silvery mercury lake. The water layer was saturated with sodium chloride and the product was extracted with ether. The ethereal extract was dried ($MgSO_4$), concentrated, and distilled, giving 3.36 g (67%) of the bicyclic ether **2**, bp 71° (28 mm) [lit.[16] bp 66–68° (15 mm)].

***cis*-2-Oxabicyclo[3.3.0]octane (9).**—2-(2-Cyclopentenyl)ethanol (**19**, 5.6 g) was treated with 16 g of mercuric acetate in 100 ml of 50% THF in water for 0.5 hr. The product was treated with 50 ml of 3 *M* sodium hydroxide and demercurated with 2.5 g of sodium borohydride in 50 ml of 3 *M* sodium hydroxide. The water layer was saturated with sodium chloride and the product was dried ($MgSO_4$), concentrated, and distilled, giving 4.2 g (75%) of the bicyclic ether **9**, bp 49–50° (28 mm).

1-Allylcyclohexanol (21a).—Allyl chloride (38 g) was slowly added to 12 g of magnesium in 100 ml of dry ether. The reaction flask was kept at 0° by means of an ice–water bath and the addition of the allyl chloride was made at the rate of 1 drop/10–12 sec. The addition took 7 hr. Cyclohexanone (49 g) in 50 ml of ether was added slowly to the Grignard reagent with vigorous stirring. The reaction mixture was allowed to stir overnight at room temperature. Water (20 ml) was added to decompose unchanged the Grignard reagent. Saturated ammonium chloride solution (23 ml) was added to the reaction mixture. The mixture was stirred at room temperature for 15 min. A white solid formed, and the ethereal layer was decanted. The ethereal extract was dried ($MgSO_4$), concentrated, and distilled, giving 32 g (23%) of the unsaturated alcohol **21a**, bp 58.0–58.5° (1.4 mm). Gas chromatography (silicone rubber at 125°) showed the product to be homogeneous.

3-(1-Hydroxycyclohexyl)propanol (22a).—1-Allylcyclohexanol (**21a**, 7 g) was dissolved in 50 ml of THF (dried over sodium). Sodium borohydride (1 g) was added, and the mixture was treated with 5 g of 47% boron trifluoride etherate at room temperature. After addition was complete the solution was stirred at room temperature for 1 hr. Water (5 ml) was added to decompose excess diborane. The reaction mixture was treated with 30 ml of 3 *M* sodium hydroxide, followed by 30 ml of 30% hydrogen peroxide. The mixture was stirred for 1 hr at room temperature and extracted with ether. The ethereal extract was washed with 20% sodium hydroxide and water, dried ($MgSO_4$), concentrated, and distilled, giving 3.65 g (51%) of a very viscous liquid, bp 100–115° (0.2 mm). Gas chromatography (silicone rubber at 140°) showed two products. The first product (10% of the mixture) was identified as 1-(1-hydroxycyclohexyl)-2-

(14) Absolute yields were determined by introduction of 0.1863 g of ethyl cyclohexylcarboxylate into the product mixture for use as an internal standard, and based on LTA.

(15) A. Segre, R. Viterbo, and G. Parisi, *J. Amer. Chem. Soc.*, **79**, 3503 (1957).

(16) S. E. Cantor and D. S. Tarbell, *ibid.*, **86**, 2902 (1964).

(17) It was calculated that 399 ml of hydrogen would be necessary to hydrogenate the sample totally, and 23 ml would be necessary to reduce the platinum oxide.

(18) A few drops of the reaction mixture was added to a 3 *M* sodium hydroxide solution. A yellow color indicates that the reaction is incomplete.

propanol (**23a**). The second product was identified as 3-(1-hydroxycyclohexyl)propanol (**22a**): ir (CS_2) strong hydrogen bonding and little free OH absorption; nmr (CCl_4) τ 6.2 (t, 2), 5.0 (broad s, 2), 8.5 (m, 14). After 4 days, large crystals developed in the ethereal solution. They were found to be **22a**, mp 66–68° (lit.[19] mp 60°).

Anal. Calcd for $C_9H_{18}O_2$ (**23a**): C, 68.3; H, 11.4. Found: C, 68.0; H, 11.6.

1-Oxaspiro[4.5]decane (6).—The diol **22a** (1.0 g) was treated with 2 g of tosyl chloride in 10 ml of pyridine for 18 hr at 40–50°. The product was poured onto cracked ice and extracted with ether. The ethereal extract was washed with 6 *M* hydrochloric acid, water, 10% sodium bicarbonate solution, and water, dried ($MgSO_4$), and concentrated. The crude mixture (0.5 g) was shown to be homogeneous on gas chromatography (silicone rubber programmed from 50 to 100°): ir (CS_2) 1145, 1120, 1085, 1050, 925, 905 cm^{-1}. 1-Oxaspiro[4.5]decane (6) was previously prepared by the treatment of 3-(1-hydroxycyclohexyl)propyl *n*-pentyl ether with tosyl chloride in pyridine.[20]

1-(1-Hydroxycyclohexyl)-2-propanol (23a).—1-Allylcyclohexanol (1.4 g) was treated with 3.12 g of mercuric acetate in 20 ml of THF–water. The yellow suspension disappeared in 10 sec and the reaction was stirred at room temperature for 15 min. Sodium hydroxide (3 *M*, 10 ml) was added, followed by 0.5 g of sodium borohydride in 10 ml of 3 *M* sodium hydroxide. The product was extracted with ether (the water layer being saturated with sodium chloride). The ethereal extract was washed with water, dried ($MgSO_4$), and concentrated. Gas chromatography of the crude product showed one major peak: ir (CS_2) 3400 (strong hydrogen-bonded OH absorption), 2960, 2925, 2850 cm^{-1}; nmr (CCl_4) τ 4.3 (s, 2), 6.0 (m, 1), 8.5 (m, 10), 8.8 (d, 3).

1-Allylcyclopentanol (21b).—The reaction of allylmagnesium chloride (23 g of allyl chloride and 15 g of magnesium turnings) and cyclopentanone (25 g) gave 10.9 g (29%) of the alcohol **21b**, bp 71–73° (20 mm) [lit.[21] bp 63° (10 mm)].

3-(1-Hydroxycyclopentyl)propanol (22b).—1-Allylcyclopentanol (5.3 g) was treated with 1.5 g of sodium borohydride and 5.0 g of 47% boron trifluoride etherate in 200 ml of THF (dried over sodium) under a nitrogen atmosphere. The mixture was stirred at room temperature overnight. Unchanged diborane was destroyed with 10 ml of water; the mixture was treated with 30 ml of 3 *M* sodium hydroxide, followed by addition of 30% hydrogen peroxide. The product was extracted with ether. The ethereal extract was washed with 6 *M* sodium hydroxide and water, dried ($MgSO_4$), concentrated, and distilled, yielding 1.25 g (20%) of a viscous liquid, bp 122–130° (5 mm). Gas chromatography (silicone rubber programmed from 50 to 180°) showed two peaks. The first peak (28%) on the basis of its retention time, ir, and the analogous reaction in the preparation of **22a** was tentatively assigned as the diol **23b**. The second peak (72%) was assigned as the diol **22b**, mainly because of the nmr signal at τ 6.4 (triplet corresponding to the methylene hydrogens α to the primary hydroxyl group).

1-Oxaspiro[4.4]nonane (12).—A mixture of **22b** and **23b** (0.8 g) was treated with 2.0 g of tosyl chloride in pyridine for 18 hr at 50°. The product was poured onto cracked ice and extracted with ether. The ethereal extract was washed with water, 6 *M* hydrochloric acid, water, sodium bicarbonate solution, and water, dried ($MgSO_4$), and concentrated. Gas chromatography (diethylene glycol succinate) of the crude product showed only one major product: ir (CS_2) 1165, 1100, 1050, 970, 945, 920, 900 cm^{-1}; nmr (CCl_4) τ 6.3 (t, 2), 8.1–8.5 (m, 12).

Anal. Calcd for $C_8H_{14}O$: C, 76.2; H, 11.1. Found: C, 76.2; H, 11.2.

Registry No.—Lead tetraacetate, 546-67-8; **1**, 4442-79-9; **5**, 1124-63-6; **8**, 766-00-7; **9**, 18320-80-4; **11**, 767-05-5; **12**, 176-10-3; **21a**, 1123-34-8; **23a**, 18321-43-2; 1-cyclohexen-1-ylmorpholine, 670-80-4.

(19) J. Colonge, R. Falcotet, and R. Gaumont, *Bull. Soc. Chim. Fr.*, 211 (1958).

(20) W. B. Renfrow, D. Oakes, C. Lauer, and T. A. Walter, *J. Org. Chem.*, **26**, 935 (1961).

(21) G. Crane, C. E. Boord, and A. L. Henne, *J. Amer. Chem. Soc.*, **67**, 1237 (1945).

The Synthesis of Imidate Hydrochlorides by Reaction of Ethyl Chloroformate with Amides and Thionamides

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The scope of the reaction of ethyl chloroformate with amides as a preparation of ethyl imidate hydrochlorides has been investigated. The imidate salts have been prepared successfully in good yields from aliphatic amides containing from one to eight carbon atoms, both straight and branched chain. The N-methyl and N-ethyl derivatives of these aliphatic amides reacted in the same way to give N-substituted imidate hydrochlorides. Attempts to employ the reaction with aromatic amides or N-substituted amides in which the substituent is larger than ethyl were unsuccesful. In certain cases a side reaction occurred. Thus the hemihydrochlorides of acetamide and N-methylcaprylamide were obtained as a second product from acetamide and N-methylcaprylamide, respectively. N-Methylacetamide gave its hemihydrochloride as the only product of the reaction. Thionamides have been found to react with ethyl chloroformate in a similar way, giving the ethyl imidate hydrochloride and carbonyl sulfide as products. The hydrochloride salts of ethyl acetimidate, ethyl propionimidate, ethyl isobutyrimidate, ethyl benzimidate, and ethyl N-phenylacetimidate have been prepared from thioacetamide, thiopropionamide, thioisobutyramide, thiobenzamide, and thioacetanilide, respectively. The reactivity of thionamides is considerably greater than that of the analogous oxygen compounds. The rate curve for the reaction, using propionamide, shows it to be autocatalytic. A possible mechanism for the reaction is suggested.

Although imidates (imino ethers, imido esters) and their salts have been known for nearly a century,[2] and are useful intermediates for the synthesis of a variety of compounds,[3] there has been only one general direct method for their preparation, namely, the method of Pinner,[4] which involves synthesis of the imidate hydrochloride from the appropriate nitrile and alcohol with anhydrous hydrogen chloride (eq 1). The salt

$$RCN + R'OH + HCl \longrightarrow RC(=NH_2Cl)OR' \quad (1)$$

(1) National Science Foundation Undergraduate Research Participant, Grant No. GY-83.

(2) A. Pinner and F. Klein, *Ber.*, **10**, 1889 (1877).

(3) R. Roger and D. G. Neilson, *Chem. Rev.*, **61**, 179 (1961).

(4) A. Pinner, "Die Imidoaether and ihre Derivative," Oppenheim, Berlin, 1892, pp 1–85.

is then easily converted into the free imidate by treatment with potassium carbonate solution. Several other methods of synthesis of specific imidates have been reported, and these have been reviewed by Roger and Nielson.[3]

The Pinner synthesis suffers from some limitations. Long periods of time are often required to obtain the product, and yields are frequently poor. Its most serious limitation lies in the fact that it is not applicable to the preparation of N-substituted imidates. Indeed, very few compounds of this type have been reported, especially where the N substituent is alkyl.

In 1956, Hechelhammer[5] announced the preparation of ethyl formimidate hydrochloride, ethyl acetimidate hydrochloride, and O-ethylcaprolactim hydrochloride by the reaction of ethyl chloroformate with formamide, acetamide, and ϵ-caprolactam, respectively (eq 2). He suggested general applicability of the reaction, although little experimental detail was given.

$$RCONH_2 + EtOCOCl \longrightarrow RC(=NH_2Cl)OEt + CO_2 \quad (2)$$

This reaction was of interest to us, since it represented potentially another general method of preparation of imidate hydrochlorides, which might prove superior to the Pinner method in terms of convenience and yield. Of particular interest was the applicability of the reaction to the preparation of N-substituted imidate hydrochlorides, since no other direct method of synthesis of these compounds is known.

Accordingly, an investigation was undertaken to determine the extent to which this reaction has general applicability as a useful method of preparation of imidate hydrochlorides, and to learn something of the mechanism by which the reaction proceeds.

Results and Discussion

Reaction of Unsubstituted Amides.—Reactions of ethyl chloroformate with 13 different simple amides were attempted. Ten of these yielded the expected imidate hydrochlorides in reasonably good yields, by mixing the reactants without solvent at temperatures below 50°. The products (**1**–**10**) are listed in Table I together with their melting points and percentage yields. Each of these compounds was also prepared by the method of Pinner,[4] and the melting points and percentage yields by that method are given in Table I for comparison. For those imidate hydrochlorides which have been previously reported by the Pinner synthesis, the literature melting points are also included in the table.

Acetamide showed unique behavior, in that, in addition to ethyl acetimidate hydrochloride (**1**), a second product was formed—acetamide hemihydrochloride (**11**). The two compounds, which were

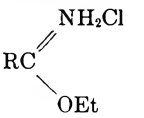
$(CH_3CONH_2)_2HCl$
11

formed in a ratio by weight of ~2:3 **1**:**11**, were easily separable, since **1** is readily soluble in chloroform and **11** is not. When the reaction was run in dioxane or in tetrahydrofuran as solvent, the only product formed was **11**, in essentially 100% yield.

(5) Hechelhammer, German Patent 948,973 (Sept 13, 1956).

TABLE I

IMIDATE HYDROCHLORIDES OF TYPE



Compd no.	R	$RCONH_2$ + EtOCOCl: Mp, °C[a]	Yield, %	RCN + EtOH + HCl: Mp, °C[a]	Yield, %	Lit. mp, °C
1	CH_3	113	32	112–113	54	98–100[b]
2	CH_3CH_2	92–93	65	93–94	36	90–92[b]
3	$CH_3(CH_2)_2$	64–65	83	56–58	48	64–65[b]
4	$(CH_3)_2CH$	89	68	83	85	76[c]
5	$CH_3(CH_2)_3$	Liq[d]	72	Liq[d]	62	
6	$(CH_3)_2CHCH_2$	88–89	75	89–90	47	90[c]
7	$CH_3(CH_2)_4$	Liq[d]	75	Liq[d]	63	Liq[e]
8	$(CH_3)_2CH(CH_2)_2$	Liq[d]	80	Liq[d]	67	Liq[e]
9	$CH_3(CH_2)_5$	Liq[d]	75	Liq[d]	45	67[f]
10	$CH_3(CH_2)_6$	Liq[d]	88	34	55	

[a] Really decomposition temperature; melting is accompanied by gas evolution. [b] See ref 4. [c] N. S. Drosdov and A. F. Bekhli, *J. Gen. Chem. USSR*, **14**, 280 (1944). [d] A viscous syrup at room temperature, which crystallized on storing at 0°, but remelted on return to room temperature. [e] A. Pinner, *Ber.*, **17**, 171 (1884). [f] A. Pinner, *ibid.*, **28**, 473 (1895).

The three amides which were used unsuccessfully in the reaction were benzamide, *p*-nitrobenzamide, and α-phenylacetamide. None of those showed any signs of reacting with ethyl chloroformate, even though a variety of reaction conditions were employed, including temperatures up to 80° for periods up to 60 hr. It should be noted that excessive temperatures must be avoided in this reaction since it is well known that imidate hydrochlorides are thermally unstable.[3,4]

One may cautiously conclude, on the basis of the small sample of amides used, that the reaction constitutes a general method for the preparation of unsubstituted imidate hydrochlorides from aliphatic amides (generally in higher yields than by the Pinner method), but is unsatisfactory for at least some aromatic ones.

Reaction of N-Substituted Amides.—Thirteen ethyl N-alkyl imidate hydrochlorides were prepared from N-alkylamides and ethyl chloroformate. These compounds (**12**–**24**) are listed in Table II. Reaction conditions were essentially the same as those employed for the unsubstituted amides.

N-Methylcaprylamide yielded two products, in approximately equal amounts by weight—the expected ethyl N-methylcaprylimidate hydrochloride (**23**) and another product identified as N-methylcaprylamide hemihydrochloride (**25**).

When the reaction was attempted with N-methylacetamide, no imidate hydrochloride was produced, but rather N-methylacetamide hemihydrochloride (**26**) was obtained in nearly quantitative yield.

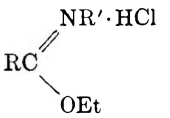
$(CH_3(CH_2)_6CONHCH_3)_2 \cdot HCl$ **25** $(CH_3CONHCH_3)_2 \cdot HCl$ **26**

Attempts to carry out the reaction on two additional N-substituted amides were unsuccessful. Neither N-*n*-butylacetamide nor acetanilide (N-phenylacetamide) showed any signs of reaction when mixed with ethyl chloroformate at temperature up to 60° for periods up to 12 hr.

It appears that the reaction is generally applicable

TABLE II

IMIDATE HYDROCHLORIDES OF TYPE



Compd no.	R	R′	Yield, %	Analytical data[a] Calcd Neut equiv	Calcd % N	Calcd % Cl	Found Neut equiv	Found % N	Found % Cl
12	H	CH_3	88	123.5	11.34	28.69	122.3	11.20	28.50
13	H	CH_3CH_2	92	137.6	10.18	25.76	136.6	10.08	25.60
14	CH_3	CH_3CH_2	78	151.6	9.24	23.38	151.2	9.22	23.42
15	CH_3CH_2	CH_3	67	151.6	9.24	23.38	150.2	9.33	23.22
16	CH_3CH_2	CH_3CH_2	75	165.7	8.46	21.40	164.2	8.56	21.06
17	$CH_3(CH_2)_2$	CH_3	80	165.7	8.46	21.40	164.5	8.50	21.25
18	$CH_3(CH_2)_2$	CH_3CH_2	76	179.7	7.80	19.73	178.2	7.68	19.40
19	$CH_3(CH_2)_3$	CH_3CH_2	69	193.7	7.23	18.30	192.2	7.32	18.00
20	$CH_3(CH_2)_4$	CH_3	73	193.7	7.23	18.30	192.8	7.21	18.21
21	$CH_3(CH_2)_4$	CH_3CH_2	77	207.8	6.74	17.06	206.4	6.80	17.10
22	$CH_3(CH_2)_5$	CH_3CH_2	84	221.8	6.32	15.98	220.2	6.30	15.91
23	$CH_3(CH_2)_6$	CH_3	44	221.8	6.32	15.98	221.0	6.30	16.00
24	$CH_3(CH_2)_6$	CH_3CH_2	74	235.8	5.96	15.03	234.5	6.05	14.85

[a] Additional evidence for identification of the compounds was obtained by hydrolysis of each compound to the corresponding amine hydrochloride and ester, and comparison of their infrared spectra with those of authentic samples; see Experimental Section.

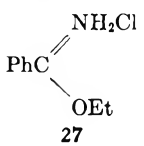
to the preparation of N-methyl- and N-ethylalkylimidate hydrochlorides. Whether it can be extended to N-substituted aryl compounds, or compounds in which the N substituent is larger than ethyl, requires further investigation.

Reaction of Thionamides.—It was found that thionamides undergo a reaction with ethyl chloroformate similar to that of the amides, the products being the ethyl imidate hydrochloride and carbonyl sulfide (eq 3). Thus the hydrochloride salts of ethyl acet-

$$RCSNH_2 + EtOCOCl \longrightarrow RC(NH_2Cl)OEt + COS \quad (3)$$

imidate (**1**), ethyl propionimidate (**2**), and ethyl isobutyrimidate (**4**) were prepared by the reaction of ethyl chloroformate with thioacetamide, thiopropionamide, and thioisobutyramide, respectively.

In addition, ethyl benzimidate hydrochloride (**27**) and ethyl N-phenylacetimidate hydrochloride (**28**) were prepared successfully from thiobenzamide and thioacetanilide, respectively, by this reaction. These



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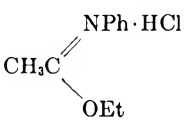


28

latter two preparations are of particular interest, since they represent successful reactions of thionamides, the oxygen analogs of which did not react with ethylchloroformate, as reported above.

The reactions of the thionamides proceeded at a considerably faster rate than those of the corresponding amides. For example, acetamide required 1.5 hr at 45° for complete reaction, whereas the reaction of thioacetamide was complete in 5 min at a temperature of 30°. (Furthermore, no side reaction occurred in the latter case as it did in the former.)

One may conclude that the use of thionamides in this reaction is probably a more satisfactory and more general method of preparing imidate hydrochlorides than is the use of amides. A serious limitation, of course, is the lack of availability of thionamides.

Kinetic Studies.—Throughout this investigation it was observed that reaction between ethyl chloroformate and an amide or thionamide did not begin immediately upon mixing. A short induction period was required, after which the reaction proceeded slowly at first and gradually increased in rate. In an effort to explain this phenomenon a study of the reaction rate was undertaken.

Propionamide was selected as the model amide for the rate study, since it is obtainable in high purity, does not undergo any side reactions (as does, for example, acetamide), and reacts at a rate convenient for study.

The reaction between propionamide and ethyl chloroformate was carried out at 30° and the progress of the reaction was followed by absorption of the liberated CO_2, the amount of which was determined at 15-min intervals by weighing the absorption tube. A plot of millimoles CO_2 liberated *vs.* time gave an S-shaped curve typical of autocatalytic reactions. The curve obtained from a typical run is shown in Figure 1. In order to establish that the reaction is indeed autocatalytic, it was repeated under identical conditions, but with small amounts of the product, ethyl propionimidate hydrochloride, added. The results, two of which are also shown in Figure 1, confirmed autocatalysis.

In view of the fact that the reaction is heterogenous, as well as autocatalytic, a detailed study of the kinetics would be extremely complex.

A possible mechanism which is consistent with the observations is shown in Scheme I. It involves nucleophilic attack of the oxygen of the amide (or of the sulfur of the thionamide) on the carbonyl carbon of the ethyl chloroformate, with elimination of the chloride ion. This is followed by nucleophilic attack of the ethoxy oxygen with elimination of carbon dioxide (or carbonyl sulfide).

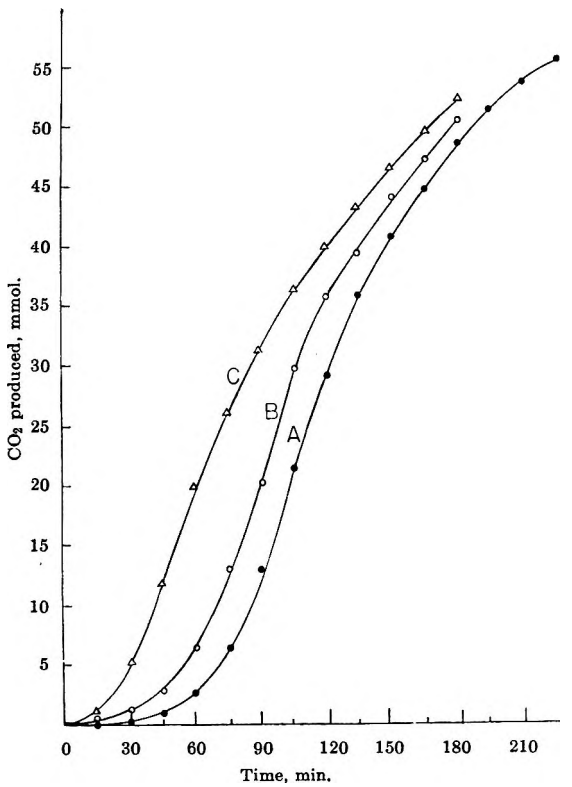
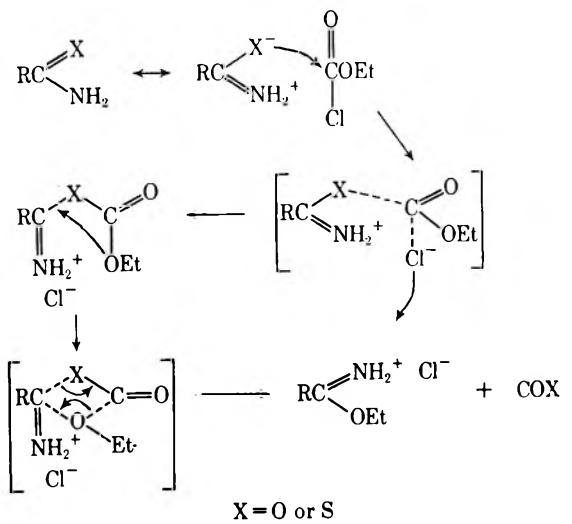


Figure 1.—Production of CO_2 from 105 mmol of propionamide + 105 mmol of ethyl chloroformate at 30°: A, no catalyst; B, 1 mmol of ethyl propionimidate hydrochloride added; C, 10 mmol of ethyl propionimidate hydrochloride added.

SCHEME I



While this postulated mechanism does not explain the autocatalysis of the reaction, it is consistent with the products formed and with the higher reactivity of the thionamides because of the greater nucleophilicity of sulfur than of oxygen.

Experimental Section

Melting points were taken in an open capillary and are corrected. Infrared spectra were recorded on a Perkin-Elmer Model 137B infrared spectrophotometer. Neutral equivalents were determined by potentiometric titration with standard 0.1 *N* NaOH solution using a Beckman zeromatic pH meter. Chloride analyses were by the modification of Caldwell and Moyer[6] of the Volhard method. Analyses for nitrogen were by a modification of the Kjeldahl method.[7]

Materials.—The ethyl chloroformate was obtained from Eastman Organic Chemicals. All nitriles, amides, and thionamides used as starting materials were obtained commercially, except the following, which were synthesized as indicated. Caproamide, isocaproamide, heptamide, and caprylamide were prepared from the acyl chlorides and ammonia by the method Philbrook;[8] α-phenylacetamide was prepared by hydrolysis of the nitrile according to the method of Wenner.[9] The N-methyl derivatives of butyramide, caproamide, and caprylamide, and the N-ethyl derivatives of propionamide, butyramide, valeramide, caproamide, heptamide, and caprylamide were obtained from the acyl chloride and the amine by the method of D'Alelio and Reid.[10] Thiopropionamide was prepared by the method of Pesina,[11] and thioisobutyramide by the method of Taylor and Zoltewicz.[12]

Synthesis of Unsubstituted Imidate Hydrochlorides (1–10).—The apparatus consisted of a 250-ml, three-necked, round-bottomed flask suspended in a water bath. The flask was fitted with a well-sealed stirrer, a dropping funnel, and a water-cooled condenser. A connecting tube at the top of the condenser was extended into a saturated solution of $Ba(OH)_2$, so that the evolution of CO_2 could be followed.

In a typical run 0.1 mol of amide was placed in the flask and 0.1 ml of ethyl chloroformate was added all at once from the dropping funnel. The temperature of the water bath was maintained at 40–45° and the mixture was stirred. After approximately 15 min the reaction began, as evidenced by the evolution of CO_2. Stirring was continued until CO_2 evolution ceased. (Reaction time varied between 1.5 and 5 hr.) The product was washed repeatedly with anhydrous ether and placed in a vacuum desiccator over H_2SO_4. The products, per cent yields, and melting points are shown in Table I.

Attempts to employ this procedure with benzamide, *p*-nitrobenzamide, and α-phenylacetamide gave no reactions.

Compounds **1–10** were also prepared from the appropriate nitriles, ethanol, and dry HCl by the method of Pinner.[4] Infrared spectra ($CHCl_3$) of the compounds prepared each of the two ways were identical. Table I shows yields and melting points of products.

Acetamide Hemihydrochloride (11).—In the preparation of ethyl acetimidate hydrochloride (**1**), as described above, 5.9 g (0.1 mol) of acetamide and 10.8 g (0.1 mol) of ethyl chloroformate yielded a solid crystalline mass weighing 9.1 g. This solid was extracted with dry chloroform. Evaporation of the chloroform solution gave 3.9 g of **1**. The residue from the extraction was 5.2 g of **11**, mp 124–125° (lit.[2] mp 125°).

Anal. Calcd for $C_4H_{11}ClN_2O_2$: neut equiv, 154.6; Cl, 22.93. Found: neut equiv, 154.0; Cl, 22.99.

The ir spectrum (KBr) was identical with that of **11** prepared by the method of Strecker.[13]

Synthesis of N-Substituted Imidate Hydrochlorides (12–24).—The apparatus and procedure were the same as described for the preparation of **1–10**, except that dry petroleum ether (bp 30–60°) was used for washing the products rather than ethyl ether, owing to higher solubility of the N-substituted imidate salts in the latter solvent. All the products were liquids. Attempts to distil them, even at very low pressures, resulted in decomposition. The products, per cent yields, and analytical data are presented in Table II.

Attempts to employ this procedure with N-*n*-butylacetamide and with acetanilide gave no reaction.

Compounds **12–24** were further characterized by identification of their hydrolysis products. To a sample of the imidate hydro-

(6) J. R. Caldwell and H. V. Moyer, *Ind. Eng. Chem., Anal. Ed.*, **7**, 38 (1935).

(7) W. Reiman, J. D. Neuss, and B. Naiman, "Quantitative Analysis," McGraw-Hill Book Co., Inc., New York, N. Y., 1951, p 161–163.

(8) G. E. Philbrook, *J. Org. Chem.*, **19**, 623 (1954).

(9) W. Wenner in "Organic Syntheses," Coll. Vol. IV, N. Rabjohn, Ed., John Wiley & Sons, Inc., New York, N. Y., 1963, p 760.

(10) G. F. D'Alelio and E. E. Reid, *J. Amer. Chem. Soc.*, **59**, 109 (1937).

(11) A. G. Pesina, *J. Gen. Chem. USSR*, **9**, 804 (1939).

(12) E. C. Taylor and J. A. Zoltewicz, *J. Amer. Chem. Soc.*, **82**, 2656 (1960).

(13) A. Strecker, *Ann.*, **103**, 321 (1857).

chloride was added an equimolar amount of H_2O. A reaction occurred immediately. The ethyl ester was distilled off; the amine hydrochloride remained as residue. These were identified by comparison with ir spectra of authentic samples.

N-Methylcaprylamide Hemihydrochloride (25).—In the preparation of N-methylcaprylimidate hydrochloride (**23**), described above, 4.0 g (0.025 mol) of N-methylcaprylamide and 2.7 g (0.025 mol) of ethyl chloroformate gave two products: one solid, one liquid. The mixture was extracted with anhydrous ethyl ether, which dissolved the liquid but not the solid. Evaporation of the ether from solution gave 2.44 g of **23**. The residue from the extraction was 2.33 g of **25**, mp 38° (lit.[10] mp 38–40°).

Anal. Calcd for $C_{18}H_{39}ClN_2O_2$: neut equiv, 351.0; Cl, 10.10. Found: neut equiv, 347.8, Cl, 10.30.

The ir spectrum was identical with that of **25** prepared by the method of Blicke and Burckhalter.[14]

N-Methylacetamide Hemihydrochloride (26).—In the apparatus described 14.6 g (0.2 mol) of N-methylacetamide and 21.7 g (0.2 mol) of ethyl chloroformate were stirred at 40°. After 30 min reaction was complete and the solid product was washed with anhydrous ethyl ether, giving 18.2 g of **26** (99.6% yield), mp 89–90° (lit.[14] mp 87–89°).

Anal. Calcd for $C_6H_{15}ClN_2O_2$: neut equiv, 182.6; Cl, 19.41. Found: neut equiv, 183.8; Cl, 19.51.

The ir spectrum was identical with that of **26** prepared by the method of Blicke and Burckhalter.[14]

Preparation of Imidate Hydrochlorides from Thionamides.—The apparatus and general procedure were the same as described above for the preparation of **1**–**10** and **12**–**24**.

A. Ethyl Acetimidate Hydrochloride (1).—Thioacetamide (5.0 g, 0.66 mol) and ethyl chloroformate (7.2 g, 0.066 mol) were mixed at 30°. The reaction was complete in 5 min. The resulting crystals were washed with ether and dried *in vacuo:* yield of **1**, 7.6 g (94%); mp 112–113°.

B. Ethyl Propionimidate Hydrochloride (2).—Thiopropionamide (5.8 g, 0.065 mol) and ethyl chloroformate (7.1 g, 0.065 mol) were mixed at 30°. The reaction was complete in 5 min. Anhydrous ether (50 ml) was added to the liquid and allowed to stand overnight at 0°. The white crystals were filtered, washed with ether, and dried *in vacuo:* yield of **2**, 7.9 g (88%); mp 92°.

C. Ethyl Isobutyrimidate Hydrochloride (4).—Thioisobutyramide (2.0 g, 0.02 mol) and ethyl chloroformate (2.2 g, 0.02 mol) were allowed to react at 30°, with the reaction being completed in 10 min. The white crystalline mass was washed with anhydrous ether and dried *in vacuo:* yield of **4**, 1.4 g (45%); mp 82°.

D. Ethyl Benzimidate Hydrochloride (27).—Thiobenzamide (3.0 g, 0.022 mol) and ethyl chloroformate (2.7 g, 0.022 mol) were mixed at 30°. The reaction was complete in 30 min, and the resulting crystals were washed and dried as above: yield of **27**, 2.7 g (66%); mp 128° (lit.[4] mp 125°).

The ir spectrum was identical with that of **27** prepared from benzonitrile and ethanol by the method of Pinner.[4]

E. Ethyl N-Phenylacetimidate Hydrochloride (28).—Thioacetanilide (7.6 g, 0.05 mol) and ethyl chloroformate (5.4 g, 0.05 mol) were mixed at 40°, and the reaction was complete in 45 min. The solid product was washed with anhydrous ether, then with dry dioxane, and stored *in vacuo:* yield of **28**, 6.0 g (60%); mp 92–93° (lit.[15] mp 100°).

Anal. Calcd for $C_{10}H_{14}ClNO$: neut equiv, 199.7; Cl, 17.75; N, 7.01. Found: neut equiv, 206.0; Cl, 17.32; N, 6.89.

The compound was further characterized by identification of its hydrolysis products. To a sample of **28** was added an equimolar amount of H_2O, and the mixture distilled. The distillate was identified as ethyl acetate and the residue as aniline hydrochloride by comparison of their ir spectra with those of authentic samples.

Rate Studies.—The apparatus was the same as that used in the preparation of the imidate hydrochlorides, modified as follows. The dropping funnel was mounted on top of a side-arm adapter, the side arm of which was fitted with a delivery tube from a nitrogen tank. The condenser was cooled by pumping through it acetone from a Dry Ice–acetone mixture. (This was found necessary in order to prevent ethyl chloroformate from being swept out of the system by the nitrogen stream.) The delivery tube from the top of the condenser was attached to one stem of a three-way stopcock. To each of the other stems was attached a 150-mm absorption tube packed with indicating CO_2 absorbent.[16] This stopcock arrangement permitted selective absorption into either of the tubes. The propionamide used was Eastman Organic Chemicals No. 675, recrystallized three times from benzene (mp 79.5–80°).

In a typical experiment, the propionamide was placed in the flask and the system was purged with nitrogen for 1 hr. The weighed absorption tubes were attached, and the stopcock was turned so that the exit gases could pass through tube no. 1. The ethyl chloroformate was added from the dropping funnel, and the timer started. Stirring was continued throughout, and the water bath was maintained at 30 ± 0.1°. Nitrogen was allowed to flow through the system continuously to sweep out the CO_2 as formed.

After 15 min the stopcock was turned to close absorption tube no. 1 and open no. 2. Tube no. 1 was disconnected, weighed, and reconnected. This procedure was repeated every 15 min, alternating the gas flow through the two absorption tubes.

Registry No.—**5**, 18542-63-7; **10**, 18542-64-8; **12**, 18542-65-9; **13**, 18542-66-0; **14**, 18542-67-1; **15**, 18542-68-2; **16**, 18542-69-3; **17**, 18542-70-6; **18**, 18542-71-7; **19**, 18559-84-7; **20**, 18559-85-8; **21**, 18559-86-9; **22**, 18559-87-0; **23**, 18598-45-3; **24**, 18559-88-1; ethyl chloroformate, 541-41-3.

Acknowledgments.—The authors wish to thank Fred J. Reichley and Thomas R. Weaver for their assistance in preparing several of the compounds and performing a number of the analyses.

(14) F. F. Blicke and J. H. Burckhalter, *J. Amer. Chem. Soc.*, **64**, 451 (1942).

(15) G. D. Lander, *J. Chem. Soc.*, 591 (1902).

(16) Mallcosorb A. R. 30–50 mesh, Mallinckrodt Chemical Works, St. Louis, Mo. 63160.

The Synthesis of 4-Hydroxyarylene Ethers by the Equilibration of Phenols with Poly(2,6-dimethyl-1,4-phenylene ether)[1]

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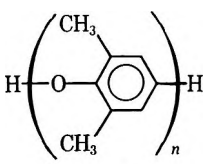
Received July 24, 1968

Hydroxyarylene ethers, **6**, have been synthesized by equilibrating phenols with poly(2,6-dimethyl-1,4-phenylene ether). The mixtures of phenolic products were converted into thermally stable derivatives (acetates, methyl ethers, trimethylsilyl ethers) and separated by fractional distillation. The purified derivatives were cleaved to the free hydroxyarylene ethers. With the trimethylsilyl ethers, the cleavage proceeded quantitatively at room temperature. The equilibration reactions were initiated with either benzoyl peroxide or 3,3′,5,5′-tetramethyl-4,4′-diphenoquinone. Phenol, resorcinol, halophenols, alkylphenols, alkoxyphenols, and aryloxyphenols equilibrated extensively with the polymer. Phenols with strong electron-withdrawing groups generally were unreactive. The molecular weight distribution of the low molecular weight products depended on the initial ratio of starting phenol to polymer.

Many 4-aryloxyphenols redistribute in the presence of an initiator to form a mixture of phenols.[2,3] For example, 4-(2,6-dimethylphenoxy)-2,6-dimethylphenol (**2**) is converted into an equilibrium mixture of 2,6-

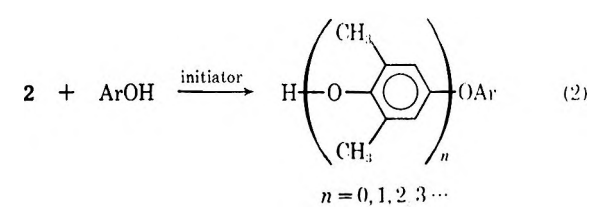


1, $n=1$
2, $n=2$
3, $n=3$
4, $n=4$

dimethylphenol (**1**) and higher molecular weight hydroxyphenylene ethers (reaction 1), and the quantities

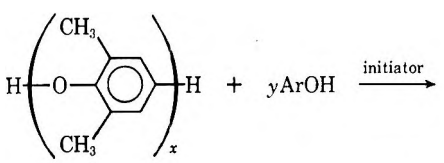
$$2 \xrightarrow{\text{initiator}} 1 + 2 + 3 + 4 + \ldots \qquad (1)$$

of the products at equilibrium occur in the order **1** > **2** > **3** > **4** > .... When a second phenol is present during the redistribution of **2**, a coequilibration may occur in addition to reaction 1 and a second series of products can result (reaction 2). This report describes



$n = 0, 1, 2, 3 \cdots$

a synthetic method for the preparation of 4-hydroxyarylene ethers which utilizes reactions which are similar to 1 and 2. Instead of using a "dimer" as **2**, an equilibration mixture is attained from the coredistribution of a high molecular weight hydroxyarylene ether, poly(2,6-dimethyl-1,4-phenylene ether) (**5**), with a phenol. Reaction 3 describes the conversion. When ArOH is compound **1**, the products are the same as those from reaction 1. When ArOH is a phenol other than



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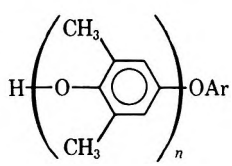


6, $n = 0, 1, 2, 3 \cdots$ (3)

1, the products are the same as those from reaction 2, and only trace quantities of the products from reaction 1 are present. Since the polymer, **5**, is readily available,[4,5] the equilibration of **5** with phenols often provides a convenient synthetic method for the preparation of entire series of 4-hydroxyarylene ethers. In many instances (*e.g.*, halogenated products or compounds with two or more ether linkages), syntheses by conventional organic procedures often require many more steps and result in very low yields.[6]

The equilibration mixture, **6**, which contained the starting phenol and hydroxyarylene ethers ranging from $n = 1$ up to methanol-insoluble polymer ($n >$ *ca.* 10), in most cases was highly reactive[2,3] and would redistribute during isolation. To avoid redistribution, the phenols were converted into esters or ethers which did not redistribute.[7] The separation procedure varied with the specific conditions but involved some or all of the following operations: (a) precipitation of the methanol-insoluble polymer if much was present; (b) extraction of the phenol, ArOH, and certain other impurities with aqueous base; (c) conversion of the hydroxyarylene ethers into thermally stable derivatives, *e.g.*, the trimethylsilyl ether (eq 4);[8] (d) fractional distillation of the derivatives; and (e) hydrolysis of the purified derivative. The trimethyl-

(1) A portion of this work was described at the Phoenix Meeting of the American Chemical Society, Division of Polymer Chemistry, Preprints, 1966, p 178.

(2) G. D. Cooper, A. R. Gilbert, and H. Finkbeiner, ref 1, 1966, p 166.

(3) D. A. Bolon, *J. Org. Chem.*, **32**, 1584 (1967).

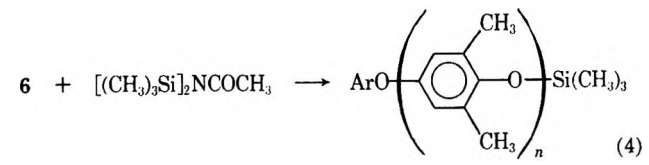
(4) A. S. Hay, H. S. Blanchard, G. F. Endres, and J. W. Eustance, *J. Amer. Chem. Soc.*, **81**, 6335 (1959); A. S. Hay, *J. Polym. Sci.*, **58**, 585 (1962).

(5) G. F. Endres and J. Kwiatek, *ibid.*, **58**, 593 (1962).

(6) Alternate procedures would require methods such as the Ullmann ether synthesis [H. E. Unganade, *Chem. Rev.*, **38**, 405 (1946)] or involve aryl iodonium intermediates [H. Ziegler and C. Marr, *J. Org. Chem.*, **27**, 3335 (1962), and references therein].

(7) G. D. Cooper, H. S. Blanchard, G. F. Endres, and H. L. Finkbeiner, *J. Amer. Chem. Soc.*, **87**, 3996 (1965).

(8) J. F. Klebe, H. Finkbeiner, and D. M. White, *ibid.*, **88**, 3390 (1966).



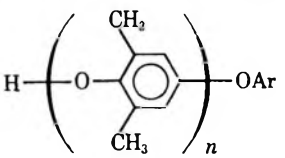
(4)

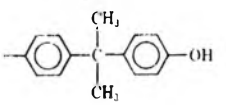
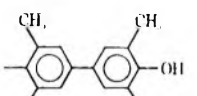
silyl ethers were convenient derivatives since they were stable during distillation and the protective group could be hydrolyzed after distillation under conditions which were sufficiently mild to prevent redistribution of the free 4-hydroxyarylene ether.

The major products which were isolated from preparative-scale equilibrations with 2,6-dimethylphenol, phenol, *p*-bromophenol, 3,3′-5,5′-tetramethyl-4,4′-dihydroxybiphenyl (**20**), and 4,4′-isopropylidenediphenol are listed in Table I.[9] In some cases, the intermediate trimethylsilyl ethers were crystalline solids (*e.g.*, the trimethylsilyl ether of **11**, mp 68–70°) and could be purified by recrystallization. The products in Table I which are new compounds have been characterized by infrared (ir) and nuclear magnetic resonance (nmr) spectroscopy, elemental analysis, and thin layer and gas chromatographic behavior. The preparation of these compounds illustrates the use of halo- and alkylphenols and unsubstituted and difunctional phenols in equilibrations for synthetic purposes. The scope of the reaction is discussed in more detail, below, after several other features of the reaction have been presented.

TABLE I

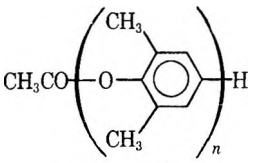
PRODUCTS FROM THE EQUILIBRATION OF PHENOLS (ArOH) WITH POLY(2,6-DIMETHYL-1,4-PHENYLENE ETHER)



Compd no.	*n*	Ar	Mp, °C
2	1	2,6-Dimethylphenyl	108.5–109[a]
3	2	2,6-Dimethylphenyl	112.5–112.7[b]
4	3	2,6-Dimethylphenyl	165–167 (acetate)
7	1	Phenyl	Amorphous
8	2	Phenyl	Amorphous
9	3	Phenyl	Amorphous
10	1	4-Bromophenyl	62.5–63.5
11	2	4-Bromophenyl	100–102
12	1		201.5–202.5
13	1		118–119

[a] Lit.[3] mp 111°. [b] Lit.[8] mp 112–113°.

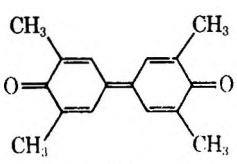
The quantities of products from a large-scale equilibration of 2,6-dimethylphenol with polymer **5** illustrate yields for a reaction where the acetates of the dimer, trimer, and tetramer were isolated. From 1000 g of



14, $n = 2$
15, $n = 3$
16, $n = 4$

2,6-dimethylphenol and 1000 g of polymer, the isolated derivatives were **14** (293 g), **15** (220 g), and **16** (35 g). Only a portion of **16** was isolated. Gas chromatographic analysis indicated that approximately 100 g was in the reaction mixture.

A variety of oxidizing agents can serve as initiators for the equilibrations. The two materials used in this study were benzoyl peroxide and 3,3′,5,5′-tetramethyl-1,4-diphenoquinone (**17**). *o*-Chloranil (**18**) and 2,4,6-tri-*t*-butylphenoxyl (**19**) were moderately effective initiators but were not used in preparative reactions. *p*-Benzoquinone and *p*-chloranil did not produce extensive equilibration. Side reactions, principally with the phenol, rapidly decreased the concentrations of the latter two initiators.



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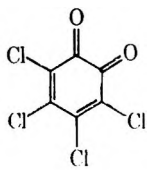

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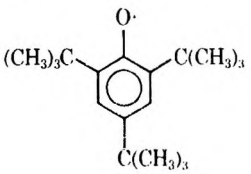

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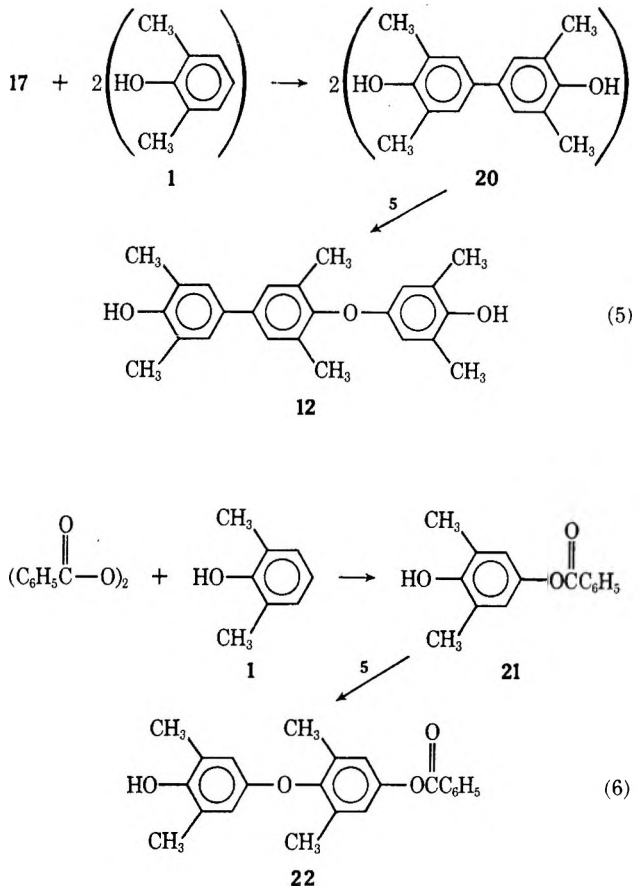
The quantities of benzoyl peroxide and **17** varied from 3 to 10% of the weight of the polymer. The latter quantity was used only when smaller quantities did not produce extensive equilibration. Low initiator concentrations were preferred since the quantities of side products were less.

Several side products from reactions of the initiators were isolated. With **17** as the initiator, phenols with low oxidation potentials were oxidized usually to carbon–carbon coupled dimers.[10] In the case of 2,6-dimethylphenol, the product was 3,3′,5,5′-tetramethyl-4,4′-dihydroxybiphenyl (**20**). Compound **20** equilibrated with the polymer to produce compound **12** (eq 5) and higher oligomeric products. (This side reaction was used preparatively; see Table I.) With benzoyl peroxide as an initiator, the sequence of reactions shown in eq 6 occurred. The formation of

(9) A preparative-scale equilibration using 2,4,6-trimethylphenol is described in ref 8.

(10) A. S. Hay, *Tetrahedron Lett.*, 4241 (1965); R. G. R. Bacon and O. J. Stewart, *Chem. Commun.*, 977 (1967).



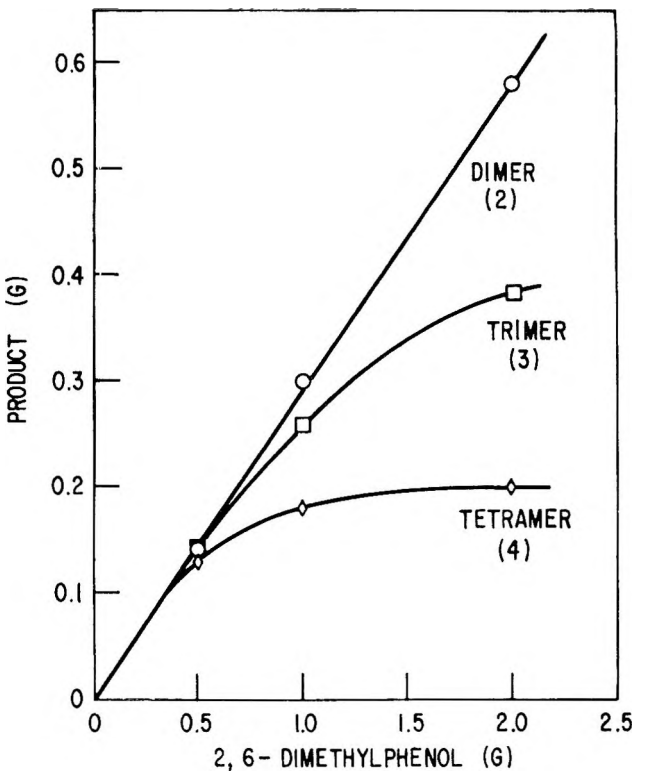


Figure 1.—Change in product composition with initial 2,6-dimethylphenol concentration for the equilibration with 1.00 g of polymer **5** at 80° for 2 hr. The quantity of initiator **17** was 3 wt % of the 2,6-dimethylphenol.

4-benzoyloxy-2,6-xylenol (**21**) from the reaction of benzoyl peroxide with 2,6-xylenol has been reported.[11,12] An extensive equilibration of **21** with polymer **5** to form **22** and higher oligomers occurred and is described in a later section. Another source of **21** is the reaction of benzoyl peroxide with the polymer. This is indicated by the isolation of **21** in small amounts from equilibrations which did not have **1** as the starting phenol. The yields of the side products were low; typical values based on the equilibration of 100 g of polymer with 100 g of 2,6-dimethylphenol were 2 g of **20** and 0.5 g of **12** from 3 g of initiator **17** and 2 g of **21** and 0.5 g of **22** from 10 g of benzoyl peroxide.

The relative quantity of each component in the equilibrated reaction mixture depends on the number average degree of polymerization, $\overline{DP}_n$, of the mixture. When polymer was equilibrated completely with an equal weight of 2,6-dimethylphenol, the distribution of the products was the same as that for the equilibration of the dimer **2** alone. In this case, the molar concentration of 2,6-dimethylphenol was almost equal to the molar concentration of monomeric units in the polymer, *i.e.*, $x = y$ in reaction 3, and the $\overline{DP}_n$ was almost 2. Similarly, a monomer–polymer solution with a $\overline{DP}_n$ of 3 was converted into the same distribution which was attained from equilibration of the trimer **3**. The effect of changes of the $\overline{DP}$ is illustrated in Figure 1 for three 2,6-dimethylphenol concentrations. For a $\overline{DP}$ of 3 (0.50 g of **1**/g of **5**), the weight ratio of **2**:**3**:**4** was approximately 1:1:1. For a $\overline{DP}$ of 1.5 (2.0 g of **1**/g of **5**) the ratio was approximately 3:2:1. The changes in product distribution can be interpreted as mass law effects on the many equilibration reactions which are occurring. Two equilibrium reactions are represented by eq 7 and 8. Compound **6′** is an oligomer with one less monomeric unit than in **6**. An increase in the phenol **1** drives the equilibrium to the right and

$$1 + 6 \rightleftarrows 2 + 6' \quad (7)$$

$$2 + 6 \rightleftarrows 3 + 6' \quad (8)$$

the dimer **2** is increased. The increase in **2** causes a corresponding shift in equilibrium 8 to the right and the concentration of **3** is increased. The increase of **3** is not so pronounced as the increase in **2**, however, since the equilibrium concentration of **2** is less than that of **1**. The effect of the concentration of **1** on higher oligomer concentrations is progressively less as the size of the oligomer increases.

From the data in Figure 1, an equilibrium constant can be calculated for the equilibrium between compounds **1**, **2** and **3** (eq 9). The value, $K_2 = 2.3 \pm 0.2$, is in agreement with the value of 2.44 for the redistribution of **2**.[2] For equilibrium 10, $K_3 = 0.91 \pm 0.1$. Equilibrium constants for analogous redistribution of higher oligomers also appear to be near unity. Only the equilibrium constant which involves an equilibrium with component **1**, a phenol which cannot redistribute (reaction 1), has the high value.

$$2(2) \rightleftarrows 1 + 3 \quad (9)$$

$$2(3) \rightleftarrows 2 + 4 \quad (10)$$

(11) S. L. Cosgrove and W. A. Waters, *J. Chem. Soc.* (London), 3189 (1949); 388 (1951).

(12) C. Walling and R. B. Hodgdon, *J. Amer. Chem. Soc.*, **80**, 228 (1958).

The reactivity of the polymer, **5**, in the equilibration is dependent on its molecular weight and on the nature of the phenolic end group. The phenolic end group is the site of initial reaction in the polymer chain. This was demonstrated by the inability of completely acetylated polymer to coredistribute under equilibration conditions. Since the concentrations of phenolic end groups are inversely proportional to the molecular weight, low polymer has a higher molar concentration of end groups than an equal weight of high polymer. For low polymer faster equilibration results and fewer side reactions, as reactions 5 and 6, occur. The other factor is the nature of the phenolic end group. The concentration of irregularities in the structures of the phenolic end groups appears to increase with higher molecular weight owing to side reactions during polymerization which reduce the reactivity of some of the polymer molecules. For these reasons, equilibration is more extensive and side products are less with low molecular weight polymer. The use of very low molecular weight polymer for equilibrations with phenols other than 2,6-dimethylphenol is avoided, however, since the molar concentration of polymer will be sufficiently high to allow the buildup of an appreciable amount of equilibration products from a redistribution reaction similar to reaction 1. Thus, polymers with molecular weights between *ca.* 2000 and 10,000 (intrinsic viscosity in chloroform at 30° from *ca.* 0.1 to 0.3 dl/g) have been used most successfully in these preparations.

The scope of the equilibration between phenols and poly(2,6-xylylene oxide) is indicated by the results of equilibrations with 28 phenols which are summarized in Table II. Extensive equilibration (as indicated by low yields of recovered polymer) occurred with phenol, many alkylated and halogenated phenols, and certain phenols with an oxygen atom in the *meta* or *para* position. In general, compounds that equilibrate poorly are the phenols which have lowest oxidation potentials and undergo side reactions with the initiator or phenols that have the highest oxidation potentials and are inert (*e.g.*, *p*-nitrophenol). Steric effects may account for the lower reactivity with *o*-bromophenol than with *p*-bromophenol. Two of the phenols in Table II, **20** and **21**, are side products from the initiators. Their ability to react with polymer is demonstrated here.

The polymer for the series of reactions in Table II had a relatively high intrinsic viscosity (0.34 dl/g, $\bar{M}_n$ *ca.* 15,000) to provide a less reactive system than would result with lower molecular weight polymers. Thus, the reactivity scale of the more active phenols was, in effect, expanded. As a result, some of the active phenols had intermediate reactivity in this case, and did equilibrate more extensively with polymers that were more reactive.

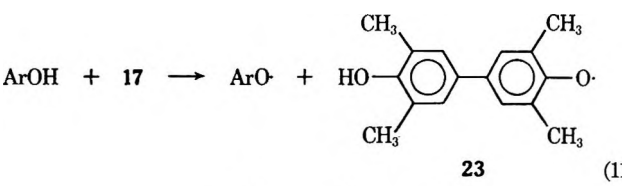
Benzoyl peroxide and 3,3′,5,5′-tetramethyl-4,4′-diphenoquinone were compared for equilibrations with several phenols (Table II). In these cases, benzoyl peroxide was either equally effective or more effective than the diphenoquinone. In certain cases, however, the diphenoquinone was preferred since the 4-aryloxy-2,6-xylenol (**6**, $n = 1$) could be separated more easily from side product **20** than from side product **21**.

The mechanism of the equilibration of poly(2,6-dimethyl-1,4-phenylene ether) with phenols appears to

TABLE II
EQUILIBRATION OF POLY-(2,6-DIMETHYL-1,4-PHENYLENE ETHER) WITH VARIOUS PHENOLS

Phenol	Yield of recovered polymers for two initiators: Benzoyl peroxide, %	3,3′,5,5′-Tetramethyl-4,4′-diphenoquinone, %
Phenol	6	
o-Bromophenol	31	48
m-Bromophenol	28	
p-Bromophenol	11	
p-Iodophenol	16	35
p-Chlorophenol	5	
2,6-Dichlorophenol	64	
Pentachlorophenol		86
o-Cresol	3	4
m-Cresol	5	17
p-Cresol	4	
2,6-Xylenol (**1**)	4	6
Mesitol	47	
2,6-Dimethyl-4-(benzoyloxy)phenol (**21**)	10	
p-Methoxyphenol	46	
p-Phenoxyphenol	4	
Hydroquinone monobenzoate		13
Hydroquinone		98
Resorcinol		33
4,4′-Dihydroxydiphenyl ether		95
4,4′-Isopropylidenediphenol		4
3,3′,5,5′-Tetramethyl-4,4′-biphenyl (**20**)		60
p-Hydroxybenzonitrile	88	
2,6-Diphenylphenol	64	
p-Nitrophenol	90	
β-Naphthol		64
Methyl *p*-hydroxybenzoate		88
Methyl salicylate		96

be very similar to the mechanism described for the redistribution of compound **2**[2] and the coredistribution of phenols with compound **2**.[3] The initiation step is the oxidation of the phenolic group. With the diphenoquinone **17** as an initiator, the monomer and the polymer are converted into the corresponding phenoxy radicals (eq 11 and 12). The reduced diphenoquinone, **23**, can either abstract another hydrogen and form **20** or can transfer a hydrogen to reduce an aryloxy radical. The radicals ArO· and **24** couple to form a quinone ketal, **25** (eq 13), one of the types of intermediates in the propagation step. With benzoyl peroxide as an initiator, the initial step may be the formation of a quinolbenzoate, **26** (eq 14), in analogy with the formation of 4-benzoyloxy-2,4,6-trimethyl-2,5-cyclohexadienone from benzoyl peroxide and mes-



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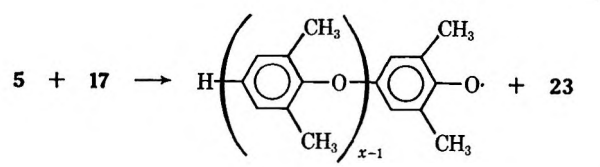

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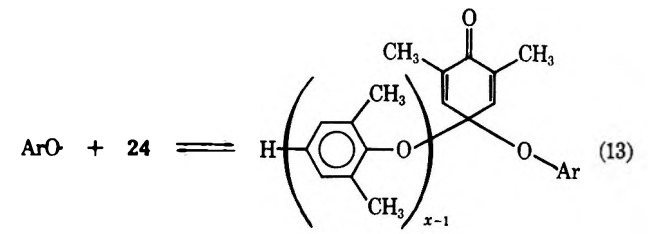

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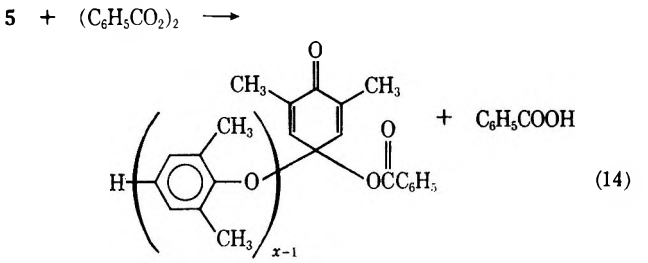
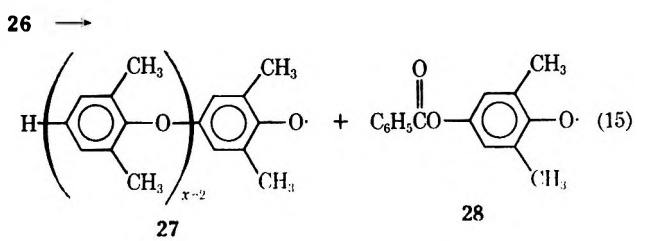


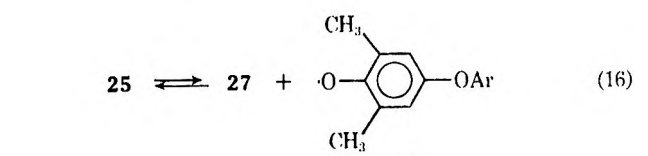
26

itol.[11] Compounds **25** and **26** can dissociate to form a polymer radical **27** (which reacts similarly to **24**) and the radical **28** (eq 15) which can be reduced to form the side product **21** or can equilibrate further.

The steps in the propagation reaction involve the same reversible dissociations of quinone ketals which were described by Bolon,[3] *e.g.*, eq 16–18, etc. In-



27 28



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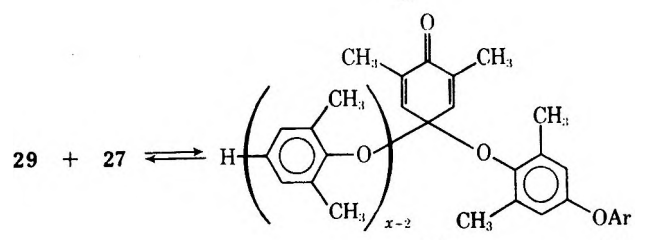

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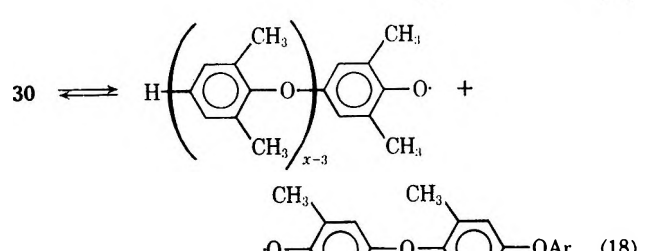

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termediates such as **29** and **31** can react further with other phenoxy radicals such as **24** and **27** or can abstract hydrogen atoms from other phenols to form **6** and new phenoxy radicals.

Strong support for the quinone ketal dissociation mechanism[2,3] is given by the structures of the products which were isolated in this study. This mechanism predicts that only the terminal aryloxy rings of the hydroxyarylene ethers are derived from the phenol, ArOH. All of the remaining rings are derived from the polymer. The nmr studies of the composition of the hydroxyarylene ethers indicated that they do have structure **6**.

Experimental Section[13]

Poly(2,6-dimethyl-1,4-phenylene ether) (**5**).—The polymers were prepared by a modification of the method of Endres and Kwiatek.[5] 2,6-Dimethylphenol (10.0 g, 0.082 mol; three times recrystallized) was added to an oxygenated, stirred solution of cuprous chloride (0.50 g, 0.005 mol; reprecipitated from hydrochloric acid with methanol and dried) and pyridine (100 ml; reagent grade) in a flask in a stirred water bath at 20°. Oxygen (0.15 ft³/hr) was bubbled into the solution. The temperature of the reaction mixture rose to 23° after 7 min. After 17 min, the temperature began to drop and the reaction mixture was transferred to a beaker and stirred vigorously. Methanol (500 ml; containing 5 ml of concentrated hydrochloric acid) was added to precipitate the polymer. The polymer was collected on a filter, washed two times by trituration with 500 ml of hot methanol, and dried at 50° for 20 hr at reduced pressure. The polymer weighed 8.6 g; its intrinsic viscosity in chloroform at 30° was 0.37 dl/g. Small decreases in reaction times produced polymers with lower viscosities. For example, a 15-min reaction produced a polymer with an intrinsic viscosity of 0.11 dl/g.

Small-Scale Equilibration Reactions.—Poly(2,6-dimethyl-1,4-phenylene ether) (0.500 g; intrinsic viscosity in chloroform at 30°, 0.34 dl/g), the substituted phenol[14] (0.0042 mol), and either 3,3′,5,5′-tetramethyl-4,4′-diphenoquinone (**17**, 15.0 mg, 0.063 mmol) or benzoyl peroxide (50 mg, 0.21 mmol) in benzene (25 ml) were heated at reflux for 2 hr and then the solution was cooled to 25°. Methanol (250 ml) was added dropwise and the precipitated polymer was transferred quantitatively to a filter, washed thoroughly with methanol, dried at 50° (10 mm) for 24 hr, and weighed. The yields of recovered polymers are listed in Table II. A 5-ml aliquot of the filtrate was concentrated on a rotary evaporator, converted into the trimethylsilyl ether derivative by adding 2 drops of bis(trimethylsilyl)acetamide, and analyzed by gas chromatography on a 2-ft silicone rubber column with a program from 100 to 300° at 10°/min. The composition of the methanol-soluble fractions was similar to that of the equilibration of the dimer **2** and was proportional to the quantities of isolated products from large-scale preparative equilibrations.

Preparation of Low Molecular Weight Hydroxyarylene Ethers, "Dimers," "Trimers," and "Tetramers."—The details of the procedures varied according to the reactivity of the particular equilibration mixture. If the yield of methanol-insoluble polymer was relatively high, a precipitation step was used. If a large quantity of initiator **17** was required, a base extraction step was used to remove the 3,3′,5,5′-tetramethyl-4,4′-dihydroxybiphenyl (**20**). In many cases a small-scale reaction (described above) was used to determine the preferred procedure.

Equilibration with 2,6-Xylenol. Preparation of 4-(2,6-Dimethylphenoxy)-2,6-dimethylphenol (2), 4-[4-[2,6-Dimethylphenoxy)-2,6-dimethylphenoxy]-2,6-dimethylphenol (3), and 4-{4-[4-(2,6-Dimethylphenoxy)-2,6-dimethylphenoxy]-2,6-dimethylphenoxy}-2,6-dimethylphenol (4).—Low molecular

(13) Melting points were determined on a Leitz hot-stage microscope and are corrected. Boiling points and distillation pressures are approximate. Nmr spectra were measured on a Varian A-60 spectrometer unless stated otherwise.

(14) All phenols and initiators were purified by recrystallization or redistillation.

weight poly(2,6-dimethyl-1,4-phenylene ether) (5) (100 g; intrinsic viscosity in chloroform at 30°, 0.14 dl/g), 2,6-dimethylphenol (100 g, 0.82 mol), 3,3′,5,5′-tetramethyl-4,4′-diphenoquinone (17, 3.0 g, 0.013 mol), and benzene (2 l.) were heated at reflux with stirring for 2 hr. The solution was concentrated to 700 ml with a rotary evaporator and extracted with aqueous 10% sodium hydroxide to remove 2,6-xylenol and 20. The organic layer was washed with 5% hydrochloric acid and then with water. Methanol (2 l.) was added over a 30-min period to the benzene solution. The precipitated polymer was removed by filtration and the filtrate was concentrated to a viscous oil (59 g). A solution of the oil in benzene (500 ml) and bis(trimethylsilyl)-acetamide (100 g, 90% pure, 0.45 mol) in benzene was heated for 2 hr, then concentrated to an oil which was fractionally distilled at reduced pressure. The cuts given in Table III were obtained.

TABLE III

Fraction	Bp (mm), °C	Wt, g	Principal components, trimethylsilyl ether derivatives
A	76 (2.5)	20	1
B	142 (0.8)	25	2
C	190 (0.6)	21	3
D	220 (0.005)	13	4

The trimethylsilyl groups were removed by dissolving the fractionated trimethylsilyl ether (10 g) in methanol (200 ml) at room temperature and adding 1 drop of hydrochloric acid and sufficient water (*ca.* 100 ml) to reach the cloud point. On cooling (0°), the product crystallized out of the solution and was collected on a filter, washed with cold aqueous methanol, and dried at room temperature under reduced pressure. A second crop of crystals was obtained by the addition of more water to the filtrate. The over-all yields of the dimer and trimer from fractions B and C were 20.2 g of 2, and 13.8 g of 3. Compounds 2 and 3 were identical with authentic samples.[3,5]

Redistillation of the highest boiling cut, D, produced a light amber, glassy solid which was 90% trimethylsilyl ether of 4 according to gas chromatography and nmr. The sample did not crystallize either as the silyl ether or when converted into the free phenol. The bands in the nmr spectrum (in carbon tetrachloride, TMS reference) due to the trimethylsilyl ether of 4 occurred at 0.21, 2.05, 2.09, 2.13, 6.24, 6.37, and 6.96 ppm with the relative intensity ratio 9:3:6:3:2:4:2. Compound 4 was converted into the acetate derivative, mp 165–167°, which was identical with compound 16 which is described below.

Equilibration with Phenol. Preparation of 4-Phenoxy-2,6-dimethylphenol (7), 4-(4-Phenoxy-2,6-dimethylphenoxy)-2,6-dimethylphenol (8), and 4-[4-(4-Phenoxy-2,6-dimethylphenoxy)-2,6-dimethylphenoxy]-2,6-dimethylphenol (9).—Phenol (100 g, 1.06 mol), poly(2,6-dimethyl-1,4-phenylene ether) (45 g; intrinsic viscosity, 0.62 dl/g), and 3,3′,5,5′-tetramethyldiphenoquinone (17, 4.5 g, 0.02 mol) in benzene (500 ml) were heated at reflux for 15 min. The solution was concentrated at atmosphere pressure to 250 ml over a 20-min period. Hexane (1500 ml) was added to precipitate the remaining polymer. After filtration (which removed 10 g of polymer), the filtrate was concentrated, trimethylsilylated, and fractionally distilled. The product yields after hydrolysis to the free phenols are listed in Table IV. Compound 7 was identical (nmr and ir spectra) with an

TABLE IV

Product	Wt, g	Bp (mm), °C, of trimethylsilyl ether
7	21	112 (0.05)
8	6.5	185 (0.02)
9	1.0	215 (0.02)

authentic sample.[3] The ir spectrum of the pure liquid showed characteristic absorption at 3500, 1240, 1210, 890, 760, and 700 cm^{-1}. The nmr spectrum (in deuteriochloroform, TMS reference) showed singlet bands at 2.15, 4.85, and 6.75 ppm and a complex grouping at 6.8–7.3 ppm in the relative intensity ratio 6:1:2:5.

The ir spectrum of the pure liquid trimethylsilyl ether of 8 showed bands at 1230, 1210, 860, 760, and 700 cm^{-1} which were characteristic of the aryl ether links, the isolated aryl hydrogens, and the monosubstituted benzene ring. The nmr spectrum (in carbon tetrachloride, TMS reference) showed singlet bands at 0.23, 2.10, 2.15, 6.42, and 6.76 ppm and a complex grouping at 6.8–7.3 ppm in the relative intensity ratio 9:6:6:2:2:5.

The ir spectrum of the pure liquid sample of the trimethylsilyl ether of 9 showed bands at 1230, 1210, 860, 760, and 700 cm^{-1} which are characteristic of the ether links, the isolated aryl hydrogens, and the monosubstituted benzene ring. The nmr spectrum (in deuteriochloroform, TMS reference) showed bands at 0.23, 2.08, 2.14, 6.50, and 6.75 ppm and a series of bands from 7.0 to 7.5 ppm in the relative intensity ratio 9:6:12:2:4:5.

Equilibration with *p*-Bromophenol. Preparation of 4-(4-Bromophenoxy)-2,6-dimethylphenol (10) and 4-[4-(4-bromophenoxy)-2,6-dimethylphenoxy]-2,6-dimethylphenol (11).—A solution of poly(2,6-dimethyl-1,4-phenylene ether) (100 g; intrinsic viscosity, 0.34 dl/g), *p*-bromophenol (144 g, 0.83 mol), and benzoyl peroxide in benzene (2000 ml) was heated to reflux. After 2 hr, bis(trimethylsilyl)acetamide (223 g, 90% pure, 1.0 mol) was added. After 1 hr, the reaction mixture was cooled, concentrated, and distilled rapidly. The distillate boiling higher than the trimethylsilyl ether of *p*-bromophenol was redistilled carefully. The yields and boiling points of the trimethylsilyl ethers follow: trimethylsilyl ether of 10, 37 g, bp 120° (0.03 mm); trimethylsilyl ether of 11, 17 g, bp 150° (0.03 mm). The nmr spectrum (in deuteriochloroform, TMS reference) of the trimethylsilyl ether of 10 showed singlet bands at 0.25, 2.16, and 6.64 ppm and a quartet at 6.70, 6.75, 7.27, and 7.32 ppm in the relative intensity ratio 9:6:2:4. The trimethylsilyl ether was hydrolyzed in nearly quantitative yield by dissolving it in methanol–water and adding 1 drop of hydrochloric acid. Compound 10 was recrystallized from hexane: mp 62.5–63.5°. The ir spectrum of the sample in a KBr pellet showed bands at 3440, 1193, 875, and 820 cm^{-1} which are characteristic of the hydroxyl group, the ether link, and the isolated and two adjacent aryl hydrogens. The nmr spectrum (in carbon tetrachloride, TMS reference) showed singlet bands at 2.20, 4.58, and 6.64 ppm and a quartet at 6.70, 6.75, 7.26, and 7.41 ppm in the relative intensity ratio 6:1:2:4.

Anal. Calcd for $C_{14}H_{13}BrO_2$: C, 57.4; H, 4.5; mol wt, 293. Found: C, 57.7; H, 4.5; mol wt (Mechrolab osmometer in chloroform), 285.

The trimethylsilyl ether of 11 was recrystallized from hexane, mp 68–70°. The nmr spectrum (in deuterochloroform; TMS reference) showed singlet bands at 0.23, 2.09, 2.14, 6.37, and 6.73 ppm and a quartet at 6.81, 6.97, 7.34, and 7.49 ppm in a relative intensity ratio of 9:6:6:2:2:4.

Anal. Calcd for $C_{23}H_{29}BrO_3Si$: C, 62.0; H, 6.0; Br, 16.5; mol wt, 485. Found: C, 61.9; H, 5.9; Br, 16.6; mol wt (Mechrolab osmometer in benzene), 475.

The trimethylsilyl ether of 11 was hydrolyzed in nearly quantitative yield by dissolving it in methanol–water and adding 1 drop of hydrochloric acid. Compound 11 was recrystallized from hexane: mp 100–102°. The ir spectrum in a KBr pellet showed bands at 3400, 1230, 1190, 878, 850, and 820 cm^{-1} which are characteristic of the hydroxyl group, the two aryl ether links, the two types of isolated aryl hydrogens, and two adjacent aryl hydrogens.

Anal. Calcd for $C_{22}H_{21}BrO_3$: C, 63.8; H, 5.1; mol wt, 413. Found: C, 63.7; H, 5.1; mol wt (Michrolab osmometer in benzene), 392.

Equilibration with 20. Preparation of 4-(3,5-Dimethyl-4-hydroxyphenoxy)-4′-hydroxy-3,3′,5,5′-tetramethylbiphenyl (12).—To a stirred mixture of 3,3′,5,5′-tetramethyl-4,4′-dihydroxybiphenyl (20, 100 g, 0.41 mol) and 3,3′,5,5′-tetramethyl-4,4′-diphenoquinone (17, 15 g, 0.063 mol) in benzene (2000 ml) at 80° was added poly(2,6-dimethylphenylene ether) (50 g; intrinsic viscosity, 0.27 dl/g). After 16 hr at reflux, a gas chromatographic analysis indicated the presence of approximately 30 g of 12. Bis(trimethylsilyl)acetamide (204 g, 0.92 mol, based on 90% purity) was added dropwise. After 2 hr, the mixture was concentrated and then distilled at reduced pressure to yield two high boiling fractions: bis(trimethylsilyl ether) of 20, 80 g, bp 155° (0.01 mm); bis(trimethylsilyl ether) of 12, 40 g, bp 190° (0.01 mm). Hydrolysis of these fractions gave nearly quantitative yields of the free diols. The product from the first fraction, mp 224–226°, was identical with an authentic sample of 20.[11] The hydrolysis product from the second fraction was a solid which was recrystallized from chloroform–hexane and sublimed: 12,

mp 201.5–202.5°. The ir spectrum of this substance (in a KBr pellet) showed strong bands at 3450, 1185, and 860 cm^{-1} which are characteristic absorptions for the hydroxyl group, the ether link, and the isolated aryl hydrogens of the 1,2,3,5-tetrasubstituted aryl groups, respectively. The nmr spectrum (in perdeuteriodimethyl sulfoxide, TMS reference) showed singlet bands at 2.05, 2.20, 6.27, 7.15, 7.25, 7.70, and 8.20 ppm in the relative intensity ratio 12:6:2:2:2:1:1.

Anal. Calcd for $C_{24}H_{26}O_3$: C, 79.6; H, 7.2; mol wt, 362.5. Found: C, 79.3; H, 7.3; mol wt (Mechrolab osmometer in chloroform), 359.

Equilibration with 4,4′-Isopropylidenediphenol. Preparation of 4-[4-(Hydroxyphenylisopropylidene)phenoxy]-2,6-dimethylphenol (13).—A solution of low molecular weight poly(2,6-dimethyl-1,4-phenylene ether) (20.0 g; intrinsic viscosity, 0.11 dl/g), 4,4′-isopropylidenediphenol (40 g, 0.175 mol), 3,3′,5,5′-tetramethyl-4,4′-diphenoquinone (0.60 g, 0.0025 mol), and benzene (600 ml) was heated at reflux 2 hr. Bis(trimethylsilyl)-acetamide (64 g, 0.28 mol, 90% pure) was added dropwise and the sclution was heated at reflux for 1 hr. The solution was distilled through a 3-ft spinning-band column to yield two high boiling fractions: bis(trimethylsilyl ether) of 4,4′-isopropylidenediphenol, 45 g, bp 130–135° (0.01 mm); bis(trimethylsilyl ether) of **13**, 28 g, bp 195–200° (0.01 mm.)

A small sample of the bis(trimethylsilyl ether) of **13** was redistilled. The ir spectrum of this compound (pure liquid) showed absorptions at 1240, 880, and 840 cm^{-1} which are characteristic of the diaryl ether link and the isolated aryl hydrogens, and two adjacent aryl hydrogens, respectively. The nmr spectrum (in carbon tetrachloride, TMS reference) showed singlet bands at 0.32, 1.68, and 2.22 ppm and a complex of nine bands at 6.6–7.2 ppm in the relative intensity ratios 18:6:6:10.

Anal. Calcd for $C_{29}H_{40}O_3Si_2$: C, 70.7; H, 8.1. Found: C, 70.7; H, 8.2.

Hydrolysis of these fractions by dissolving them in methanol–water and adding 1 drop of hydrochloric acid at 25° produced the free diols in nearly quantitative yield. The 4,4′-isopropylidenediphenol was identical with the starting material. Compound **13** was recrystallized from methanol–hexane: mp 118–119°. The ir spectrum of this compound in a KBr pellet showed absorption at 3400, 1210, 882, 830, and 812 cm^{-1} which are characteristic of the hydroxyl group, the ether link, and the isolated and two different sets of two adjacent aryl hydrogens, respectively.

Anal. Calcd for $C_{23}H_{24}O_3$: C, 79.3; H, 6.9; mol wt, 348. Found: C, 79.2; H, 6.8; mol wt (Mechrolab osmometer in benzene), 337.

Preparation of 4-(2,6-Dimethylphenoxy)-2,6-dimethylphenylacetate (14), 4-[4-(2,6-Dimethylphenoxy)-2,6-dimethylphenoxy]-2,6-dimethylphenylacetate (15), and 4-{4-[4-(2,6-Dimethylphenoxy)-2,6-dimethylphenoxy]-2,6-dimethylphenoxy}-2,6-dimethylphenylacetate (16).—A sample of low molecular weight poly(2,6-dimethyl-1,4-phenylene ether) (1000 g; intrinsic viscosity, 0.3 dl/g), 2,6-xylenol (1000 g, 8.2 mol), 3,3′,5,5′-tetramethyl-4,4′-diphenoquinone (**17**, 30 g, 0.13 mol), and benzene (5000 ml) were heated at reflux with stirring 4 hr. Pyridine (712 g, 9.0 mol) was added to the reaction mixture, acetic anhydride (919 g, 9.0 mol) was added over a 15-min period, and the solution was heated at reflux. After 2 hr, the benzene, pyridine, and acetic anhydride were removed at reduced pressure in a rotary evaporator. A rapid distillation at 0.1 mm with a Claisen still head produced two fractions: (A) 800 g, bp 50–190°; (B) 295 g, 190–230°. Fraction A was fractionally distilled through a spinning-band column at 0.05 mm. When the still pot contained *ca.* 100 g of material, fraction B was added and the distillation was continued. The products given in Table V were obtained.

Table V

Component	Bp (mm), °C	Mp, °C, recrystallized	Yield, g
Acetate of 2,6-xylenol	50	20–21	547
14	130	123–124	293
15	190	121–122	220
16	220	165–167	35

Several side products were obtained: the diacetate of compound **20**, 22 g, which boiled in the range between compounds **14** and **15**; the diacetate of **12**, 10 g; the acetates of the "pentamer" and the "hexamer" which were identified by gas chromatography but not isolated in pure form, *ca.* 3 g and 1 g, respectively.

The diacetates of **12** and **20** and compounds **14** and **15** were identical with the acetate derivatives of authentic samples of the parent compounds (by mixture melting points and ir and nmr spectra). The ir spectrum of compound **16** in a KBr pellet showed bands at 1756, 1225, 1190, 850, and 770 cm^{-1} which are characteristic of the carbonyl group, the ether links, the isolated aryl hydrogen, and the three adjacent aryl hydrogens. The nmr spectrum (in carbon tetrachloride, TMS reference, on a Varian HA-100 spectrometer) showed doublet bands ($J \sim 0.2$ cps) at 2.00, 2.03, 2.05, and 2.12 ppm and singlet bands at 2.15, 6.33, 6.37, and 6.95 ppm in the relative intensity ratios 6:6:6:6:3:2:4:3.

Anal. Calcd for $C_{34}H_{36}O_5$: C, 77.8; H, 6.9; mol wt, 525. Found: C, 77.5; H, 7.2; mol wt (Mechrolab osmometer in chloroform), 534.

Effect of Monomer–Polymer Ratio on Product Distribution.—Three equilibration reactions were carried out on samples of poly(2,6-dimethyl-1,4-phenylene ether) (**5**), 2,6-dimethylphenol (**1**), and 3,3′,5,5′-tetramethyl-4,4′-diphenoquinone (**17**) in benzene at 80°. The quantities of reagents are given in Table VII

Table VI

1, g	5, g	17, g	Benzene, ml
0.50	1.00	0.015	25
1.00	1.00	0.030	50
2.00	1.00	0.060	100

After 2 hr, excess bis(trimethylsilyl)acetamide was added to each mixture and the trimethylsilylated products were analyzed by gas chromatography. An inert internal standard, 4-methoxyphenyl 3-phenoxyphenyl ether, was present in each mixture to permit quantitative determination of the products (see Figure 1).

Conversion of Poly(2,6-dimethyl-1,4-phenylene ether) into the Acetate and Attempted Equilibration of the Acetate.—Poly(2,6-dimethyl-1,4-phenylene ether) (10 g; intrinsic viscosity, 0.34 dl/g) was heated at reflux in a mixture of 120 ml of toluene, 120 ml of pyridine, and 8 ml of acetic anhydride for 3 hr under nitrogen and then allowed to cool to 25° overnight. The polymer was isolated by precipitation with methanol and drying at 50° (10 mm) for 24 hr. The ir spectrum of the product (2.5% solution in carbon disulfide in a 1.0-cm cell) indicated that the phenolic hydroxyl absorption at 3610 cm^{-1} was not present. The intrinsic viscosity was 0.34 dl/g.

The acetylated polymer (0.50 g), 2,6-dimethylphenol (0.50 g), initiator **17** (0.015 g), and benzene were heated at 80° for 2 hr. The polymer was precipitated with methanol, washed with methanol, and dried. The polymer weighed 0.50 g and had an intrinsic viscosity of 0.34 dl/g.

Registry No.—**1** (trimethylsilyl ether derivative), 16286-54-7; **2** (trimethylsilyl ether derivative), 15770-98-6; **3** (trimethylsilyl ether derivative), 15770-99-7; **4** (acetate), 15770-86-2; **4** (trimethylsilyl ether derivative), 15875-06-6; **7** (trimethylsilyl ether derivative), 15770-79-3; **8** (trimethylsilyl ether derivative), 15875-05-5; **9** (trimethylsilyl ether derivative), 15770-95-3; **10**, 15770-93-1; **10** (trimethylsilyl ether derivative), 15770-96-4; **11**, 15770-94-2; **11** (trimethylsilyl ether derivative), 15770-97-5; **12**, 15770-87-3; **12** [bis(trimethylsilyl ether derivative)], 15946-65-3; **13**, 16719-51-0; **13** [bis(trimethylsilyl ether derivative)], 16781-29-6; **14**, 15770-84-0; **15**, 15770-85-1; **20** [bis(trimethylsilyl ether derivative)], 16286-53-6; bis(trimethylsilyl ether) of 4,4′-(isopropylidenediphenol), 4387-16-0; acetate of 2,6-xylenol, 876-98-2.

Acknowledgment.—The author is indebted to Dr. J. R. Ladd for carrying out several large-scale reactions and to Mr. H. J. Klopfer and Mr. S. S. Rosenblum for their technical assistance.

Evidence of Reversible Zwitterion Formation in the Reaction of 7-Ketonorbornane and Dimethyloxosulfonium Methylide[1]

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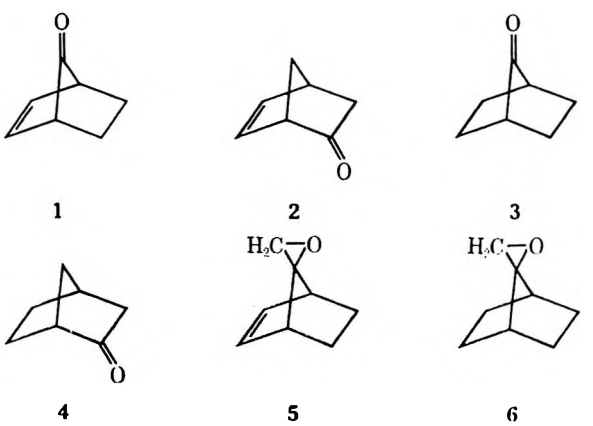
Dimethyloxosulfonium methylide reacts with excess 7-ketonorbornane in dimethyl sulfoxide at room temperature to produce a complex mixture containing spiro[norbornan-7,2′-oxacyclopropane], methyl 7-(7-hydroxynorbornyl)carbinyl sulfoxide, bis[7-(7-hydroxynorbornyl)carbinyl] sulfoxide and no unreacted ketone. We attribute this unusual and heretofore unobserved reaction type to steric crowding by the *exo*-2,3 hydrogens of the ketone which forces the betaine-type intermediate to adopt a conformation from which hydride transfer rather than intramolecular displacement is the dominant reaction. When the reaction is stopped prior to completion, a metastable intermediate can be isolated which reacts with 7-ketonorbornene to produce spiro[norborn-2-en-*anti*-7,2′-oxacyclopropane] in addition to the other products. It is suggested that this reversibly formed insoluble intermediate is the betaine-type zwitterion derived from the addition of bis[7-(7-hydroxynorbornyl)-carbinyl]oxosulfonium methylide to 7-ketonorbornane.

In the course of a recent investigation into the reactivity of some unsaturated bicyclic ketones toward dimethyloxosulfonium methylide,[2] we examined the competitive reaction of equimolar quantities of 7-ketonorbornene (**1**) and 7-ketonorbornane (**3**) with a less than stoichiometric amount of ylide. Contrary to the individual behavior of **1**,[3] of dehydronorcamphor (**2**), and of norcamphor (**4**) with this ylide, the mixture

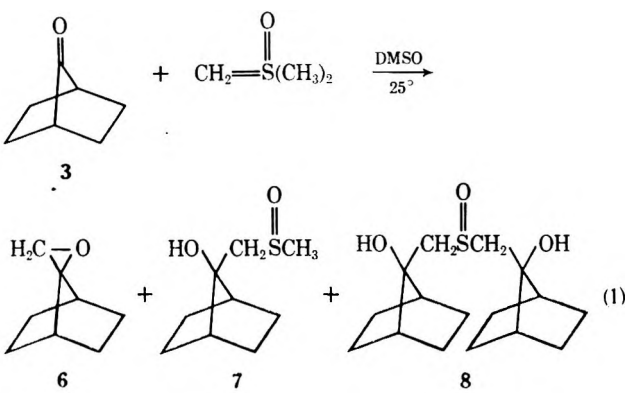


1 **2** **3** **4** **5** **6**

produced large amounts of a sulfur-containing solid. Although a high yield of spiro[norborn-2-en-*anti*-7,2′-oxacyclopropane] (**5**) was also obtained, very little spiro[norbornane-7,2′-oxacyclopropane] (**6**) was formed and almost no unreacted **3** could be recovered. With the expectation that it could provide a better insight into some aspects of ketone–ylide reactions which are not yet fully understood,[4] we undertook a more thorough investigation of the anomalous behavior of 7-ketonorbornane (**3**) toward dimethyloxosulfonium methylide. The results of this study are reported here.

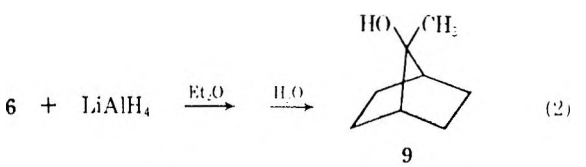
Results

The reaction of 7-ketonorbornane (**3**) with dimethyloxosulfonium methylide in dimethyl sulfoxide (DMSO) at 25° ultimately produces spiro[norbornan-7,2′-oxacyclopropane] (**6**), methyl 7-(7-hydroxynorbornyl)-carbinyl sulfoxide (**7**), and bis[7-(7-hydroxynorbornyl)-carbinyl] sulfoxide (**8**), *e.g.*, eq 1.



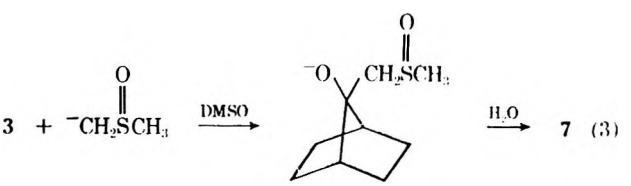
3 **6** **7** **8** (1)

The structure of the epoxide, **6**, was established by reduction with lithium aluminum hydride to the known 7-methyl-7-hydroxynorbornane (**9**, eq 2).[3] That of



9 (2)

7 follows from the fact that it can also be prepared from **3** and methylsulfinyl carbanion (eq 3).[5]



(3)

The structure of **8** is suggested by spectral and analytical data. The infrared (ir) spectrum exhibits hydroxyl and sulfoxyl absorptions but no carbon–carbon double bond or carbonyl bands. The proton magnetic resonance (pmr) spectrum (Figure 1) shows a complex multiplet at δ 1.1–2.2 (relative area, 10), two singlets at 3.22 and 3.26 (relative area, 2), and a concentration-dependent singlet at ~3.5 (relative

(1) Portions of this work have been presented at the 40th Annual Meeting of the South Carolina Academy of Science, Greenville, S. C., April 1967 [*Bull. S. Carolina Acad. Sci.*, **29**, 51 (1967)], and at the 19th Southeastern Regional Meeting of the American Chemical Society, Atlanta, Ga., Nov 1967, Abstract 236.

(2) R. S. Bly, C. M. DuBose, Jr., and G. B. Konizer, *J. Org. Chem.*, **33**, 2188 (1968).

(3) R. K. Bly and R. S. Bly, *ibid.*, **28**, 3165 (1963).

(4) *Cf.* E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **87**, 1353 (1965).

(5) E. J. Corey and M. Chaykovsky, *ibid.*, **87**, 1345 (1965).

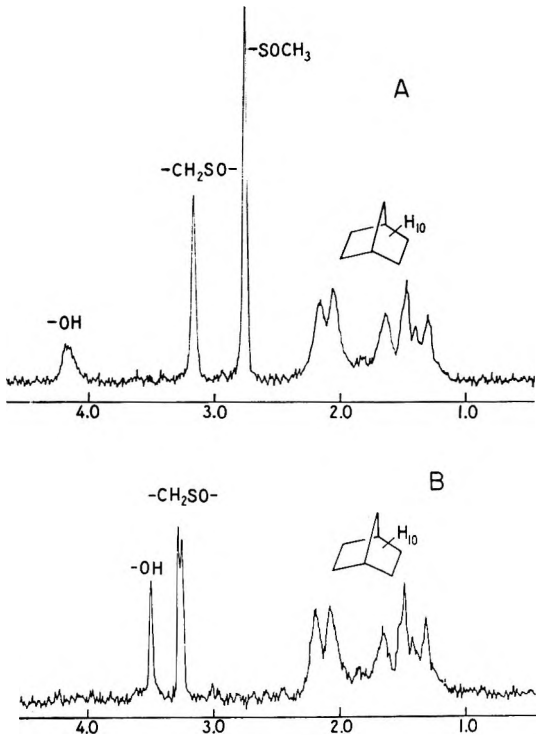
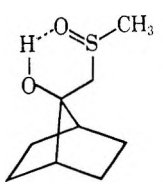


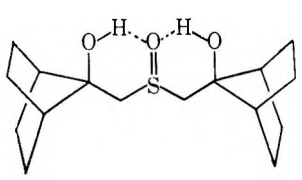
Figure 1.—The 60-MHz pmr spectra of (A) methyl 7-(7-hydroxynorbornyl)carbinyl sulfoxide and (B) bis[7-(7-hydroxynorbornyl)carbinyl] sulfoxide determined in deuteriochloroform and reported in parts per million with tetramethylsilane (δ 0.00) as internal standard.

area, 1). The high-field multiplet is essentially superimposable on the corresponding region in the spectrum of **7** and exhibits the characteristic splitting pattern of the ten hydrogens on a 7,7-disubstituted norbornyl skeleton. The singlets at δ 3.22 and 3.26 can be assigned to the nonequivalent methylene hydrogens adjacent to a sulfoxyl group[6] and the singlet at 3.5 to a hydroxyl proton. Since the elemental analysis corresponds to an empirical formula of $C_{16}H_{26}O_3S$, each molecule must contain two magnetically equivalent structural units of this type (*cf.* Figure 1). Hence **8** is clearly bis[7-(7-hydroxynorbornyl)carbinyl] sulfoxide.

The hydroxyl hydrogens of both **7** and **8** form strong



7



8

intramolecular hydrogen bonds with the sulfoxyl oxygen. In a 0.005 *M* solution in carbon tetrachloride, the O–H stretch of **7** appears as a single sharp absorption at 3430 cm^{-1}. The spectrum of **8** exhibits a strong, bonded-hydroxyl peak at 3440 cm^{-1} and a much weaker nonbonded one at 3620 cm^{-1}.[7]

The relative amounts of **6**, **7**, and **8** produced are dependent upon the time of reaction and upon the mole ratio of 7-ketonorbornane (**3**) to dimethyloxosulfonium methylide, ketone/ylide (K/Y). Product analyses from a series of experiments in which these factors were varied are summarized in Table I. Since

TABLE I

PRODUCTS OF THE REACTION OF 7-KETONORBORNANE (**3**) WITH DIMETHYLOXOSULFONIUM METHYLIDE

Run no.	Mole ratio of ketone/ylide	Reaction time, hr	Weight, mg (yield, %) 6	7	8	3	10
1	0.92	1	296 (52)	78 (9)	48 (7)	0	0
2	0.92	27	272 (48)	65 (7)	39 (6)	0	0
3[a]	0.92	1	305 (54)	100 (11)	29 (4)	0	0
4	1.84	1	142 (25)	48 (5)	55 (8)	0	212[b]
5	1.84	24	209 (37)	75 (9)	170 (35)	10 (~2)	Trace
6	2.80	1	82 (9)	25 (2)	83 (8)	5 (~1)	644[b]

[a] Ketone was added over a 10-min period. [b] Probably contains a small amount of **8**.

the isolated product balance in each of these heterogeneous reactions is at best ~70%, the data do not permit an evaluation of such factors as a change in the rate of stirring or addition of ketone, a variation in concentration of the reactants, or small differences in temperature. However, certain general trends appear to be significant.

The optimum yield of epoxide **6** is obtained when approximately equimolar amounts of ketone and ylide are used (K/Y = 0.92). An increase in K/Y results in a decrease in the relative amount of **6**, an increase of **8**, and no significant change in the amount of **7**.

Increasing K/Y also has the effect of retarding the rate of appearance of the three final products. When K/Y = 0.92, the over-all yield of **6**, **7**, and **8** after 1 hr is 69%. The yield under these conditions decreases slightly at longer reaction times, perhaps because of further side reactions between the products and the excess ylide. When K/Y = 1.84 the over-all yield of **6**, **7**, and **8** after 1 hr drops to 38%, when K/Y = 2.80, to 9% (*cf.* runs 1, 4, and 6, Table I). These decreases in **6**, **7**, and **8** are accompanied by the appearance of a new material, **10**, which precipitates from the reaction mixture together with **8** when water is added. This new material is apparently an intermediate in the overall reaction, for with increasing reaction times less **10** and more of **6**, **7**, and **8** can be isolated. For example, when the reaction where K/Y = 1.84 is allowed to proceed for 24 hr, instead of being stopped after 1 hr, the total yield of **6**, **7**, and **8** increases to 71% and no **10** is obtained.

We have as yet been unable to isolate the intermediate **10** in sufficiently pure form to allow a rigorous structure proof. While the solid can be stored at −20° for several days it decomposes readily when heated either dry or as a heterogeneous mixture in an organic solvent. The material is too insoluble in cold water or in organic solvents to permit the determination of a meaningful nmr spectrum. Its ir spectrum (KBr) has strong hydroxyl and sulfoxyl bands but shows only a weak and very broad absorption in the carbonyl region (~1800 cm^{-1}). An elemental analysis, performed on the crude material, indicates that more than two 7-ketonorbornane moieties are associated with each sulfoxyl unit. Since the ir spectra of samples obtained from reactions with differing ketone to ylide ratios show only minor dif-

(6) K. Mislow, M. M. Green, P. Laur, J. T. Melillo, T. Simmons, and A. L. Ternay, Jr., *J. Amer. Chem. Soc.*, **87**, 1958 (1967).
(7) L. P. Kuhn, *ibid.*, **74**, 2492 (1952).

ferences, it appears that **10** consists largely of a single compound, but we cannot rule out the possibility of one or more minor contaminants. Possible structures for this intermediate are considered in the Discussion.

In order to establish the nature of its decomposition product(s), a sample of **10** was suspended in benzene and heated at the boiling point for 3 hr (eq 4). The volatile products were sublimed and analyzed by gas–liquid partition chromatography (glpc). The sublimate constituted ~50 wt % of the recovered products and consisted of the epoxide **6** and the starting ketone, **3** (mole ratio, 0.9:1.0). An nmr analysis of the nonvolatile products confirmed the presence of the two sulfoxides **7** and **8** (mole ratio, 2:1). Both the volatile and the nonvolatile fractions contained traces of DMSO which may have been a contaminant in the starting material.

$$10 \xrightarrow[\text{benzene}]{80^\circ} 3 + 6 + 7 + 8 + \text{DMSO (?)} \qquad (4)$$

The proportion of products produced during the decomposition of **10** is apparently dependent upon the temperature and/or reaction time for, when a suspension of the intermediate in DMSO is stirred for 6 days at room temperature, **6** and **3** are produced in a mole ratio of 1.8:1.0 while **7** and **8** are formed in the ratio of 1.3:1.0.

Additional products are produced when the decomposition is accomplished by stirring a suspension of **10** for 6 days at room temperature, in a DMSO solution containing two molecular equivalents of the more reactive[8] ketone **1** (eq 5). A glpc and spectral analysis

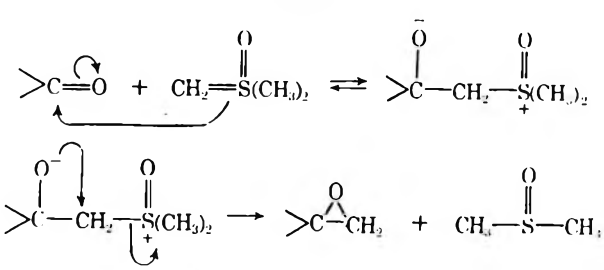
$$10 + 1 \xrightarrow[\text{DMSO}]{25^\circ} 3 + 5 + 6 + 7 + 8 \qquad (5)$$

of the volatile components reveals the presence of the unsaturated oxide, **5**,[3] as well as **6** and **3** (mole ratio, 1.7:1.0:4.0) and some unreacted **1**. An nmr analysis of the nonvolatile components again demonstrates the presence of both **7** and **8** (mole ratio, 1.0:1.5) as well as a trace of one or more unsaturated materials.

Discussion

The reaction of a ketone with dimethyloxosulfonium methylide is usually thought of as a two-step reaction:[9] a nucleophilic attack by the ylide on the carbonyl carbon to give an intermediate betaine-type zwitterion followed by the intramolecular nucleophilic displacement of dimethyl sulfoxide to produce the epoxide (Scheme I). The first step is frequently considered reversible and rate limiting since this has been demonstrated in the case of group V ylides,[10] the latter step irreversible and rapid since epoxides are normally stable in DMSO. In fact, however, there appears to have been no conclusive demonstration that a betaine-type zwitterion is actually an intermediate in the reaction of an oxosulfonium ylide much less that its formation is reversible.[4]

SCHEME I



Clearly the reaction of dimethyloxosulfonium methylide with 7-ketonorbornene (**3**) represents a case which cannot be fully explained on the basis of Scheme I. While such a reaction path could still account for the formation of the observed oxide **6**, a different process is necessary to explain the formation of the sulfoxides **7** and **8**. It is unlikely that this process involves an alkylsulfinyl carbanion, $RSOCH_2^-$, for such intermediates are appreciably more basic than oxosulfonium ylides,[5,11,12] or betaines and appear to be formed in significant concentration only at a considerably higher temperature[5] than is required for the transformations which we observe.

We believe the reaction of dimethyloxosulfonium methylide with 7-ketonorbornane (**3**) to proceed as outlined in Scheme II. In essence the proposal is that the initially formed zwitterion **11**, though fairly stable, is hampered from attaining the preferred *trans* coplanar conformation for intramolecular displacement of DMSO by steric crowding between the *exo*-2,3 hydrogens of the norbornane ring and the sulfoxyl methyl groups and in order to minimize such steric interactions adopts instead the cyclohexanelike conformation shown. In this conformation 1,5-hydrogen transfer to produce the new ylide **12** becomes the dominant reaction. Once formed, **12** may add another molecule of ketone to produce a second betaine-type intermediate, **13**, which is then either converted into methyl 7-(7-hydroxynorbornyl)carbinyl sulfoxide (**7**) and the epoxide **6** by an intramolecular nucleophilic displacement or undergoes another 1,5-hydrogen shift to produce a third ylide, **14**. Attack by a third molecule of ketone then yields the intermediate **15** which decomposes to bis[7-(7-hydroxynorbornyl)carbinyl] sulfoxide (**8**) and another molecule of epoxide **6**.

Though as far as we are aware intramolecular proton transfers from carbon to oxygen to re-form an ylide have not previously been observed in oxosulfonium ylide reactions, the acidic nature of the methyl hydrogens in trimethyloxosulfonium salts has been demonstrated by deuterium-exchange studies[12] and such shifts are known to occur in other cases.[13]

The effects produced by varying the ratio of ketone to ylide are in accord with the reaction sequence proposed in Scheme II. Since each intramolecular displacement would produce equimolar amounts of sulfoxide and saturated epoxide, at least half of the ultimate products of the over-all reaction should consist of epoxide **6**. Within the experimental limitation of our inability to determine the amount of dimethyl sulfoxide formed, this appears to be so. As more ketone is

(8) *Cf.* footnote 11, ref 2.

(9) (a) A. W. Johnson, "Ylid Chemistry," Academic Press, New York, N. Y., 1966, Chapter 9; (b) H. König, *Fortschr. Chem. Forsch.*, **9**, 487 (1967).

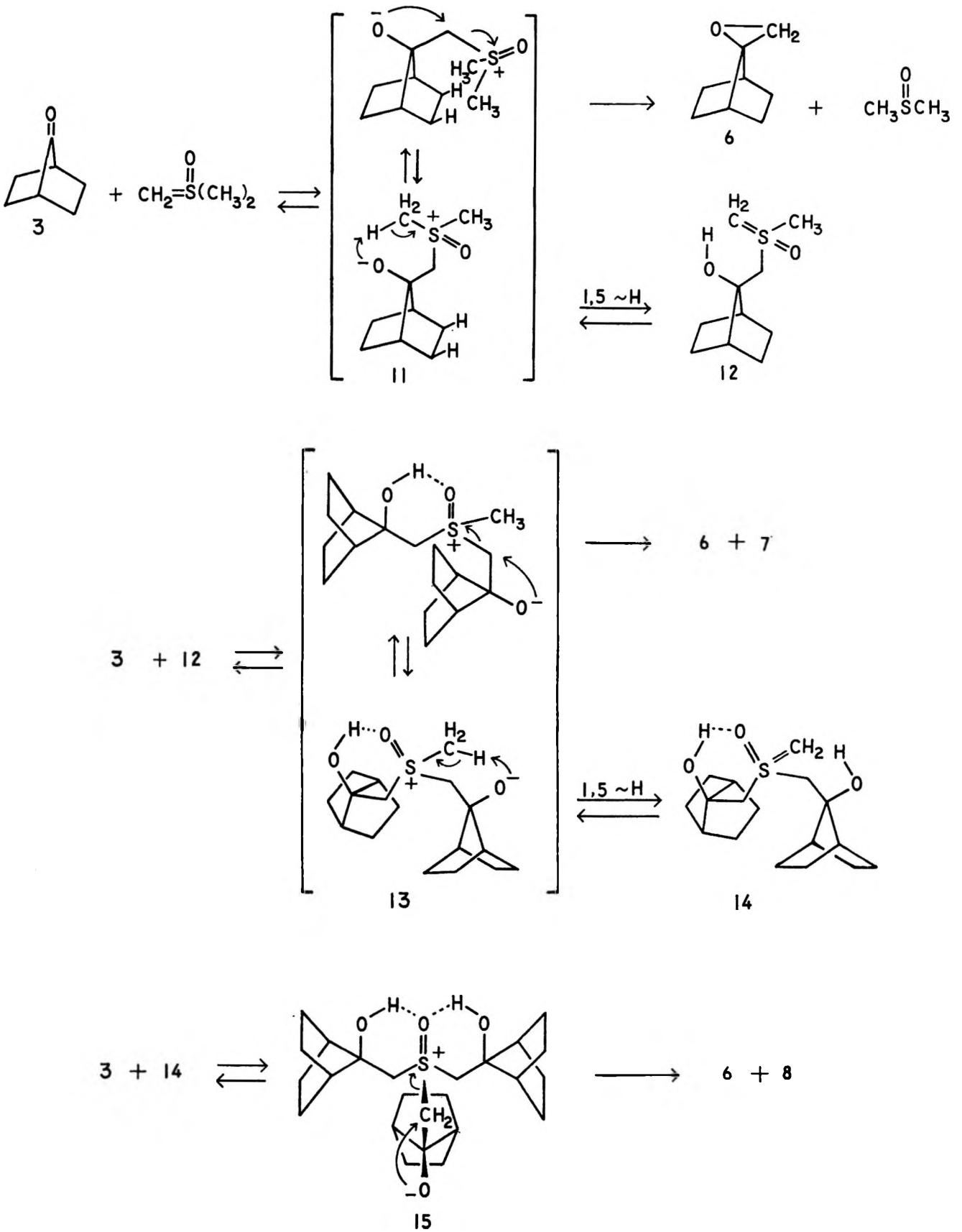
(10) (a) A. Maercker, *Org. Reactions*, **14**, 305 (1965), and references cited therein; (b) see also Chapters 7 and 8, ref 9a.

(11) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **84**, 867 (1962).

(12) (a) W. von E. Doering and A. K. Hoffman, *ibid.*, **77**, 521 (1955); (b) S. G. Smith and S. Winstein, *Tetrahedron*, **3**, 317 (1958).

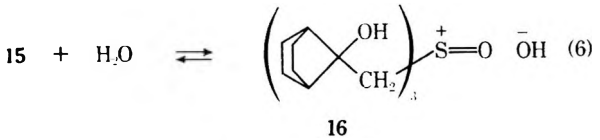
(13) (a) A. G. Hartmann, *J. Amer. Chem. Soc.*, **87**, 4972 (1965); (b) A. W. Johnson and R. B. LaCount, *ibid.*, **83**, 417 (1961).

SCHEME II



allowed to react with a given amount of ylide, a larger fraction of the total products are formed from the most sterically crowded trisubstituted zwitterion **15**, and both the over-all rate and the ratio of **7** to **8** in the products (*cf.* Table I) are decreased.

In view of the fact that it seems to contain three norbornyl units per sulfur atom, it is likely that the insoluble metastable intermediate, **10**, is either the zwitterion **15** or perhaps tris[7-(7-hydroxylnorbornyl)-carbinyl]oxosulfonium hydroxide (**16**), produced from



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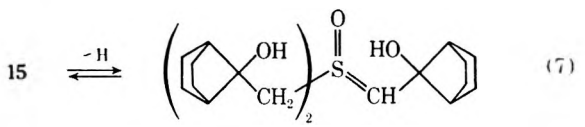
15 upon the addition of water, *viz.*, eq 6. The ylide 17, which might be formed from 15 by a further proton shift, appears to be a less likely alternative since no

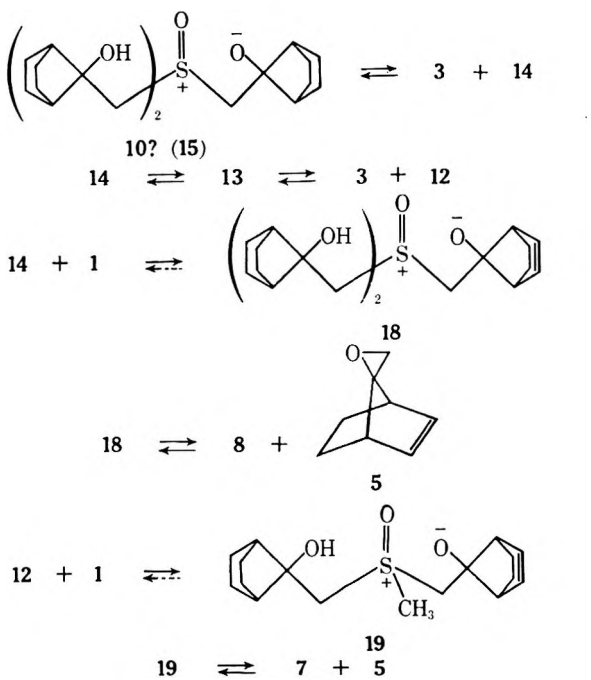


17

products which might have resulted from the further reaction of such an ylide with more ketone have been observed.

The thermal dissociation of 10 in the absence of excess ketone to regenerate 3 in addition to appreciable amounts of 6, 7, and 8, clearly indicates that the ketone–ylide addition steps can be reversed. That they are in fact reversible under the reaction conditions is established by the observation that the addition of the more reactive 7-ketonorbornene (1) to a suspension of 10 in DMSO produces large amounts of the unsaturated epoxide, 5, as well as the saturated ketone, 3. The probable route for the formation of 5 from the reaction of 10 and 1 is shown in Scheme III. The

SCHEME III



greater amount of 8 relative to 7 which is observed in the products of the decomposition indicates that 18 is the more important product-forming intermediate in this case. This observation and the absence of appreciable amounts of unsaturated sulfoxides support our earlier suggestion that both the initial addition of ylide and subsequent displacement of sulfoxide are facilitated by the double bond of 1.[2]

Among the ketones whose reactions with dimethyloxosulfonium methylide have been studied, 7-ketonorbornane (3) is unique. Its strain-induced bias for nucleophilic addition[3] and the steric effect of its *exo* hydrogens combine to render it an ideal substrate with which to demonstrate and study the reversible formation of zwitterionic intermediates.

Experimental Section[14]

The Preparation of Methyl 7-(7-Hydroxynorbornyl)carbinyl Sulfoxide (7).—A mixture of 0.122 g (5.1 mmol) of sodium hydride (0.225 g of a 54% suspension in mineral oil) and 10 ml of DMSO was heated with stirring under a nitrogen atmosphere at 65–70° until no more hydrogen was evolved. The mixture was cooled to room temperature and a solution of 0.505 g (4.6 mmol) of 7-ketonorbornane (3) in 5 ml of DMSO was added. Stirring was continued for 1 hr after which the reaction mixture was poured into 30 ml of water. The aqueous solution was washed with pentane and extracted with five ~15-ml portions of chloroform. The chloroform extract was washed with saturated sodium chloride, dried (Na_2SO_4), and distilled at atmospheric pressure. The residue was washed with a small amount of pentane and filtered to give 708 mg (75.3%) of crude product. Recrystallization from pentane gave 463 mg of pure 7: mp 111.5–112.5°; ir (KBr) 3380 (O—H), 1040, 1050 (C—O), 1015 cm^{-1} (S=O); nmr (*cf.* Figure 1A) ($CDCl_3$) δ 4.0 (s, concentration dependent, 1 OH), 3.13 (s, 2 >CCH_2SO–), 2.73 (s, 3 –$SOCH_3$), 2.2–1.1 (m, 10 >CH + >CH_2).

Anal. Calcd for $C_9H_{16}O_2S$: C, 57.41; H, 8.57; S, 17.03. Found: C, 57.44; H, 8.53; S, 17.31.

The Reaction of 7-Ketonorbornane with Dimethyloxosulfonium Methylide. A. Isolation and Identification of Products.—Trimethyloxosulfonium iodide (2.20 g, 10.0 mmol) was added in one portion to a nitrogen-blanketed suspension of 0.243 g (10.1 mmol) of sodium hydride (0.450 g of a 54% suspension in mineral oil) in 10 ml of DMSO. The mixture was stirred at room temperature until no more hydrogen was evolved. A solution of 1.10 g (10.0 mmol) of 7-ketonorbornane (3) in 15 ml of DMSO was added during ~10 min. The reaction mixture was stirred for 1 hr, poured into 40 ml of ice–water, and extracted with five 25-ml portions of pentane (fraction 1). A white solid remained suspended in both the aqueous layer and the pentane extract. Filtration of both layers gave a total of 0.188 g of insoluble product (fraction 2). The aqueous solution was extracted with five 25-ml portions of chloroform (fraction 3).

Fraction 1 was washed with 10 ml of saturated sodium chloride, dried (Na_2SO_4), and concentrated to ~1 ml. Sublimation of the residue at 70° (20 mm) gave 0.655 g of spiro[norbornan-7,2′-oxacyclopropane] (6): ir (CCl_4) 3040, 1245, 900, 835 cm^{-1}; nmr (CCl_4) δ 2.77 (s, 2 >$\overline{CCH_2O}$), 2.2–1.1 (m, 10 >CH + >CH_2).

Anal. Calcd for $C_8H_{12}O$: C, 77.37; H, 9.74. Found: C, 77.01; H, 9.93.

The structure assignment of 6 was confirmed by reduction with lithium aluminum hydride to give 7-methyl-7-hydroxynorbornane (9).[3]

Fraction 2 was recrystallized from chloroform to give 95 mg of a white solid: mp 211–212°; ir (KBr) 3420, 3330 (OH stretch, bonded), 1307, 1302 (OH, bending), 1059 (CO), 1005 (S=O), 1110, 1080, 1035 cm^{-1}; nmr (*cf.* Figure 1B) ($CDCl_3$) δ 3.5 (s, concentration dependent, 2 OH), 3.26 (s, 2 >CCHHSO–), 3.22 (s, 2 >CCHHSO–), 2.2–1.1 (m, 20 >CH + >CH_2).

Anal. Calcd for $C_{16}H_{26}O_3S$: C, 64.39; H, 8.78; S, 10.74. Found: C, 64.42; H, 8.75; S, 10.95.

We have assigned the structure 8, bis[7-(7-hydroxynorbornyl)-carbinyl] sulfoxide, to this compound on the basis of these spectral and analytical data.

(14) Melting points are uncorrected. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. The ir spectra were determined on a Perkin-Elmer grating spectrophotometer, Model 337, except for the high-dilution spectra which were run on a Perkin-Elmer Model 521 using 1-cm quartz cells. The nmr spectra were determined on a Varian A-60 spectrophotometer. The glpc analyses are corrected for differences in thermal conductivity of the components and were run on an F & M Model 500 gas chromatograph using a 10 ft × 0.25 in. column packed with 20% of a 2:1 mixture of Quadrol and SAIB[2] on 60–80 mesh, nonacid-washed Chromosorb P.

When **8** was recrystallized from acetone–water, it precipitated as a monohydrate: ir (KBr) ~3370 (very broad), 3450 (sh), 3280 (sh) (OH, bonded), 1322, 1305 (OH bending), 1032 (CO?), 975 (S=O), 1087, 1129 cm^{-1}; the nmr, except for a more intense OH resonance, is identical with that of the anhydrous product.

Anal. Calcd for $C_{16}H_{26}O_3S \cdot H_2O$: C, 60.73; H, 8.92; S, 10.13. Found: C, 60.64; H, 8.96; S, 10.11.

Anhydrous **8** could be regenerated by heating of the monohydrate at 70° (1 mm) overnight or by recrystallizing it from chloroform.

The composition of this fraction was found to be dependent upon the reaction time as well as the ratio of starting ketone to ylide. When the reaction was allowed to proceed for several hours or when the K/Y ratio was low, fraction 2 consisted almost entirely of **8** or its monohydrate. However, when short reaction times and high K/Y ratios were employed only traces of **8** could be detected by ir. Instead large amounts of a new material (**10**) were isolated: ir (KBr) 3400 (broad, OH stretching, bonded), 1498, 1475, 1400, 1380, 1310, 1200, 1181, 1165, 1141, 1130, 1109, 1082, 1045, 1025 cm^{-1}. This product is almost totally insoluble in cold water, aqueous acid or base, acetone, chloroform, or benzene. It undergoes extensive decomposition when allowed to stand at room temperature or when heated with benzene or chloroform (*vide infra*). An analytical sample[15] was prepared by washing the crude product with chloroform and drying it at room temperature (1 mm) for 1 hr.

Anal. Calcd for $C_{24}H_{38}O_4S$: C, 68.21; H, 9.06; S, 7.59. Found: C, 66.37; H, 9.09; S, 8.13.

Fraction 3 was washed with saturated sodium chloride, dried (Na_2SO_4), and evaporated under reduced pressure to give 0.270 g of a semisolid residue. Fractional recrystallization from chloroform–hexane gave two crystalline materials. The more-soluble product (34 mg, mp 111–113°) was identical with authentic **7**, *vide supra*, while the less soluble product (38 mg, mp 210–212°) was identical with **8**, isolated from fraction 2.

B. Dependence of Product Composition on Reaction Conditions.—Solutions containing 0.505 g (4.6 mmol) of 7-ketonorbornane (**3**) in 5 ml of DMSO were added rapidly with stirring to samples of differing amounts of dimethyloxosulfonium methylide in 5 ml of dimethyl sulfoxide. The mixtures were stirred at room temperature for 1–24 hr, each was poured into ~25 ml of ice–water, and the products separated into three fractions as described in part A.

Fraction 1 was analyzed by glpc on the Quadrol/SAIB column at 115°, the solvent was distilled at atmospheric pressure, and the residue was sublimed at 70° (20 mm). The yields of the epoxide **6** and recovered ketone **3** were estimated from the glpc analyses and from the weight of the sublimate. The results are summarized in Table I.

Fraction 2 was dried under vacuum at room temperature and the crude product was analyzed by ir.

Fraction 3 was dried at 100° (1 mm), weighed, dissolved in a measured volume of deuteriochloroform, and analyzed by nmr. The sulfoxides **7** and **8** constituted the major part of this fraction. Each sample also showed a sharp singlet of varying intensity at δ 2.65 which was presumably due to traces of DMSO. The nmr spectra of the crude mixtures suggested the presence of one or more other components. Runs 4 and 6 each showed a resonance at δ 4.9 which was absent in the spectra of the authentic **7** and **8**. In each sample the relative area of the δ 1.0–2.5 region was somewhat larger than that calculated for **7** and **8**. We estimate that the unidentified components constitute 10–30% of the total weight of fraction 3. The amounts of **7** and **8** in each sample can be estimated by comparing the peak areas at δ 3.13 and 3.25 (*i.e.*, the corresponding $>CCH_2SO-$ signals) with those of standard solutions of known concentration. The results are summarized in Table I. In the case of **8**, the values given represent the total product isolated from fractions 2 and 3.

The Reaction of the Metastable Intermediate (10) with 7-Ketonorbornene (1).—To a solution of 33 mg (0.31 mmol) of 7-ketonorbornene (**1**) in 2 ml of DMSO was added 66 mg (0.15 mmol) of **10** (from run 6; *cf.* Table I) and the mixture was stirred at room temperature. After ~2 days all of the solid had dissolved. Stirring was continued for an additional 4 days. The solution was poured into ~10 ml of cold water and extracted successively with five 3-ml portions of pentane and five 3-ml portions of chloroform. The pentane extract was concentrated to ~1 ml and analyzed by glpc on the Quadrol/SAIB column at 115°. Unreacted **1** constituted about half of the volatile components. The chromatogram showed three additional peaks with relative retention times (areas) of 1.0 (25%), 1.4 (15%), and 1.7 (60%). The products were collected from the Quadrol/SAIB column and identified from their ir spectra as **5**, **6**, and **3**, respectively.

The chloroform extract was washed with saturated sodium chloride, dried (Na_2SO_4), and evaporated under reduced pressure to give 27 mg of crystalline residue. An nmr analysis showed this fraction to consist of a mixture of **7** and **8** (mole ratio, 1.0:1.5).

The Decomposition of the Intermediate 10. A. In Benzene.—A mixture of 100 mg of **10** and 2 ml of benzene was heated under reflux for 3 hr, cooled, poured into 4 ml of pentane, and filtered to give 33 mg of crystalline product. An nmr analysis indicated the presence of **7** and **8** in a mole ratio of 1.7:1.0. The filtrate was analyzed by glpc on the Quadrol/SAIB column, concentrated under atmospheric pressure, and distilled in a short-path still [70° (20 mm)] to give 32 mg of a liquid composed of **6** (47%) and **3** (53%). The nmr spectrum of the residue showed a small amount of **7** (estimated ~4 mg) and a trace of DMSO.

B. In DMSO.—A suspension of 35 mg of **10** in 2 ml of DMSO was stirred at room temperature for 6 days. The mixture was worked up in the usual manner and analyzed by glpc and nmr. The volatile pentane-soluble products consisted of **6** (65%) and **3** (35%). The nonvolatile chloroform-soluble products were composed of **7** and **8** (mole ratio 1.3:1.0) and of unidentified product(s) (30%).

Registry No.—Dimethyloxosulfonium methylide, 14407-16-0; **3**, 10218-02-7; **6**, 159-42-2; **7**, 18592-72-8; **8**, 18592-73-9.

Acknowledgment.—Several of the careful though apparently conflicting observations on which this work is based were made by Mr. F. Bartow Culp, Jr., and Mr. George B. Konizer. It is a pleasure to acknowledge their assistance and that of the Petroleum Research Fund of the American Chemical Society for their generous financial support of this problem since its inception, Grant No. 911-A4.

(15) In addition to **10** the sample probably contains some **8** and may be contaminated with a trace of DMSO.

The Nuclear Magnetic Resonance Spectra of Some 1-Alkyl-2-phenyl-3-aroylazetidines and Related Compounds. Dispersion Effects and Conformational Analysis[1a]

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Received April 26, 1968

Chemical shifts and coupling constants for geminal and vicinal protons of the azetidine ring have been determined for several *cis*-1-alkyl-2-phenyl-3-aroylazetidines (IVa–f). Similarly, the chemical shifts of azetidine ring protons at C-2 and C-4 have been determined for the corresponding *trans*-3-deuterioazetidines (V′a–f). The geminal coupling, $J_{a'b'}$, from the spectra of V′ and the vicinal coupling, $J_{c'd'}$, from the spectra of V were also determined. The observed trend in the chemical shifts is rationalized in terms of a large contribution from intramolecular van der Waals dispersion effects. On the basis of the nmr spectral data of IVa–f, we suggest that the conformation of the azetidine ring is a function of the steric requirement of the N-alkyl substituent, and that the azetidines bearing the smaller N substituents are puckered to a greater extent. Even in the open-chain compounds, 2-[α-(N-triethylcarbinylamino)benzyl]-4′-phenylacrylophenone (IIIa) and the *t*-butylamino analog (IIIb), deshielding due to van der Waals interactions is apparently important. The preparations and characterizations of 12 new azetidines are described.

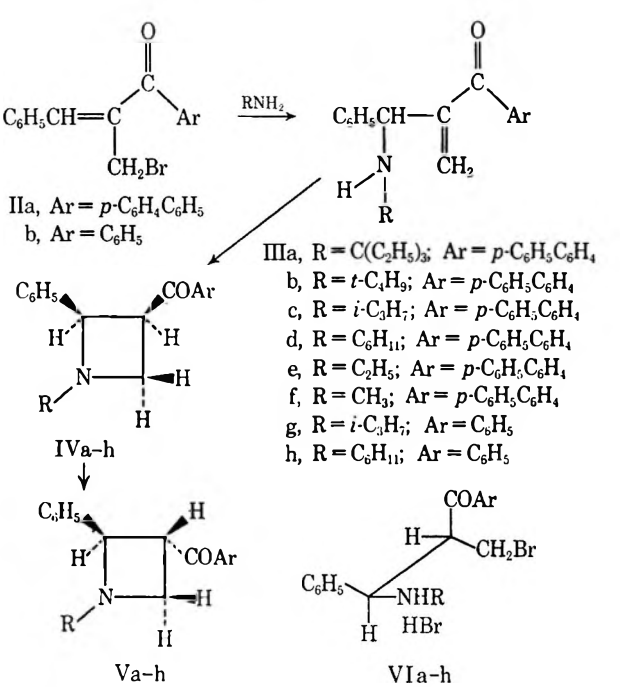
In previous communications[2] we reported on the synthesis, epimerization, and configurational assignment of several N-*t*-butylazetidines. The magnitude of vicinal proton–proton couplings was then used as an aid in configurational assignment along with infrared (ir), ultraviolet (uv), and chemical data. More recently, additional support for the original assignments was obtained through mass spectral studies.[3] As a continuation of our studies we have examined the effect of the nature of the N-alkyl substituent on the course of these cyclizations leading to various N-substituted azetidinyl ketones. Therefore, a large number of these compounds have been prepared and their spectra determined.

We felt that a detailed analysis of the pmr spectra of these cyclic compounds would give some insight into the probable conformation of the four-membered ring. This has been attempted for *cis* compounds by comparison of various ring proton couplings and the relative magnitudes of intramolecular van der Waals dispersion effects exerted upon ring protons by large N-alkyl substituents.

Preparation of Materials.—The reaction of α-(bromomethyl)chalcones (IIa and b) with 2 equiv of primary amines gave [α-(N-alkylamino)benzyl]acrylophenones (IIIa–h) in high yield[4] (Scheme I). Much shorter reaction times were required for reactions involving the less bulky amines. Thus, the reaction of IIa with 2 equiv of triethylcarbinylamine at room temperature required at least 24 hr for completion, whereas the reaction of IIa with 2 equiv of ethylamine under identical conditions required only 1.5 hr. In each case, the reaction time and amine concentration were controlled to minimize rearrangement of the first formed 2-[α-(N-alkylamino)benzyl]acrylophenones (III).

The reaction of the 2-[α-(N-alkylamino)benzyl]-acrylophenones with hydrogen bromide gave α-phenyl-

SCHEME I



β-aroyl-γ-bromopropylamine hydrobromides of type VI which upon treatment with base produced the new *cis*-C-aroylazetidines (IVa and c and IVe–h) in good yield[2] (Scheme I). Thus, the cyclization of these γ-bromopropylamines appears to be general with respect to the N-alkyl group, although the yield of azetidine drops sharply as the steric requirement of the N-alkyl group is reduced (*i.e.*, isolated yields ranged from 92% when R is *t*-butyl to 38% when R is methyl). These results are consistent with the suggestion by Vaughan[5] that in a given series a bulky N substituent favors cyclization and increases the stability of the azetidine ring. In all cases studied very high stereoselectivity toward formation of the *cis*-3-aroylazetidine (IV) was observed. However, in several instances the nmr spectrum of the crude mixture was taken after the bulk of the *cis* compound had been removed by

(1) (a) Presented in part at the 155th National Meeting of the American Chemical Society, San Francisco, Calif., April 1968, Organic Chemistry Abstracts, p 72. (b) To whom inquiries should be addressed.

(2) (a) N. H. Cromwell and E. Doomes, *Tetrahedron Lett.*, 4037 (1966); (b) J.-L. Imbach, E. Doomes, R. P. Rebman, and N. H. Cromwell, *J. Org. Chem.*, **32**, 78 (1967).

(3) J.-L. Imbach, E. Doomes, N. H. Cromwell, H. E. Baumgarten, and R. G. Parker, *ibid.*, **32**, 3123 (1967).

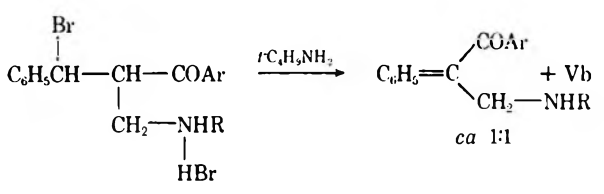
(4) See N. H. Cromwell and R. P. Rebman, *ibid.*, **32**, 3830 (1967), for previous paper.

(5) W. R. Vaughan, R. S. Klonowski, R. S. McElhinnery, and B. B. Millward, *ibid.*, **26**, 138 (1961).

crystallization and it indicated the presence of small amounts (<5%) of *trans* isomer, the origin of which was not determined with certainty. In view of the facile epimerization of the *cis* compounds, these small amounts of *trans* compounds might arise by epimerization of the former during crystallization.

The *cis*-1-alkyl-2-phenyl-3-aroylazetidines (IVa–h) were readily epimerized to the thermodynamically more stable *trans* isomers in high yield (>95%). Epimerization was achieved by warming *cis* compounds IV in methanol which contained a catalytic amount of sodium methoxide[2] or simply by refluxing IV in methanol without added catalyst for 14 hr. Thus, the steric requirement of the N-alkyl substituent seems to have little effect upon the position of the *cis–trans* equilibrium. Although reasonably stable in hydrocarbons, compound IVb partially isomerized when heated at 88–98° for 14 hr, whereas compound IVd was stable under these conditions. The isomerization of IVb in hydrocarbons and in methanol without added catalyst is probably induced by intermolecular catalysis due to the weakly basic azetidine ring nitrogen.

erythro-β-phenyl-β-N-*t*-butylamino-α-(bromomethyl)-4-phenylpropiophenone hydrobromide (VIb), from the addition of HBr to IIIb, was isolated and characterized. When VIb was allowed to react with an excess (>2 equiv) of *t*-butylamine in chloroform solution a quantitative yield of IVb was obtained, with no detectable amount of elimination product (IIIb). The isolation of VIb and its reaction with base were of considerable importance in connection with the mechanism of the reaction of primary alkylamines with the β-aroylallyl system (IIa and b) since under identical conditions β-aroylallylbromides (IIa and b) yielded only the corresponding β-aroylallylamines with no detectable amount of cyclic product.[4] This rules out the intermediacy of the free base of compounds such as VI for the latter type of reaction, implying that the reaction proceeds in one step. Although γ-bromopropylamine hydrobromide VIIb was not obtained in pure form, the fact that 2 equiv of hydrogen bromide/mol was generated when crude VIIb was treated with excess *t*-butylamine indicates, as was previously suggested,[2b] that there is indeed competition between cyclization and elimination. The products of the reaction were *trans*-azetidine Vb and α-(N-*t*-butylaminomethyl)-4′-phenylchalcone.[2a]

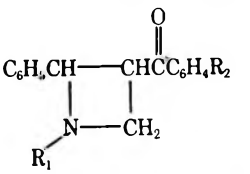


R = *t*-C_4H_9; Ar = *p*-$C_6H_5C_6H_4$

As was pointed out previously,[2] spectral methods may be employed in determining the gross structure and the configurations of these azetidinyl ketones. We have now studied a large number of isomeric aroylazetidines and have observed differences in the uv and ir spectra which parallel those previously found in studies involving isomeric pairs of substituted aroylaziridines.[6] Thus the *trans* isomers (V) (see Table I) show uv λ_{max} with increased molar extinction coefficients (ε) compared with those of the parent saturated ketones,[7] $C_6H_5CH_2CH_2COC_6H_4C_6H_4$-*p* and $C_6H_5CH_2CH_2COC_6H_5$. The *cis* isomers IV also show uv spectra with increased λ_{max} (nearly identical with the values for the *trans* isomer) but with ε values less than those of the parent ketones. The polarization effects in these structures are of a lower order than in the aziridines and a full theoretical treatment must await further studies. Nevertheless, these *cis*- and *trans*-arylaroylazetidines are readily distinguished from each other by careful comparison of the extinction coefficients of the aroyl bands resulting from the $\pi \rightarrow \pi^*$ transitions. The lowered extinction coefficient for the *cis* isomers IV results from steric crowding between the 2-phenyl and 3-aroyl groups causing carbonyl–aryl[8] (and possibly carbonyl four-ring[2a]) interactions to have a lower probability than in the parent ketones (and *trans* isomers V).

TABLE I

SUMMARY OF SPECTRAL DATA FOR



Compd	R_1	R_2	Confign	λ_{max}, mμ (ε × 10^{-3})	$\nu_{C=O}$, cm^{-1}
IVa	$(C_2H_5)_3C$	*p*-C_6H_5	*cis*	282 (23.1)	1683
Va	$(C_2H_5)_3C$	*p*-C_6H_5	*trans*	282 (26.8)	1680
IVb	*t*-C_4H_9[a]	*p*-C_6H_5	*cis*	282 (22.8)	1683
Vb	*t*-C_4H_9[a]	*p*-C_6H_5	*trans*	282 (26.2)	1680
IVc	C_6H_{11}[b]	*p*-C_6H_5	*cis*	282 (23.2)	1684
Vc	C_6H_{11}[b]	*p*-C_6H_5	*trans*	282 (26.1)	1680
IVd	*i*-C_3H_7	*p*-C_6H_5	*cis*	282 (23.0)	1683
Vd	*i*-C_3H_7	*p*-C_6H_5	*trans*	282 (26.3)	1680
IVe	C_2H_5	*p*-C_6H_5	*cis*	282 (22.7)	1683
Ve	C_2H_5	*p*-C_6H_5	*trans*	282 (26.1)	1680
IVf	CH_3	*p*-C_6H_5	*cis*	282 (22.7)	1685
Vf	CH_3	*p*-C_6H_5	*trans*	282 (26.2)	1680
IVg	*i*-C_3H_7	H	*cis*	240 (10.5)	1688
Vg	*i*-C_3H_7	H	*trans*	241 (15.4)	1682
IVh	C_6H_{11}	H	*cis*	240 (10.5)	1688
Vh	C_6H_{11}	H	*trans*	242 (15.0)	1682
IVi	*t*-C_4H_9[c]	H	*cis*	240 (10.9)	1688
Vi	*t*-C_4H_9[c]	H	*trans*	242 (15.5)	1680

[a] See ref 2a. [b] See ref 3. [c] See ref 2b.

The stretching vibrations of the carbonyl groups in both the *cis*- (IV) and *trans*-arylaroylazetidines (V) lead to ir absorption bands of lower frequency than those of the parent ketones. The *trans* isomers show lower frequencies than the *cis* compounds and thus again the effect of steric crowding is observed with the

(6) N. H. Cromwell, R. E. Bambury, and J. L. Adelfang, *J. Amer. Chem. Soc.*, **82**, 4241 (1960).

(7) See, for example, N. H. Cromwell and R. J. Mohrbacher, *ibid.*, **79**, 401 (1957); note that, for $C_6H_5CH_2CH_2COC_6H_4C_6H_4$-*p*, λ_{max} is 276 mμ (ε 25,100) and $\nu_{C=O}$ is 1690 cm^{-1}, and, for $C_6H_5CH_2CH_2COC_6H_5$, λ_{max} is 238 mμ (ε 12,400) and $\nu_{C=O}$ is 1694 cm^{-1}.[6]

(8) The intensity of the benzoyl band ($\pi \rightarrow \pi^*$) in the uv for α-substituted acetophenones decreases as the steric requirement of the α substituent is increased; see G. D Hedden and W. G. Brown, *ibid.*, **75**, 3744 (1953). On the other hand such substitution was found to shift the ir carbonyl bands to lower wave numbers; see J. L. Adelfang, P. H. Hess, and N. H. Cromwell, *J. Org. Chem.*, **26**, 1402 (1961).

latter. A full theoretical discussion of these mild ground-state effects must also await further experimental results.

Proton Magnetic Resonance Spectra.[9]—For each *cis* isomer (IVa–h) studied one ring proton appears upfield with respect to the remainder of the azetidine ring protons. The upfield proton (designated as H_a) for compounds IVa–e appears as either a triplet or a doublet of doublets depending upon the magnitude of couplings with H_b and H_c (see structure IV). However, for compound IVf, H_a appears as a triplet of doublets which collapsed into a well-defined triplet for IV'f (where H_d is replaced by deuterium). Thus, by a first-order graphical analysis it was found that H_a apparently couples with H_d through four σ bonds by 1.9 Hz. The proton at C-4 which is *trans* to the aroyl group would be expected to absorb at the highest field of the ring protons since the major deshielding experienced by this proton is due to the nearby nitrogen atom and the N-alkyl substituents. Thus, H_a is assigned as shown in structure IV.

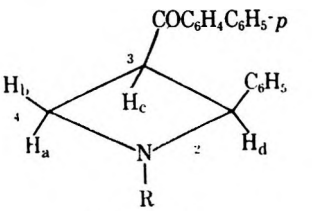
When H_d was replaced by deuterium, simple first-order AMX or ABX spectra resulted for ring protons which could be analyzed by the graphical method (structure IV'). From the coupling constants and chemical shifts obtained in this manner, a theoretical spectrum was calculated. The calculated and the observed spectra were in excellent agreement. In the spectra of 2-deuterioazetidines (IV'a–f) the downfield doublet for what would be H_d was absent and therefore confirmed the assignment of this proton. Thus, both the chemical shift of H_d and the spin–spin coupling constant (J_{cd}) were obtained from the spectra of IVa–f. The proton assignment at C-3 of the azetidine ring was based upon broadening of this resonance band due to the expected vicinal coupling of this proton with the deuterium atom at C-2 in IV'. Thus, H_c was assigned to the slightly broadened doublet of doublets. The proton at C-4 which is *cis* to the 3-aroyl group was assigned to the well-defined doublet of doublets which appeared immediately upfield from the slightly broaden multiplet due to H_c. A combination of the spectra of IV and IV' allows the assignment of resonance frequencies and the various coupling constants for ring protons (Tables II and III).

An additional interesting characteristic of the nmr spectra of the *cis*-2-phenyl-3-aroylazetidines is found in the aromatic region. In the spectrum of each *cis* isomer studied there is an upfield multiplet (with respect to the remainder of the aromatic protons) which corresponds to two (or three) protons. This upfield multiplet is almost identical for both the *p*-phenylbenzoyl and benzoyl compounds (although overlap is more severe in the spectra of the latter) suggesting that this multiplet is due to protons contained in the 2-phenyl group. The spectra of the *trans* isomers show only complex multiplets for the aromatic protons with no apparent separation. This difference in the aromatic region alone aids in differentiating isomers in this series of azetidines.

(9) The proton magnetic resonance (pmr) spectra were determined as *ca.* 15% deuteriochloroform solutions at 60 MHz and the chemical shifts are reported in hertz relative to internal tetramethylsilane (0.0 Hz). The pertinent coupling constants were determined on either 100- or 250-Hz sweep width. The sweep width was calibrated before and after each spectrum with a chloroform (437 Hz) in deuteriochloroform solution relative to tetramethylsilane (0.0 Hz) as internal standard.

TABLE II

CHEMICAL SHIFTS OF RING PROTONS OF SOME *cis*-1-ALKYL-2-PHENYL-3-AROYLAZETIDINES[a]



IV (H_d = D)

Compd	R	Hz: H_a	H_b	H_d	H_c
IVa	$(C_2H_5)_3C$	216	239	321	263
IVb	*t*-C_4H_9	201	237	297	256
IVc	*i*-C_3H_7	183	*ca.* 249	276	*ca.* 259
IVd	C_6H_{11}	184	251	278	263
IVe	C_2H_5	181	249	275	263
IVf	CH_3	182	249	272	263

[a] Chemical shifts of H_d were obtained from spectra of IVa–f and those of H_a, H_b, and H_c by analysis of the spectra IV'a–f. These chemical shifts are reproducible and accurate within ±1 Hz.

TABLE III

COUPLING CONSTANTS FOR RING PROTONS OF SOME *cis*-1-ALKYL-2-PHENYL-3-AROYLAZETIDINES[a]

Compd	Hz: $\lvert J_{ab}\rvert$[b]	J_{ac}[b]	J_{bc}[b]	J_{cd}[c]
IVa	6.8[a]	7.8	3.5	9.5
IVb	6.9	8.0	3.4	9.5
IVc	*ca.* 7	*ca.* 7	3.0	9.0
IVd	6.8	7.4	3.0	9.0
IVe	6.5	7.5	2.8	8.5
IVf	6.6	7.4	2.8	*ca.* 7.5

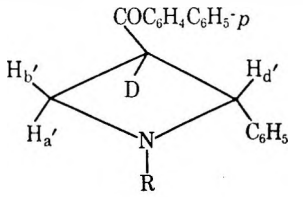
[a] These coupling constants are reproducible within ±0.2 Hz. [b] Obtained by analysis of the AMX or ABX spectra of IV'a–f. [c] Obtained from the spectra of IVa–f.

Since the spectra (for azetidine ring protons) of *trans* compounds were more complex and could not be reliably analyzed by the first-order graphical method, the spectra were not analyzed as explicitly for the proton–proton couplings as in the case of *cis* compounds. For each *trans* compound at least two coupling constants were determined, $J_{c'd'}$ and $J_{a'b'}$ (Table IV). However, the nmr spectra of *trans*-3-deuterioazetidines V'a–f were determined in order to obtain chemical shifts of ring protons $H_{a'}$, $H_{b'}$, and $H_{d'}$ (Table IV). In general, $H_{a'}$ and $H_{b'}$ appeared as an AB spectrum from which the chemical shifts of these protons and the geminal coupling ($J_{a'b'}$) were obtained by simple analysis. Resonance frequency assignments are based on arguments similar to those presented above for assignments in the *cis* compounds. $H_{a'}$ is assigned to the upfield doublet, $H_{b'}$ to the second doublet, and $H_{d'}$ to the singlet at lowest field of the azetidine ring protons. For *trans*-3-deuterio-N-*t*-butylazetidines $H_{a'}$ and $H_{b'}$ appear as a singlet,[2] the chemical shifts of these protons being equal. The nmr spectrum of *trans*-N-triethylcarbinylazetidine (V'a) again shows a pair of doublets for $H_{a'}$ and $H_{b'}$, but the reverse assignment is made; $H_{b'}$ is assigned to the upfield doublet for reasons given below.

The N-isopropyl methyl groups of azetidines IVc and g and Vc and g were magnetically nonequivalent, ap-

TABLE IV

CHEMICAL SHIFTS OF RING PROTONS OF SOME *trans*-2-PHENYL-3-DEUTERIO-3-AROYLAZETIDINES[a]



V'

V, D = H_c'

Compd	R	$H_{a'}$	$H_{b'}$	$H_{d'}$	Hz $\lvert J_{a'b'}\rvert$[b]	Hz $J_{c'd'}$[c]
V'a	$C(C_2H_5)_3$	231	214	303	6.0	5.2
V'b	*t*-C_4H_9	213	213	282		6.5
V'c	*i*-C_3H_7	191.5	226	264	6.8	7.0
V'd	C_6H_{11}	192	226	264.5	6.8	7.2
V'e	C_2H_5	193	230	262	6.5	7.3
V'f	CH_3	192.5	230.5	258	6.8	7.3

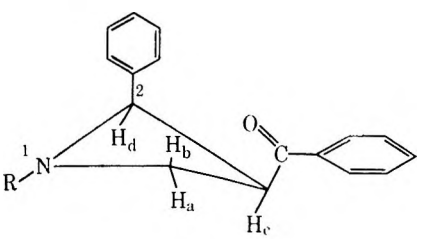
[a] These chemical shifts are reproducible and accurate within ±1 Hz and the coupling constants are reproducible and accurate within ±0.2 Hz. [b] From the AB spectra of V'a–f. [c] $J_{c'd'}$ of V (nondeuteriated).

pearing as two doublets. The degree of nonequivalence of the methyl groups in compound IVg was relatively independent of both temperature (in the range −45–50°) and solvent polarity, $\Delta\gamma$ for the methyl groups equaling 22 ± 2 Hz. The methylene protons of the N-ethyl group in Ve are magnetically nonequivalent, giving rise to a multiplet of at least 10 lines, whereas the analogous *cis* compound IVe shows a well-defined quartet for these protons.

In all isomeric pairs studied, except for N-methyl compounds (IVf and Vf), the *cis*-vicinal coupling (J_{cd}) is larger than the corresponding *trans*-vicinal coupling ($J_{c'd'}$). For compounds IVf and Vf, J_{cd} is equal to $J_{c'd'}$ within experimental error. Thus, the magnitude of proton–proton couplings alone is not sufficient grounds for configurational assignment of diastereoisomers in this type of compound.

Discussion of the Proton Magnetic Resonance Spectra.—The establishment of the configurations of these isomeric azetidines by chemical and other spectral methods allows several conclusions to be drawn from the nmr data.[10] As expected, this study shows that *cis*-vicinal couplings in this ring system are generally larger than corresponding *trans*-vicinal couplings. For example, $J_{ac} \simeq 7.5$ Hz $> J_{bc} = 2.8$–3.5 Hz for *cis* compounds IVa–f (Table III). Also, a comparison of J_{cd} and J_{ac} for these compounds illustrates the effect of substituent on the magnitude of these couplings. The increased coupling exhibited by *cis* protons across the C-2–C-3 bond when compared with *cis* proton coupling across the C-3–C-4 bond is probably a result of phenyl substitution for hydrogen at C-2 and/or a reflection of the dihedral angles between the protons involved. In substituted aziridines[10] and other related compounds,[11] the electronegativity of substituents have been shown to affect the magnitude of proton–proton couplings, and it seems reasonable the couplings in this system might be affected in a similar manner. However, the large differences in the size of some of these couplings might be best explained in terms of differences in dihedral angles which in turn would be indicative of the conformation of the azetidine ring. Dihedral angles for ring protons of *cis* structures were approximated from the values of the observed couplings.[12] The calculated values so obtained were compared with the dihedral angles obtained by inspection of Dreiding models for these compounds and good qualitative agreement was found.

Using the Karplus relationship,[13] the small values (2.8–3.5 Hz) for the *trans* couplings across the C-3–C-4 bond suggest dihedral angles on the order of 125–130° for the protons in question (H_b and H_c, A). The relatively large values for *cis* couplings (J_{cd} = 8.5–9.5 Hz) across the C-2–C-3 bond in compounds IVa–e suggest that H_c and H_d are fully eclipsed, or nearly so, and that staggering of the *cis*-phenyl and -aroyl groups is minimal. For N-methylazetidine (IVf) this same coupling is relatively small (J_{cd} = *ca.* 7.5 Hz), indicating that there is considerable staggering of H_d and H_c. The vicinal couplings along with the small geminal couplings ($\lvert J_{gem}\rvert \simeq 7$ Hz) are consistent with a nonplanar azetidine ring (A). However, the major contribution



A

to the magnitude of these geminal couplings is probably due to the overlap of the C–H bonds with the lone pair on the adjacent nitrogen atom.[14]

The fact that the apparent long-range coupling (J_{ad}) is 1.9 Hz for N-methylazetidine IVf, whereas this same coupling is less than 0.5 Hz for compounds IVa–e suggests that the four-membered ring of the former is more puckered than those of compounds containing the larger N-alkyl substituents. Since the apparent necessary geometrical requirement for long-range coupling[15] is that the protons in question form a "W" with the three carbon atoms involved (H_d–C-2–C-3–C-4–H_a) the above suggestion seems reasonable. The gradual decrease in the magnitude of the vicinal coupling (J_{cd}) as the steric requirement of the N-alkyl group is increased also supports this view (Table III). There is also an increase in the coupling $J_{c'd'}$ for *trans*-azetidines V when the steric requirement of the N-alkyl group is decreased. We suggest that as puckering of the four-ring is increased $H_{c'}$ and $H_{d'}$ become closer to *trans* pseudodiaxial and thus the increase in $J_{c'd'}$ is observed.

(10) Although the pmr data were used previously[2] in establishing configurations, the other data seems sufficient for this purpose.

(11) S. J. Brois and G. P. Beardsley, *Tetrahedron Lett.*, 5113 (1966).

(12) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959); *J. Amer. Chem. Soc.*, **85**, 2870 (1963).

(13) A. D. Cohen and T. Schaefer, *Mol. Phys.*, **10**, 209 (1966).

(14) See, for example, T. A. Crabb and R. F. Newton, *Chem. Ind.* (London), 339 (1966), and references cited therein.

(15) J. Meinwald and Y. C. Meinwald, *J. Amer. Chem. Soc.*, **85**, 2514 (1963).

This conformational variation in both V and IV can be rationalized in terms of greater 1,3 interactions in cases involving large substituents.

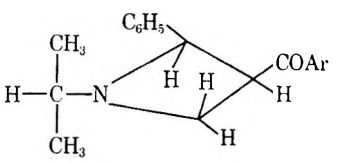
The chemical shifts of azetidine ring protons at C-2 and C-4 are sensitive functions of the steric requirement of the N-alkyl substituent, especially when the N-alkyl group is bulky.[16] Any shielding or deshielding exerted upon ring protons at C-2 and C-4 by the N-alkyl group as reflected in their chemical shifts is a combination of the anistropy of the C–C and C–H single bonds[17] and intramolecular van der Waals dispersion effects.[18] Depending upon the magnitude of each of these shielding effects a net shielding or a net deshielding might result. In the present investigation by varying the N-alkyl group it was found that N-triethylcarbinyl and N-*t*-butyl groups deshield ring protons (H_a and H_d, structure IV) by *ca.* 40 and *ca.* 18 Hz, respectively, with regard to smaller N-alkyl groups (Table II). The downfield shifts observed for H_a and H_d upon increasing the size of the N-alkyl substituent should be due primarily to the effect of this substituent since the aroyl and phenyl groups are situated on the opposite side of the azetidine ring. These results indicate that in the case of large N-alkyl groups increased deshielding resulting from intramolecular van der Waals interactions is much greater than the shielding which results from the anisotropy of the increased number of C–C and C–H single bonds when compared with smaller N-alkyl groups. However, the small observed differences in the chemical shifts in varying the N-alkyl group in the sequence, isopropyl to cyclohexyl to ethyl to methyl, indicate that the van der Waals contribution is, as expected, rather small.[16] For *trans* compounds V'a–f the situation is much more complex since $H_{b'}$ and $H_{d'}$ are *cis* to the aroyl group. Thus, the effect of the aroyl group on the chemical shifts of these protons obscures the effect of the N-alkyl substituent. The fact that opposite trends in the chemical shifts of $H_{d'}$ and $H_{b'}$ were observed, although both of these protons are *cis* to the aroyl group, suggests that the conformational orientation of the latter with respect to $H_{d'}$ is different from that with respect to $H_{b'}$.

The ring protons, H_d and H_a, are deshielded by 43 and 33 Hz, respectively, in going from an N-triethylcarbinyl to the less bulky N-isopropyl group. This difference in deshielding might reflect the relative conformational orientations of H_d and H_a with regard to the N-alkyl substituent. If H_d is pseudoaxial deshielding due to steric crowding might be expected to be greater for this proton than for the less axial H_a, in agreement with the experimental facts.

The increased shielding of the C-4 proton (H_b, IV), which is *cis* to the aroyl substituent, as the steric requirement of the N-alkyl substituent is increased, cannot be explained on the basis of intramolecular van der Waals dispersion effects and single-bond anisotropy alone and is probably a result of a large contribution from the ring-current effect of the phenyl portion of the aroyl group.[11] For example, H_b in N-*t*-butylazetidine IVb is shielded by *ca.* 13 Hz when compared with compounds bearing smaller N-alkyl substituents (Table II). Apparently, the deshielding due to the aroyl group offsets the effect of the N-alkyl substituent; otherwise an opposite trend in the chemical shift of Hb would be expected.

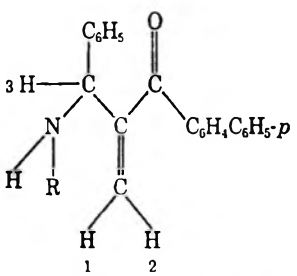
The upfield shift of two aromatic protons in the *cis* compounds is tentatively rationalized on the basis of intramolecular shielding of the *ortho* protons of the 2-phenyl group by the π cloud of the carbonyl function.

The large degree of magnetic nonequivalence of the N-isopropyl methyl groups of these N-isopropylazetidines (B) is apparently a result of the intrinsic molecular asymmetry of the relatively rigid system. A major portion of the nonequivalence is ascribed to the phenyl group at the C-2 asymmetric center.[19]



B

Deshielding due to van der Waals interactions is also prevalent in some acylic structures. The chemical shift of one of the vinyl protons of 2-[α-(N-alkylamino)-benzyl]acrylophenone derivative (C) is a function of the steric requirement of the N-alkyl group. Thus, H-1 for IIIa, IIIb, and IIIc appears at 388, 374, and 365 Hz, respectively, whereas the chemical shifts of H-2 and H-3 are relatively constant, appearing at 343 ± 2 and 306 ± 3 Hz, respectively. We suggest that H-1 is *cis* to the α-(N-alkylamino)benzyl group and its chemical shift is governed by van der Waals dispersion effects due to the steric requirements of the N-alkyl group.



IIIa, R = $C(C_2H_5)_3$
b, R = *t*-C_4H_9
c, R = *i*-C_3H_7

In a recent paper Goldberg and coworkers[20] reported some apparent anomalies in the nmr spectra of some N-neopentyl-N-methylamines and neopentylmethyl ether, the methylene protons appearing at higher field than the N- and O-methyl groups, respectively. In view of our findings and those of others,[16,18] these results can be rationalized in terms of van der Waals interactions of the *t*-butyl portion of the neopentyl group with the N-methyl or O-methyl groups which result in deshielding

(16) For a somewhat analogous result in aziridines, see S. J. Brois, *J. Amer. Chem. Soc.*, **87**, 4242 (1967); Abstracts of papers, the 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 1967, No. 0-72.

(17) J. W. Apsimon, W. G. Craig, P. V. DeMarco, D. W. Mathieson, L. Saunders, and W. B. Whally, *Tetrahedron*, **19**, 2339 (1967).

(18) For discussion of this deshielding mechanism, see A. D. Buckingham, T. Schaefer, and W. G. Schneider, *J. Chem. Phys.*, **32**, 1227 (1960); T. Schaefer, W. F. Reynolds, and T. Yonemoto, *Can. J. Chem.*, **41**, 2969 (1963); V. M. S. Gil and W. A. Gibbons, *Mol. Phys.*, **8**, 199 (1964).

(19) G. M. Whitesides, D. Holtz, and J. D. Roberts, *J. Amer. Chem. Soc.*, **86**, 2628 (1964).

(20) S. I. Goldberg, F.-L. Lam, and J. E. Davis, *J. Org. Chem.*, **32**, 1658 (1967).

of the latter. Owing to the spatial arrangement of the different groups in the molecules, interactions of this type with the methylene group are very unlikely as indicated by Dreiding models. Thus, the methyl groups are deshielded while the methylene groups are unaffected by the bulky *t*-butyl group and the reversal in chemical shift is observed.

Experimental Section[21]

α-Methyl-4′-phenylchalcone (I).—A 63-g (0.30 mol) sample of 4-phenyl-propiophenone[22] was suspended in 100 ml (an excess) of benzaldehyde and the mixture was saturated with dry hydrogen chloride until it turned dark brown. The solution became homogeneous and then solidified while kept at 0°. The tightly stoppered mixture was allowed to stand at room temperature for 48 hr. Excess hydrogen chloride and water were removed under reduced pressure at *ca.* 40°. Potassium carbonate (42 g, 0.30 mol), potassium acetate (30 g, 0.30 mol), and 800 ml of ethanol were added and the mixture was kept at reflux temperature for 96 hr. The hot solution was filtered to remove the precipitated inorganic salts, concentrated, and cooled to induce crystallization. Recrystallization and decolorization of the solid which resulted from ethanol yielded 70 g (78%) of white plates, mp 98–99° (lit.[2a] mp 99°).

2-Methyl-3-deuterio-3-phenyl-4′-phenylacrylophenone (I′).—Compound I′ was obtained when the above-described procedure was repeated using 1-deuteriobenzaldehyde[23] instead of benzaldehyde, mp 98–99°. The nmr spectra of I and I′ were identical except for the absence of the benzal proton in the spectrum of I′.

α-(Bromomethyl)-4′-phenylchalcone (IIa).—A 29.8-g (0.10 mol) sample of I was dissolved in 300 ml of carbon tetrachloride to which was added N-bromosuccinimide (18.0 g, 0.10 mol) and the mixture was heated to a gentle reflux. To the vigorously stirred refluxing mixture was added benzoyl peroxide (0.50 g, 0.002 mol) in 100 ml of the same solvent over a period of 1 hr. The reaction mixture was kept at reflux temperature with continuous stirring for an additional 3 hr. After the mixture was allowed to cool, the succinimide was removed by filtration and the solvent was removed under reduced pressure. The yellow oil which resulted was crystallized from 200 ml of a 2:1 ethyl ether–ethanol mixture. Recrystallization (decolorization with charcoal) of the yellow solid from ethyl ether yielded 29.6 g (79%) of slightly yellow crystals, mp 106–107° (lit.[2a] mp 107°).

2-[α-(N-Triethylcarbinylamino)benzyl]-4′-phenylacrylophenone (IIIa).—A 3.77-g (0.010 mol) sample of IIa and 2.30 g (0.020 mol) of triethylcarbinylamine[24] dissolved in 500 ml of *n*-hexane were allowed to react at room temperature for 30 hr. The usual work-up[4] gave 2.43 g (59%) of white crystals: mp 80–82° (methanol); ir $\nu_{C=O}$ at 1655 cm^{-1}; nmr peaks at *ca.* 445 (m, 14 H, aromatic protons), 388 and 341 (s, 1 H, each, vinyl protons), 303 (s, 1 H, benzyl proton), and *ca.* 79 and *ca.* 44 Hz (q and t, respectively, J = 7 Hz, 15 H, 3 CH_2CH_3).

Anal. Calcd for $C_{29}H_{33}NO$: C, 84.63; H, 8.08; N, 3.40. Found: C, 84.50; H, 7.97; N, 3.45.

2-[α-(N-t-Butylamino)benzyl]-4′-phenylacrylophenone (IIIb).—A 7.54-g (0.020 mol) sample of IIa was dissolved in 900 ml of *n*-hexane, *t*-butylamine (3.0 g, 0.041 mol) was added, and the mixture was allowed to react at room temperature for 24 hr. The usual work-up[4] yielded 6.21 g (84%) of white crystals, mp 89–90° (pentane) (lit.[2a] mp 90°).

2-[α-(N-Isopropylamino)benzyl]-4′-phenylacrylophenone (IIIc).—A 3.77-g (0.010 mol) sample of IIa and isopropylamine (1.2 g, 0.020 mol) dissolved in 500 ml of *n*-hexene were allowed to react at room temperature with stirring for 15 hr. The usual work-up[4] afforded 3.05 g (86%) of white crystals: mp 88–89° (petroleum ether, bp 60–69°); ir $\nu_{C=O}$ at 1655 cm^{-1}; nmr peaks at *ca.* 450 (m, 14 H, aromatic protons), 365 and 344 (s, 1 H each, vinyl protons), 305 (s, 1 H, benzyl proton), 169 (h, J = 6 Hz, 1 H, methine), 106 (s, 1 H, NH), and 66 Hz (d, 6 H, 2 CH_3).

Anal. Calcd for $C_{25}H_{25}NO$: C, 84.47; H, 7.39; N, 3.94. Found: C, 84.50; H, 7.21 N; 4.07.

2-[α-(N-Cyclohexylamino)benzyl]-4′-phenylacrylophenone (IIId).—A 3.77-g (0.010 mol) sample of IIa and cyclohexylamine (2.0 g, 0.020 mol) dissolved in 500 ml of *n*-hexane was allowed to react at room temperature for 15 hr. The usual work-up[4] yielded 2.73 g (69%) of white crystals, mp 90–91°.[25]

2-[α-(N-Ethylamino)benzyl]-4′-phenylacrylophenone (IIIe).—A 1.89-g (0.0050 mol) sample of IIa and ethylamine (*ca.* 0.65 ml, *ca.* 0.01 mol) was added and the mixture was allowed to react at room temperature for 1.5 hr. (The ethylamine was added *via* a pipet, while both were kept at 0°.) The usual work-up[4] yielded 1.23 g (72%) of white crystals: mp 63–64° (*n*-hexane); ir $\nu_{C=O}$ at 1656 cm^{-1}; nmr peaks at *ca.* 455 (m, 14 H, aromatic protons), 367 and 345 (s, 1 H each, vinyl protons), 299 (s, 1 H, benzyl proton), 158 (q, J = 7 Hz, 2 H, methylene protons), *ca.* 144 (s, 1 H, NH), and 67 Hz (t, J = 7 Hz, 3 H, CH_3).

Anal. Calcd for $C_{24}H_{23}NO$: C, 84.42; H, 6.79; N, 4.10. Found: C, 84.62; H, 6.72; N, 3.91.

2-[α-(N-Isopropylamino)benzyl]acrylophenone (IIIg).—A 3.01-g (0.010 mol) sample of α-(bromomethyl)chalcone (IIb)[4] and isopropylamine (1.20 g, 0.20 mol) were allowed to react at room temperature while being stirred magnetically for 15 hr. The usual work-up[4] afforded 2.19 g (78%) of flaky white crystals: mp 92–93° (*n*-hexane); ir $\nu_{C=O}$ at 1658 cm^{-1}; nmr peaks at *ca.* 455 (m, 10 H, aromatic protons), 364 and 343 (s, 1 H each, vinyl protons), 306 (s, 1 H, benzyl proton), 168 (h, 1 H, methine proton), *ca.* 128 (s, 1 H, NH), and 65 Hz (d, 6 H, CH_3).

Anal. Calcd for $C_{19}H_{21}NO$: C, 81.68; H, 7.58; N, 5.01. Found: C, 81.90; H, 7.59; N, 5.24.

2-[α-(N-Methylamino)benzyl]-3-bromo-4′-phenylpropiophenone Hydrobromide (VIf).—A 1.89-g (0.0050 mol) sample of IIa and *ca.* 0.5 ml (*ca.* 0.01 mol) of methylamine (added *via* a Dry Ice–acetone trap) were allowed to react at room temperature while being stirred magnetically for 0.5 hr. The solution was filtered to remove the precipitated methylamine hydrobromide and the filtrate was subjected to reduced pressure to remove any unreacted methylamine. The clear *n*-hexane solution was then subjected to a stream of dry hydrogen bromide for 0.25 hr while the mixture was stirred magnetically. Stirring was continued for 0.5 hr and then the solution was filtered to remove the slightly yellow solid which separated. Recrystallization of this material from a methanol–ethyl ether mixture yielded 0.87 g (33%) of IVf as white needles: mp 184–185°; characteristic ir peaks ($CHCl_3$) at 3400, 3100, 2950, 2850, 2500, and 2300 (NH_2^+ and CH stretching) and 1680 cm^{-1} (C=O).

Anal. Calcd for $C_{23}H_{23}NOBr_2$: C, 56.44; H, 4.67; N, 2.86; Br, 32.66. Found: C, 56.34; H, 4.82; N, 3.18; Br, 32.54.

General Procedure for the Preparation of *cis*-1-Alkyl-2-phenyl-3-aroylazetidines (IVa–h).—A sample of the appropriate 2-[α-(alkylamino)benzyl]acrylophenone derivative was dissolved in chloroform (100 ml) which had been previously saturated with dry hydrogen bromide gas, while the solution was kept at 0°. The reaction flask was tightly stoppered and kept overnight. After removal of excess hydrogen bromide under reduced pressure, the cold solution was neutralized with triethylamine (excess). The solution was then allowed to stand at room temperature for 6 hr. The solvent was evaporated under reduced pressure (without heat), the resulting residue was extracted with dry ethyl ether (200 ml), and the mixture was filtered to remove the suspended triethylamine hydrobromide. The residue which resulted upon evaporation of the ethyl ether was recrystallized from the appropriate solvent.

(21) The melting points are corrected. Their measurements were made on a Perkin-Elmer Model 21 instrument employing carbon tetrachloride solutions unless otherwise indicated. The uv spectra were obtained with a Cary Model 11 instrument employing *ca.* 10^{-4} *M* isooctane solutions. The nmr spectra were determined on a Varian A-60 spectrometer equipped with a V-6040 variable-temperature probe and controller, the spectra being determined as dilute deuteriochloroform solutions with tetramethylsilane as internal standard unless otherwise indicated. Chemical shifts are listed in hertz. For variable-temperature nmr spectra the temperature controller was calibrated by measuring resonance peak separations for methanol or ethylene glycol. The following notations are used for pmr data: s, singlet; d, doublet; t, triplet; q, quartet; h, heptet; and m, multiplet. Microanalyses were performed by Micro-Tech Laboratories, Skokie, Ill.

(22) L. M. Long and H. R. Henze, *J. Amer. Chem. Soc.*, **63**, 1939 (1941).

(23) D. Seebach, B. W. Erickson, and G. Singh, *J. Org. Chem.*, **31**, 4303 (1966).

(24) E. H. White, M. C. Chen, and L. A. Dolak, *ibid.*, **31**, 3038 (1966).

(25) The peaks in the nmr spectrum corresponding to the two vinyl protons and the benzyl proton appear at 363, 343, and 308 Hz, respectively. These peaks were erroneously reported in ref 3.

cis-1-Triethylcarbinyl-2-phenyl-3-(*p*-phenylbenzoyl)azetidine (IVa).—From a 2.06-g (0.0050 mol) sample of IIIa was obtained 1.56 g (74%) of IVa as white needles from methanol: mp 109–110°; nmr peaks at *ca.* 445 and *ca.* 416 (m, 14 H, aromatic protons), 321 (d, J = 9.5 Hz, 1 H, C-2 proton), 263 (octet, 1 H, C-3 proton), 239 (d of d, J = 6.8, J = 3.5 Hz, 1 H, C-4 proton), 216 (d of d, J = 6.8, J = 7.8 Hz), and *ca.* 78 and 54 Hz (distorted q and t, respectively, 15 H, 3 CH_2CH_3). See Table I for uv and ir data for compounds IVa–h and Va–h.

Anal. Calcd for $C_{29}H_{33}NO$: C, 84.63; H, 8.08; N, 3.40. Found: C, 84.46; H, 8.14; N, 3.43.

cis-1-*t*-Butyl-2-phenyl-3-(*p*-phenylbenzoyl)azetidine (IVb).—From a 1.85-g (0.0050 mol) sample of IIIb was obtained 1.70 g (92%) of IVb as a flaky white solid from petroleum ether (bp 60–69°), mp 165–166° (lit.[2a] mp 165°).

cis-1-Isopropyl-2-phenyl-3-(*p*-phenylbenzoyl)azetidine (IVc).—From a 1.78-g (0.0050 mol) sample of IIIc was obtained 1.41 g (79%) of IVc as a white crystalline solid from petroleum ether: mp 141–142°; nmr peaks at *ca.* 445 and *ca.* 417 (m, 14 H, aromatic protons), 276 (d, J = 9.0 Hz, 1 H, C-2 proton), 242–272 (m, 2 H, C-3 and one C-4 protons), 182 (t, J = 7.0 Hz, 1 H, C-4 proton), 152 (h, J = 6 Hz, 1 H, methine), and 62 and 40 Hz (d, J = 6 Hz, 3 H each, two nonequivalent CH_3's).

Anal. Calcd for $C_{25}H_{25}NO$: C, 84.47; H, 7.39; N, 3.94. Found: C, 84.30; H, 7.05; N, 3.94.

cis-1-Cyclohexyl-2-phenyl-3-(*p*-phenylbenzoyl)azetidine (IVd).—From a 1.98-g (0.005 mol) sample of IIId was obtained 1.46 g (74%) of IVd as white platlets from methanol:[26] mp 172–173° (lit.[3] mp 172–173°).

cis-1-Ethyl-2-phenyl-3-(*p*-phenylbenzoyl)azetidine (IVe).—From a 0.50-g (0.0015 mol) sample of IIIe was obtained 0.29 g (58%) of IVe as a flaky white solid from petroleum ether: mp 137–138°; nmr peaks at *ca.* 419 and *ca.* 446 (m, 14 H, aromatic protons), 274 (d, J = 8.5 Hz, 1 H, C-2 protons), 243–270 (m, 2 H, C-3 and one C-4 proton), 182 (t, J = 7.0 Hz, C-4 proton), 154 (d, J = 7 Hz, 2 H, methylene), and 54.5 Hz (t, J = 7 Hz, 3 H, CH_3).

Anal. Calcd for $C_{24}H_{23}NO$: C, 84.42; H, 6.79; N, 4.10. Found: C, 84.12; H, 6.83; N, 4.12.

cis-1-Methyl-2-phenyl-3-(*p*-phenylbenzoyl)azetidine (IVf).—To a 1.89-g (0.0050 mol) sample of IIa dissolved in 250 ml of *n*-hexane was added 9 drops of methylamine (*via* a Dry Ice–acetone trap) and the mixture was allowed to react at room temperature for 0.30 hr. The precipitated methylamine hydrobromide was removed by filtration and the clear filtrate was subjected to a stream of hydrogen bromide while being stirred. (The reaction vessel was equipped with a drying tube to exclude moisture.) Stirring was continued for 2 hr and the solution was then filtered to remove the slightly hygroscopic solid. Upon removal of the amine hydrobromide from the hexane solution this salt immediately absorbed moisture and attempts to dry it failed. The amine hydrobromide was dissolved in 150 ml of chloroform which was then saturated with hydrogen bromide at 0° and allowed to stand at room temperature for 6 hr. Excess hydrogen bromide was removed under reduced pressure and the resulting cold solution was neutralized with triethylamine. The solution was worked up exactly as was done in the general procedure for preparation of *cis* compounds. Recrystallization of the solid from ethyl ether yielded 0.52 g (32%) of white crystals: mp 142–143°; nmr peaks at *ca.* 445 and 420 (m, 14 H, aromatic protons), 240–280 (m, 3 H, C-2, C-3, and one C-4 proton), 182 (t of d, J = 7 and J = 1.9 Hz, respectively, 1 H, C-4 proton), and 142.5 Hz (s, 3 H, CH_3).

Anal. Calcd for $C_{23}H_{21}NO$: C, 84.37; H, 6.47; N, 4.28. Found: C, 84.52; H, 6.71; N, 4.39.

The yield of N-methylazetidine IVf was not significantly improved when pure VIf was used. Thus, treatment of a 0.40-g sample of pure VIf hydrobromide with triethylamine gave upon work-up 0.12 g (38%) of the desired product.

cis-1-Isopropyl-2-phenyl-3-benzoylazetidine (IVg).—From a 1.40-g (0.0050 mol) sample of IIIg was obtained 1.04 g (76%) of IVg as white crystals from pentane: mp 84–85°; nmr peaks at *ca.* 436 and *ca.* 415 (m, 10 H, aromatic protons), 277 (d, J = 9.0 Hz, 1 H, C-2 proton), 241–272 (m, 2 H, C-3 and one C-4 proton), 182 (t, J = 6.5 Hz, 1 H, C-4 proton), 152 (h, J = 6 Hz, 1 H, methine proton), and 62 and 40 Hz (d, J = 6 Hz, 3 H each, two nonequivalent CH_3's).

Anal. Calcd for $C_{19}H_{21}NO$: C, 81.68; H, 7.58; N, 5.01. Found: C, 81.53; H, 7.61; N, 5.04.

cis-1-Cyclohexyl-2-phenyl-3-benzoylazetidine (IVh).—From a 1.60-g (0.0050 mol) sample of 2-[α-(N-cyclohexylamino)benzyl]-acrylophenone[4] was obtained 0.98 g (61%) of IVh as a white crystalline solid from pentane: mp 102–103°; nmr peaks at *ca.* 436 and *ca.* 416 (m, 10 H, aromatic protons), 278 (d, J = 9 Hz, 1 H, C-2 proton), 240–273 (m, 2 H, C-3 and one C-4 proton), 183 (t, J = 7 Hz, 1 H, C-4 proton), and 30–150 Hz (m, 11 H, cyclohexyl protons).

Anal. Calcd for $C_{22}H_{25}NO$: C, 82.72; H, 7.89; N, 4.38. Found: C, 82.83; H, 7.95; N, 4.48.

cis-1-Alkyl-2-deuterio-2-phenyl-3-aroylazetidines (IV′a–f).—When the above scheme was carried out starting with deuterated chalcone (I′) instead of α-methyl-*p*-phenylchalcone, these compounds (IV′a–f) were obtained. These were identified by mixture melting points with the corresponding nondeuterated compounds and the identity of ir spectra.

General Procedure for the Preparation of *trans*-1-Alkyl-2-phenyl-3-aroylazetidines (Va–h).—The appropriate *cis* compound was dissolved in methanol which contained a catalytic amount of sodium methoxide (*ca.* 0.05 g); the mixture was warmed for *ca.* 1 hr and then allowed to stand at room temperature for 3 hr. The methanol was evaporated under reduced pressure and the resulting residue was extracted with dry ethyl ether. The ether was evaporated and the nmr spectrum of the residue was obtained. The products were crystallized and recrystallized from the appropriate solvent. Comparison of the spectra of the gross products with those of the corresponding crystalline products indicated that the *cis* into *trans* conversion was quantitative and occurred without detectable amounts of decomposition as determined by nmr techniques.

When deuterated methanol (CH_3OD) was used instead of methanol the *trans*-3-deuterio compounds (V′) were obtained.

trans-1-Triethylcarbinyl-2-phenyl-3-(*p*-phenylbenzoyl)azetidine (Va).—From a 0.50-g sample of IVa was obtained 0.40 g (80%) of Va as a white solid from a minimum amount of methanol: mp 75–76°; nmr peaks at 420–480 (m, 14 H, aromatic protons), 303 (d, J = 5.2 Hz, 1 H, C-2 proton), 200–250 (m, 3 H, C-3 and C-4 protons), and 76 and 52 Hz (q and t, respectively, 15 H, 3 CH_2-CH_3).

Anal. Calcd for $C_{29}H_{33}NO$: C, 84.63; H, 8.08; N, 3.40. Found: C, 84.89; H, 8.19; N, 3.26.

trans-1-*t*-Butyl-2-phenyl-3-(*p*-phenylbenzoyl)azetidine (Vb).—From a 1.00-g sample of IVb was obtained 0.91 g (91%) of Vb as white needles from methanol: mp 127–128° (lit.[2a] mp 128°).

trans-1-Isopropyl-2-phenyl-3-(*p*-phenylbenzoyl)azetidine (Vc).—From a 0.50-g sample of IVc was obtained 0.46 g (92%) of Vc as a white crystalline solid from methanol: mp 109–110°; nmr peaks at 425–480 (m, 14 H, aromatic protons), 264 (d, J = 7.0 Hz, 1 H, C-2 proton), 180-250 (m, 3 H, C-3 and C-4 protons), 151 (h, 1 H, methine proton), and 59 and 44 Hz (d, J = 6 Hz, 3 H each, two nonequivalent CH_3's).

Anal. Calcd for $C_{25}H_{25}NO$: C, 84.47; H, 7.39; N, 3.94. Found: C, 85.01; H, 7.16; N, 4.17.

trans-1-Cyclohexyl-2-phenyl-3-(*p*-phenylbenzoyl)azetidine (Vd).—From a 1.28-g sample of IVd was obtained 1.11 g (87%) of Vd as a white crystalline solid from methanol: mp 142–143° (lit.[3] mp 142–143°).

trans-1-Ethyl-2-phenyl-3-(*p*-phenylbenzoyl)azetidine (Ve).—From a 0.20-g sample of IVe was obtained 0.13 g (65%) of Ve as a white crystalline solid from *n*-pentane: mp 70–71°; nmr peaks at 425–485 (m, 14 H, aromatic protons), 262 (d, J = 7 Hz, 1 H, C-2 proton), 218–254 (m, 2 H, C-3 and one C-4 proton), 181–202 (m, 1 H, C-4 proton), 135–175 (m, 2 H, CCH_2), and 56 Hz (t, J = 6.5 Hz, 3 H, CH_3).

Anal. Calcd for $C_{24}H_{23}NO$: C, 84.42; H, 6.79; N, 4.10. Found: C, 84.92; H, 6.87; N, 4.17.

trans-1-Methyl-2-phenyl-3-(*p*-phenylbenzoyl)azetidine (Vf).—From a 0.30-g sample of IVf was obtained 0.12 g (40%) of Vf as a white solid from *n*-pentane: mp 63–64°; nmr peaks at 420–460 (m, 14 H, aromatic protons), 258 (d, J = 7.5 Hz, 1 H, C-2 proton), 218–253 (m, 2 H, C-3 and one C-4 proton), 190 (m, 1 H, C-4 proton), and 142 Hz (s, 3 H, CH_3).

Anal. Calcd for $C_{23}H_{21}NO$: C, 84.37; H, 6.47; N, 4.28. Found: C, 84.31; H, 6.54; N, 4.18.

trans-1-Isopropyl-2-phenyl-3-benzoylazetidine (Vg).—From a

(26) Recrystallization of this compound from methanol sometimes leads to a small amount of epimerization.

0.25-g sample of IVg was obtained 0.20 g (80%) of Vg as a white solid from *n*-pentane: mp 42–43°; nmr peaks at 425–480 (m, 10 H, aromatic protons), 265 (d, J = 7 Hz, 1 H, C-2 protons), 180–250 (m, 3 H, C-3 and C-4 protons), 151 (h, J = 6 Hz, 1 H, methine), and 59 and 44 Hz (two d, J = 6 Hz, 3 H each, two nonequivalent CH_3's).

Anal. Calcd for $C_{19}H_{21}NO$: C, 81.68; H, 7.58; N, 5.01. Found: C, 81.88; H, 7.64; N, 5.16.

***trans*-1-Cyclohexyl-2-phenyl-3-benzoylazetidine (Vh).**—From a 0.30-g sample of IVh was obtained 0.24 g (80%) of Vh as white needles from methanol: mp 96–97°; nmr peaks at 420–475 (m, 10 H, aromatic protons), 266 (d, J = 7.0 Hz, 1 H, C-2 proton), 150–180 (m, 3 H, C-3 and C-4 protons), and 30–150 Hz (m, 11 H, cyclohexyl protons).

Anal. Calcd for $C_{22}H_{25}NO$: C, 82.72; H, 7.84; N, 4.38. Found: C, 82.60, H, 7.93; N, 4.48.

***erythro*-2-[α-(N-*t*-Butylamino)benzyl]-3-bromo-4′-phenylpropiophenone Hydrobromide (VIb).**—A 1.50-g sample (0.004 mol) of IIIb was dissolved in 100 ml of chloroform which had been previously saturated with dry hydrogen bromide at 0°. The solution was allowed to stand at room temperature for 4 days. Excess hydrogen bromide and chloroform were removed under reduced pressure. The light brown solid which resulted was recrystallized by being dissolved in a minimum amount of dry methanol and then addition of about 100 ml of dry ethyl ether. Several crops of white crystals were collected: 1.51 g (70%); mp 175–176°; characteristic ir bands ($CHCl_3$) at 3380, 3140, 2870, 2610, 2480, 2350 ($>\overset{+}{N}H_2$), 1668 (broad and unsymmetrical, >C=O), and 1605 cm^{-1} (aromatic C=C); nmr peaks at 425–495 (m, 14 H, aromatic protons), 120–365 (broad m, 6 H, $>\overset{+}{N}H_2$ and aliphatic protons other than *t*-C_4H_9), and 80 Hz (s, 9 H, *t*-C_4H_9).

Anal. Calcd for $C_{26}H_{29}NOBr_2$: C, 58.75; H, 5.51; N, 2.64; Br, 30.01. Found: C, 58.98; H, 5.65; N, 2.60; Br, 30.08.

Reaction of γ-Bromopropylamino Ketone Hydrobromide (VIb) with Excess *t*-Butylamine.—A 0.531-g sample (0.001 mol) of VIb was dissolved in 15 ml of chloroform and the solution was slowly made basic with *t*-butylamine while the reaction mixture was kept at room temperature. The solution was allowed to stand at room temperature for 3 hr, 25 ml of dry ethyl ether was added, and the precipitated *t*-butylamine hydrobromide was removed by filtration. Evaporation of the solvent without heat, extraction of the resulting residue with dry ethyl ether, removal of the remainder of the amine salt, and evaporation of the solvent yielded a white solid. The nmr spectrum of the gross product indicated the presence of only compound IVb. Recrystallization of the product from petroleum ether (bp 60–69°) yielded flaky white crystals of IVb, 0.336 g (91%), mp 165–166° (lit.[2a] mp 165°).

***trans*-1-*t*-Butyl-2-phenyl-3-(*p*-phenylbenzoyl)azetidine *via* 2-(N-*t*-Butylaminomethyl-3-bromo-3-phenyl-4′-phenylpropiophenone Hydrobromide (VIIb).**—A 2.00-g sample (0.0054 mol) of α-(N-*t*-butylaminomethyl)-4′-phenylchalcone dissolved in 15 ml of chloroform was added to 100 ml of chloroform which had been previously saturated with dry hydrogen bromide while being kept at 0°. The solution was allowed to stand at room temperature for 4 days to ensure completion of the addition of hydrogen bromide. The excess hydrogen bromide and chloroform were removed under reduced pressure to yield a light brown solid. Several attempts to crystallize the solid from various solvent systems failed. An ether–chloroform solution (100 ml) of the product(s) was made basic with *t*-butylamine and was allowed to stand for 3 hr. Removal of the *t*-butylamine hydrobromide (1.61 g, 98% of theoretical yield was obtained assuming 2 equiv/molecule) as described above and recrystallization of the residue from methanol yielded 1.09 g (54%) of white crystals of Vb, mp 127–128° (lit.[2a] mp 128°). The spectrum of the crude mixture (after removal of amine salts and solvent) indicated the presence of only Vb and α-(N-*t*-butylaminomethyl)-4′-phenylchalcone.[2a]

Thermal Stability of *cis*-1-Alkyl-2-phenyl-3-aroylazetidines (IVb and IVd). A. In Petroleum Ether (Bp 88–89°).—A 0.20-g sample of IVd was heated in 25 ml of this solvent at reflux temperature for 14 hr, and IVd was recovered unchanged. However, the similar treatment of a 0.20-g sample of IVb lead to partial isomerization. The nmr spectrum of the gross product in the latter case indicated the presence of a 1:1 mixture of IVb and its *trans* isomer Vb by integration of the C-2 ring-proton bands.

B. In Methanol.—A 0.20-g sample of the *cis* compound was heated in 25 ml of this solvent at reflux temperature for 14 hr. The solution was concentrated and cooled at 0° to induce crystallization. The solution was filtered to remove a high yield (>90%) of the *trans* compound. Compound IVb gave Vb, mp 127–128°, while IVd gave Vd, mp 142–143°.

α-(N-*t*-Butylaminomethyl)-4′-phenylchalcone (VIII).—A 1.89-g (0.0050 mol) sample of IIa dissolved in 50 ml of chloroform was allowed to react with *t*-butylamine (1.1 g, 0.015 mol) for 24 hr. Removal of the solvent, extraction with dry ether, removal of the suspended *t*-butylamine hydrobromide by filtration, and evaporation of the solvent yielded a yellow solid. The nmr spectrum of the crude mixture indicated the presence of a quantitative yield of VIII. The product was crystallized from ethyl ether: mp 91–92° (lit.[2a] mp 92°).

Registry No.—IIIa, 18588-35-7; IIIc, 18621-07-3; IIIe, 18621-08-4; IIIg, 18588-36-8; IVa, 18599-78-5; IVb, 13871-55-1; IVc, 18599-80-9; IVd, 13970-36-0; IVe, 18599-82-1; IVf, 18599-83-2; IVg, 18599-84-3; IVh, 18599-85-4; Va, 18599-86-5; Vb, 13871-53-9; Vc, 18599-88-7; Vd, 18599-89-8; Ve, 18599-90-1; Vf, 18599-91-2; Vg, 18599-92-3; Vh, 18599-93-4; V′a, 18599-96-7; V′b, 13871-54-0; V′c, 18599-98-9; V′d, 13871-57-3; V′e, 18600-00-5; V′f, 18600-01-6; VIb, 18599-94-5; VIf, 18599-95-6.

Acknowledgment.—This work was supported in part by Grant CA-02931 from the National Cancer Institute of the U. S. Public Health Service. The authors also wish to thank Dr. C. L. Wilkins for the computerized nmr spectra of some of the compounds included in this paper.

pH-Stat Measurement of Substituent Effects in Hydroxamate Nucleophile Displacements at Carbonyl Centers

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The "charge effect" previously discussed for nucleophilic displacements on isopropyl methylphosphonofluoridate by non-α but not by α nucleophiles has been investigated in analogous reactions occurring at carbonyl centers. The catalytic coefficients determined (by use of a sensitive pH-stat of improved design) for a variety of neutral and cationic *para*-substituted benzohydroxyamates in reaction with both *p*-nitrophenyl benzoate and *p*-nitrophenyl *p*-nitrobenzoate have been plotted in both Brønsted and Hammett linear free-energy relationships. The unusual similarity of the corresponding β (Brønsted) and the ρ (Hammett) values of these esters in reaction with the same series of α nucleophiles has received some consideration. Though limited to hydroxamate nucleophiles, these data (considered in Table IV) are consistent with the conclusion that the "charge effect" could be a reflection of the differences in the mechanism of charge dispersal in the respective transition states for α and non-α nucleophiles attacking unsaturated centers.

A "charge effect" resulting from the occurrence of a cationic site in the nucleophile and increasing its reactivity (relative to its base strength) has been identified[1,2] for phenate anions in displacement reactions of methyl phosphonofluoridates. The absence of this "charge effect" has also been demonstrated[2] for a series of hydroxamic acid anions in the same reactions. The proposal has been advanced,[2] consequently, that testing for the "charge effect" may be applied as a probe of the factors involved in nucleophilic reactivity. It is based on the suggestion that all α nucleophiles[3] fail to exhibit this effect compared with non-α nucleophiles because of differences in the origins of their nucleophilic properties.

The general objective of our current program of investigation of carbonyl reactivity toward nucleophiles is to determine the scope of these conclusions regarding the "charge effect." In this report we present the results obtained in studies of the reactivity of a series of hydroxamic acid anions with carboxylic esters, undertaken for comparison with phosphonate esters[2] to evaluate the influence of the substrate in this test of the characteristics of α nucleophiles.

Experimental Section

General Preparations of Hydroxamic Acids.—Most of the benzohydroxamic acids employed in the basicity and kinetic measurements discussed below were prepared by methods described earlier.[4-9] However, the cationic hydroxamic acid which had been prepared only once previously[10] was of special interest to our objectives. We therefore report its synthesis and characterization by slightly different procedures.

Preparation of the Iodine Salt of *p*-Trimethylammoniumbenzohydroxamic Acid.—The quaternized benzoate[10] was the raw material for this step. Two solutions were prepared in separate vessels: (1) this consisted of 6.9 g of metallic sodium in 100 ml of dry methanol; (2) this consisted of 14.1 g of hydroxylamine hydrochloride in 100 ml of dry methanol. Solutions 1 and 2 were rapidly mixed at room temperature and the sodium chloride thus precipitated was filtered with suction. To the filtrate was added 30 g of the quaternized benzoate and the resulting solution was stirred for 45 hr at room temperature under a nitrogen blanket. The reaction mixture was acidified with glacial acetic acid and the excess methanol and acetic acid were evaporated to the point of near dryness. The residual solid was recrystallized four times from hot water. The crystalline product, 11 g, had mp 193.5–195° dec and analyzed satisfactorily for $C_{10}H_{15}N_2O_2I$.

Anal. Calcd for $C_{10}H_{15}N_2O_2I$: C, 37.28; H, 4.69; N, 8.10; I, 39.39. Found: C, 37.25; H, 4.82; N, 8.57; I, 39.66.

pK_a Measurements.—The pK_a values (Table I) of all the hydroxamic acids considered in this report were measured on a Sargent Model D titrimeter under the following conditions: (1) the hydroxamic acid concentration was approximately 0.001 *M* in 50% dioxane–water solution which was 0.1 *M* with respect to potassium chloride as supporting electrolyte; (2) the controlled temperature was 25 ± 0.1°; (3) the titrating medium was always covered with an oxygen-free nitrogen atmosphere; (4) the titrating base used was *ca.* 0.05 *M* KOH in 50% dioxane–water solution.

TABLE I

Compound	pK_a[a]
p-Methoxybenzohydroxamic acid	10.29
Benzohydroxamic acid	10.9
p-Chlorobenzohydroxamic acid	9.67
p-Nitrobenzohydroxamic acid	8.91
p-Trimethylammoniumbenzohydroxamic acid–iodide	8.90

[a] Measured in 50% dioxane–water solution.

Kinetic Measurements.—The rates of hydrolysis of *p*-nitrophenyl benzoate with the various benzohydroxamic acids listed in the accompanying tables were measured by means of an exclusive high speed recording pH-stat. This instrument was designed and constructed for the express purpose of pursuing very rapid hydrolytic rates at constant, preset hydrion concentrations in both aqueous and nonaqueous media. The equipment proved to be very adequate for the task of pursuing the relatively rapid reaction of hydroxamate-catalyzed *p*-nitrophenyl benzoate and *p*-nitrophenyl *p*-nitrobenzoate hydrolysis. A full description of this apparatus is given in a subsequent section of this report.

The procedural details established for making a reproducible rate run may be outlined as follows.

For *p*-Nitrophenyl Benzoate.—(1) A solution was prepared first consisting of 240 ml of 50% dioxane–water which was 0.1 *M* in KCl and either 0.005, 0.007, or 0.01 *M* in the selected hydroxamic acid. It was adjusted by addition of exactly 5 ml of water and the required amount of KOH solution to bring it to pH 11.0 at 25° under nitrogen. (2) A solution exactly 5 ml in volume and containing either 0.0005 or 0.001 *M* of *p*-nitrophenyl benzoate in pure dioxane was rapidly injected from a delivery syringe into the reaction flask. (3) The recorded data of milliliters of standard KOH solution required to maintain pH 11.0 as a function

(1) (a) J. Epstein, R. E. Plapinger, H. O. Michel, J. R. Cable, R. A. Stephani, R. J. Hester, C. Bellington, Jr., and G. R. List, *J. Amer. Chem. Soc.*, **86**, 3075 (1964); (b) J. Epstein, H. O. Michel, D. H. Rosenblatt, R. E. Plapinger, R. A. Stephani, and E. Cook, *ibid.*, **86**, 4959 (1964).

(2) J. Epstein, P. L. Cannon, Jr., H. O. Michel, B. E. Hackley, Jr., and W. A. Mosher, *ibid.*, **89**, 2937 (1967).

(3) J. O. Edwards and R. G. Pearson, *ibid.*, **84**, 16 (1962).

(4) A. L. Green, G. L. Lainsbury, B. Saville, and M. Stansfield, *J. Chem. Soc.*, 1583 (1958).

(5) B. E. Hackley, Jr., R. Plapinger, M. Stolberg, and T. Wagner-Jauregg, *J. Amer. Chem. Soc.*, **77**, 3651 (1955).

(6) R. Swidler and G. M. Sternberg, *ibid.*, **78**, 3594 (1956).

(7) M. A. Stolberg and W. A. Mosher, *ibid.*, **79**, 2618 (1957).

(8) G. F. Endres and J. Epstein, *J. Org. Chem.*, **24**, 1497 (1959).

(9) R. Swidler, R. E. Plapinger, and G. M. Sternberg, *J. Amer. Chem. Soc.*, **81**, 3271 (1959).

(10) G. Benoit and A. Funke, *Bull. Soc. Chim. Fr.*, 257 (1958).

of time were treated by the Guggenheim method for computing the pseudounimolecular rate constant k_{obsd}. (4) The catalytic coefficients k_A^- were computed from eq 1 where $[A^-]$ is the con-

$$k_{obsd} = k_{H_2O}[H_2O] + k_{OH^-}[OH^-] + k_{A^-}[A^-] \quad (1)$$

centration of the hydroxamic acid anion after plotting in each instance the linear elements of this equation, k_A^- *vs.* $[A^-]$.

For *p*-Nitrophenyl *p*-Nitrobenzoate.—(1) A solution was prepared first consisting of 240 ml of 50% dioxane–water which was 0.1 *M* in KCl and a certain molarity of the selected hydroxamic acid. It was adjusted by exactly 5 ml of water, 3 ml of pure dioxane, and the required amount of KOH solution to bring it to pH 11.0 at 6.0° under nitrogen. (2) A solution exactly 2 ml in volume and containing 0.0001 *M* of *p*-nitrophenyl *p*-nitrobenzoate in dioxane was rapidly injected from a delivery syringe into the reaction flask. The same technique was employed for the *p*-nitrophenylbenzoate runs. The concentration of the hydroxamate anion $[A^-]$ was obtained from the following well-established relationship (eq 2), where pK_a is the ionization constant

$$pH = pK_a + \log [A^-]/([HA] - [A^-]) \quad (2)$$

of a given hydroxamic acid in 50% dioxane–water and pH is 11.0 ± 0.05 for all runs. The k_A^- was equal to the slope of the line obtained from the plots of log k_{obsd} *vs.* $[A^-]$. The k_{OH^-} was computed from eq 3.

$$k_{obsd} = k_{OH^-}[OH^-] \quad (3)$$

The pH-Stat.—The schematic diagram and electronic assembly of these instruments are given in the accompanying Figures 1a and 1b. The particular advantages of these com-

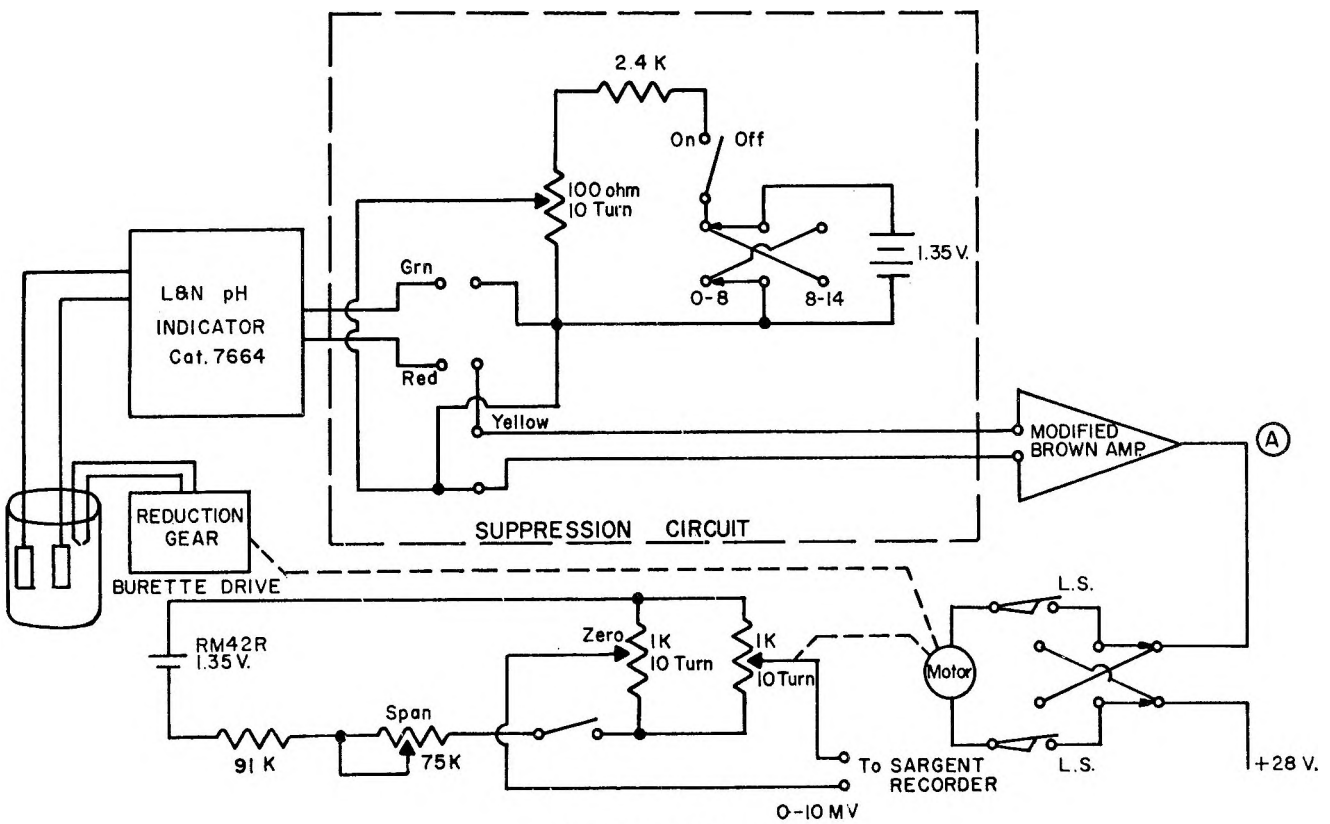


Figure 1a.—pH-Stat.

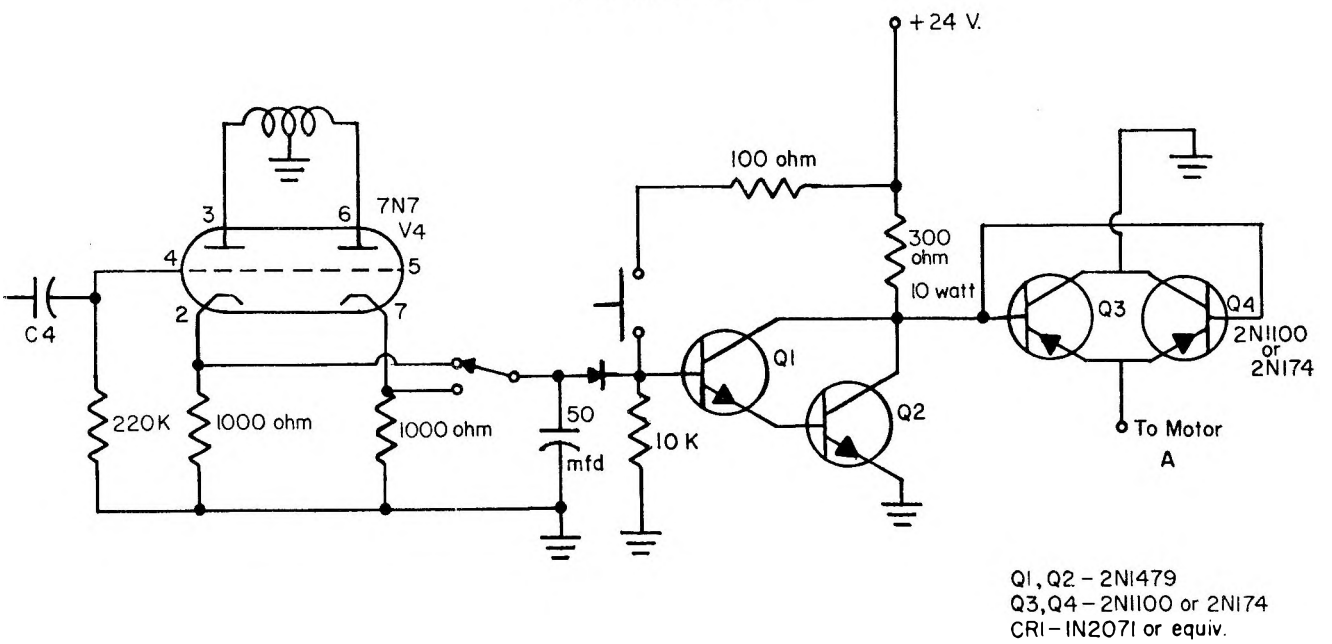


Figure 1b.—Brown amplifier modification.

TABLE II

SUMMARY OF KINETIC RESULTS FOR *p*-NITROPHENYL BENZOATE[a]

Catalysts *p*-X-$C_6H_6C(=O)NHOH$, X	Run 1 [C₀],[b] 10^2 *M*	Run 1 [C],[b] 10^2 *M*	Run 1 k_{obsd}, min^{-1}	Run 2 [C₀],[b] 10^2 *M*	Run 2 [C],[b] 10^2 *M*	Run 2 k_{obsd}, min^{-1}	Run 3 [C₀],[b] 10^2 *M*	Run 3 [C],[b] 10^2 *M*	Run 3 k_{obsd}, min^{-1}	Summary values, $k_c \times 10^2$, l. mol^{-1} min^{-1}
CH_3O	0.50	0.42	0.53	0.75	0.63	0.63	1.0	0.84	0.82	1.04
H	0.50	0.45	0.42	0.75	0.68	0.57	1.0	0.91	0.74	0.84
Cl	0.50	0.48	0.29	0.75	0.72	0.39	1.0	0.96	0.49	0.54
NO_2	0.50	0.50	0.07	0.75	0.74	0.10	1.0	0.99	0.13	0.13
$N^+(CH_3)_3$ I^-	0.50	0.50	0.07	0.75	0.74	0.11	0.96	0.96	0.13	0.14

[a] Reaction conditions discussed in Experimental Section. [b] [C_0]: initial concentration of hydroxamic acid. [C]: initial concentration of hydroxamic acid anion.

TABLE III

SUMMARY OF KINETIC RESULTS FOR *p*-NITROPHENYL *p*-NITROBENZOATE[a]

Catalysts *p*-X-$C_6H_6C(=O)NHOH$, X	Run 1 [C₀],[b] 10^3 *M*	Run 1 [C],[b] 10^3 *M*	Run 1 k_{obsd}, min^{-1}	Run 2 [C₀],[b] 10^3 *M*	Run 2 [C],[b] 10^3 *M*	Run 2 k_{obsd}, min^{-1}	Run 3 [C₀],[b] 10^3 *M*	Run 3 [C],[b] 10^3 *M*	Run 3 k_{obsd}, min^{-1}	Run 4 [C₀],[b] 10^3 *M*	Run 4 [C],[b] 10^3 *M*	Run 4 k_{obsd}, min^{-1}	Run 5 [C₀],[b] 10^3 *M*	Run 5 [C],[b] 10^3 *M*	Run 5 k_{obsd}, min^{-1}	Summary values, $k_c \times 10^3$, l. mol^{-1} min^{-1}
CH_3O	0.50	0.42	0.82	0.67	0.56	0.96	1.0	0.84	1.69							1.91
H	0.50	0.45	0.78	0.75	0.68	1.04	1.0	0.91	1.20	1.20	1.09	1.55				1.47
Cl	0.50	0.48	0.50	0.75	0.72	0.67	1.0	0.96	0.78	1.25	1.19	1.29	1.50	1.43	1.42	1.02
NO_2	1.0	0.99	0.22	1.88	1.86	0.52	2.0	1.98	0.58							0.28
$N^+(CH_3)_3$ I^-	1.0	0.99	0.25	1.49	1.50	0.30	2.0	1.98	0.49							0.24

[a,b] See Table II.

CHART I

BROWN AMPLIFIER MODIFICATIONS

1. Remove V3 from socket
2. Disconnect filmaments to V3
3. Connect pins 4 and 5 of V4 together
4. Change R8 to 220-kilohm 1-W resistor
5. Disconnect the jumper between pins 2 and 7 of V4
6. Remove R5 and R12
7. Add a 1-kilohm 1-W resistor from pin 2 of V4 to ground
8. Add a 1-kilohm 1-W resistor from pin 7 of V4 to ground

pared with the most recent[11] pH-stat equipment available for kinetic applications may be summarized as follows. (1) Proportional control: the response speed of the titrant delivery system is proportional to the degree of unbalance of the chemical system. In Malmstadt's instrument[11] incremental additions of titrant are provided. Increments are totalized on a counter and strip-chart recorder. There are some very apparent advantages for kinetics to be realized in the use of our delivery system compared with Malmstadt's. (2) Reaction *vs.* time profile: this form of data can be converted easily into its first derivative and recorded directly as reaction velocity which other modern instruments cannot accomplish. In a future article an anticipator circuit attached to this instrument to minimize overshoot due to electrode system response time lag will be described. These developments shown in Chart I were designed by Dr. Fred Fritz at this laboratory.

The rectifier section of V2 (7F7) can be removed and silicon rectifiers (IN2071 or equivalent) can be used to replace this portion of V2.

The triode state of V2 that was removed by the preceding operation can be wired and used as an extra stage of amplification if so desired.

Results

The pK_a values measured for the five *para*-substituted benzohydroxamic acids constituting the reaction series in 50% dioxane–water solution are given in Table I. The reaction rates at 25° and their dependencies on hydroxamic acid and hydroxamate anion concentrations are listed in Table II for *p*-nitrophenyl benzoate displacement reactions. Therein also are tabulated the catalytic coefficients determined from plots of these rate data, k_{obsd} *vs.* [A^-], assuming the linear relationship in eq 1 in which all lines of the reaction series members must pass through the origin, since the values of the uncatalyzed reaction coefficient, k_{OH^-}, in all cases were determined (according to eq 3) to be less than 0.01 min^{-1} and k_{H_2O} [H_2O] products were zero. Table III contains an array of the corresponding data for *p*-nitrophenyl *p*-nitrobenzoate displacements.

In Brønsted plots (Figure 2) of the log k_A - *vs.* pK_a for the reaction of the series of *para*-substituted hydroxamate anions with both ester substrates the cationic substituent (trimethylammonium), where the ionization constant is almost identical with that of the *p*-nitro, shows catalytic coefficient values which plot very close to the line comprising all the points of the respec-

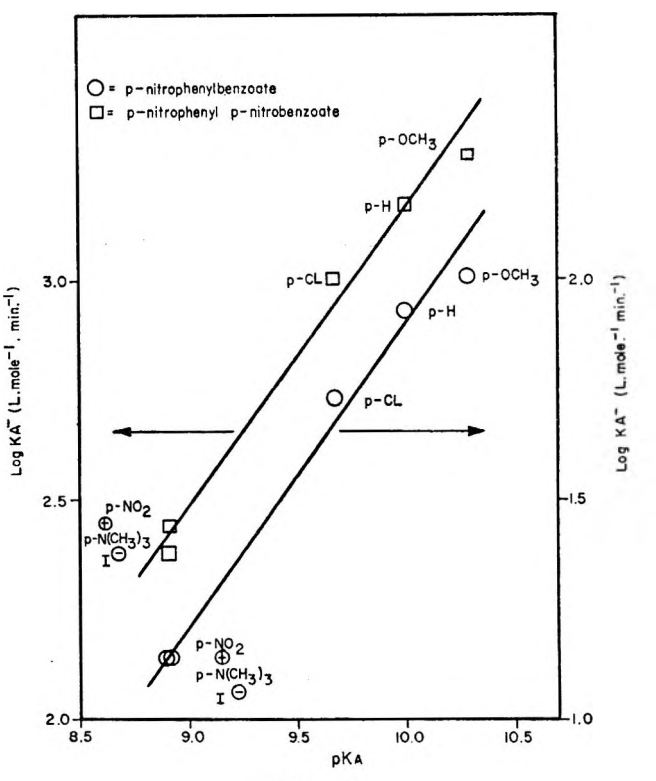


Figure 2.

(11) H. V. Malmstadt and E. H. Prepmeier, *Anal. Chem.*, **37**, 34 (1965).

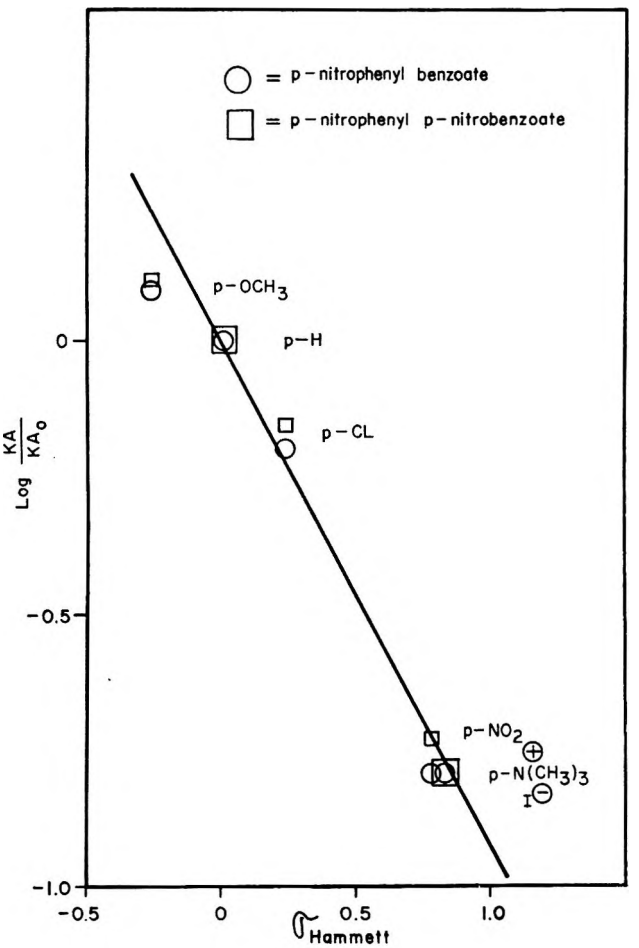


Figure 3.

tive substrate reaction series. Certainly the deviation of the cationic substituents from coincidence with the least-squares slope (the Brønsted β value) is well within experimental error and considerably less than that predicted by the "charge effect" observed for cationic phenate anion nucleophiles. It is to be noted, furthermore, that the β values of both substrates are nearly identical, being 0.67 for *p*-nitrophenyl benzoate and 0.70 for *p*-nitrophenyl *p*-nitrobenzoate. Apparently the considerable difference in electron deficiency of the respective carbonly reaction centers exerts no important influence on the reaction characteristic measured by β.

In Hammett plots (log k_A/k_{A_0} *vs.* α_H) the identical slope $\rho = -0.86$ is obtained for both ester substrates. The largest deviations from the line in either case (which are still not very large) are found for the *p*-methoxy-substituted nucleophile. A somewhat improved fit results, however, when σ^0 values[9] are used in place of σ_H (Figure 3).

It will be recalled that the normal substituent constants σ^0 are applicable in cases where the *para* substituent in an aromatic side-chain reaction exerts its influence purely through its field effect and not *via* a π inductive effect;[12] the incursion of resonance factors in the transition state furthermore seems quite unlikely.

Discussion

The complete absence of a "charge effect" in displacements by (the nucleophiles) hydroxamate anions on esters, regardless of the degree of electron deficiency at the carbon seat of reaction, might be regarded with some surprise. The interpretations of Epstein, *et al.*, suggest that there is no electrostatic contribution through repulsion of the dissociating proton in the ionization of α acids as there is in non-α acids. This interpretation clearly predicts the positive deviations observed for cationic substituents in plots of pK_a *vs.* log k_A - in the latter cases.

Except for this difference in behavior of α and non-α nucleophiles in displacement reactions on various ester substrates there are many elements of similarity to be noted from the results presented (above) and earlier studies in this area. There are, for instance, no dramatic differences in the Brønsted β values (Table IV) to

TABLE IV
LINEAR FREE-ENERGY PARAMETERS FOR PERTINENT DISPLACEMENT REACTIONS

Substrate	Nucleophile (type) reaction series	β value	ρ_H	Ref
Methylphosphonofluoridate	Phenate (non-α)	0.59	−0.80	1a
Methylphosphonofluoridate	Catecholate (non-α)	0.80		1a
Methylphosphonofluoridate	Pyrogallate (non-α)	0.76		1a
Methylphosphonofluoridate	Ketoximate (α)	0.64		1a
Methylphosphonofluoridate	Hydroxamate (α)	0.80		1a
p-Nitrophenyl benzoate	Hydroxamate (α)	0.67	−0.86	This work
p-Nitrophenyl *p*-nitrobenzoate	Hydroxamate (α)	0.70	−0.86	1a

be associated with the nature of the substrate (phosphorous or carbonyl reaction center), its degree of electron deficiency (as related to the conjugation of electron-withdrawing substituents with the reaction center), or the nature of the nucleophile (α or non-α). The same conclusion would seem to apply to the slope of the Hammett linear free-energy relations being compared in Table IV.

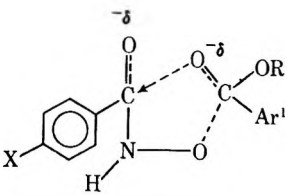
These data must be regarded as somewhat surprising in view of the earlier conclusions of Swain and Langsdorf[13] based on extensive studies of the displacement reaction. These workers demonstrated that the value of ρ is dependent on the structure of the substrate and on the structure of the nucleophile in typical cases. The clear departure of the data in Table IV from these guidelines may perhaps be correlated with the relative constancy of Brønsted β values also listed. The parameter β is usually regarded as a measure of the extent of bonding between the reactants in the transition state. These results may then be taken to signify that all of the nucleophiles (α and non-α) have achieved a comparable degree of affiliation with the reaction centers in the transition state, more or less independently of the degree of electron deficiency, or other characteristics of the reaction seat in the substrate.

An attractive explanation, in keeping with these considerations and capable of understanding the origin of the "charge effect," would suggest that the negative charge developed in the transition states of these displacement reactions is stabilized to a corresponding degree. Apparently this is true regardless of the nature of the nucleophile, so that all nucleophiles (both α and non-α), which have been studied thus far in this respect, can contribute to charge dispersal at the reac-

(12) J. O. Roberts, R. A. Clement, and J. J. Drysdale, *J. Amer. Chem. Soc.*, **73**, 2181 (1951).

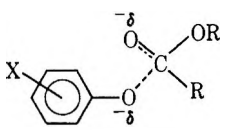
(13) C. G. Swain and W. P. Langsdorf, Jr., *ibid.*, **73**, 2813 (1951).

tion seat. In the case of α nucleophiles possessing a neighboring locus of unsaturation, a structural feature is available which is capable of coordinating the released electron pair of the carbonyl under attack. This event may be formulated in several alternative ways (for instance transition state I) in the case of the hydroxamate anion (pair) depending on where the site of electron density resides in the nucleophile.[14]



transition state I

Even though the reactivity of anions with carbonyl or phosphonyl centers may vary with structure, the position of the displacement transition state along the reaction coordinate (according to Table IV) may be relatively independent of the structure of the nucleophile. Consequently, it is of interest to compare such α anions with phenate nucleophiles which do not possess an analogous facility for accommodating the development of transition-state charge. There would, in fact, appear to be a tendency to accumulate negative charge (as represented by the transition state II) with the approach of the phenate anion to the unsaturated reaction center.



transition state II

The difference in mechanism of charge dispersal for these two types of nucleophiles may afford the explanation of the "charge effect" that is operative in the one case (non-α) and not the other. As pointed out by Epstein, *et al.*,[3] the trimethylammonio group can function as an electron sink in hydroxamic acids, and thus, as with any other electron-withdrawing group, there can be no extraordinary electrostatic contribution in the ionization of the α acid. A similar analysis can be applied to the transition state I. By contrast, the more concentrated negative charge of the phenolic transition state and the closer grouping of anion charge centers of II result in exaltation of the electrostatic effect of the cationic charge of the remote trimethylammonio group.

There is an entirely equivalent way of expressing the "charge effect" in terms of the degree of charge dispersal in I *vs.* II. Evidently the negative charge in the hydroxamate transition state is smeared out over a large number of electronegative atoms. This circumstance diminishes the magnitude of coulombic interactions with cationic centers in the attacking nucleophile. (Substituents other than those bearing a full positive charge exercise their influence through charge–dipole interactions which constitute an inverse higher power function of the distance of their separation than charge–charge interactions). By contrast the proton-anion pair developing in the phenolic transition state results in exaltation of the electrostatic effect of the cationic charge of the remote trimethylammonio group, a reflection of the closer grouping of the anionic charge centers in II.

Registry No.—*p*-Methoxybenzohydroxamic acid, 2593-85-3; benzohydroxamic acid, 1005-00-1; *p*-chlorobenzohydroxamic acid, 2593-22-8; *p*-nitrobenzohydroxamic acid, 3236-38-2; iodide salt of *p*-trimethylammoniumbenzohydroxamic acid, 18593-15-2; *p*-nitrophenyl *p*-nitrobenzoate, 1037-31-6; *p*-nitrophenyl benzoate, 959-22-8.

Acknowledgment.—This work was supported by the Physical Research Laboratory, Edgewood Arsenal, Md. 21010, under Grant DA-AMC-18-108-67A. We are greatly obliged for this support and for the many valuable discussions with Dr. J. Epstein, Dr. G. T. Davis, and others of the personnel of the Physical Research Laboratory at Edgewood.

(14) See, for instance, O. Exner and B. Kakar, *Coll. Czech. Chem. Commun.*, **28**, 1965 (1963); G. M. Sternberg and R. W. Swidler, *J. Org. Chem.*, **30**, 2362 (1965); R. E. Plapinger, *ibid.*, **24**, 802 (1959).

Fluoro Olefins. XIII.[1] The Cycloaddition Reactions of Some Fluorobutadienes

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At 150–200°, in the presence of a polymerization inhibitor (terpineol), 1,1-difluoro-1,3-butadiene reacts with chlorotrifluoroethylene and 1,1-dichloro-2,2-difluoroethylene to give 1:1 addition products arising from 3,4 cycloaddition. Under similar conditions 1,1,2-trifluoro-1,3-butadiene reacts with tetrafluoroethylene, chlorotrifluoroethylene, and 1,1-dichloro-2,2-difluoroethylene giving 1:1 addition products arising from 1,2 and 3,4 cycloaddition. Products arising from the dimerization of 1,1,2-trifluoro-1,3-butadiene were also isolated. These results are consistent with the hypothesis that a bifunctional, diradical intermediate is formed as the first step in the cycloaddition process. The structures of the 1:1 cycloaddition products were elucidated on the basis of their ^1H and ^{19}F nuclear magnetic resonance and infrared spectra.

One of the characteristic reactions of fluoro olefins containing a terminal difluoromethylene group is their ability to undergo a cycloaddition reaction with themselves or with different olefins,[3] but little attention has been paid to the cycloaddition reactions of fluorine-containing butadienes, presumably owing to either their unavailability or their tendency to polymerize on heating.

Sharkey and coworkers[4] have shown that 1,1,4,4-tetrafluorobutadiene and perfluorobutadiene readily form cycloaddition products with tetrafluoroethylene to yield the respective polyfluorovinylcyclobutanes. Coffman, *et al.*,[5] obtained an equimolar mixture of 1:1 cycloaddition products arising from 1,2 and 3,4 addition of tetrafluoroethylene to 2-fluoro-1,3-butadiene.

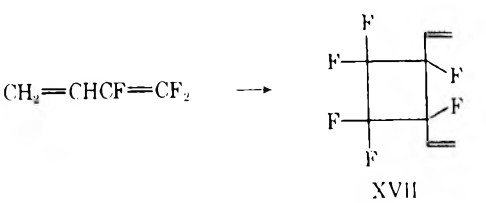
We are interested in observing the effects, if any, on the cycloaddition process when fluoro olefins were added to unsymmetrically substituted fluorobutadienes. 1,1-Difluoro-1,3-butadiene I and 1,1,2-trifluoro-1,3-butadiene II were chosen as reactants in this study as these were the most readily synthesized from available starting materials.

Results

The cyclodimerization reactions between the fluoro olefins and the butadienes were carried out in a 130-ml stainless steel autoclave at 150–200° using a mole excess of the fluoro olefin in the presence of plolymerization inhibitor. In each reaction, together with the 1:1 codimerization products, there were obtained substantial amounts of perfluorochlorocyclobutanes produced by the self dimerization of the fluoro olefin. As would be expected, large amounts of polymeric material were obtained, presumably arising from the polymerization of the butadiene; in fact both I and II polymerized at temperatures above −10° to give a white rubbery material. As a direct consequence, yields of the 1:1 cycloaddition products were generally quite low, usually in the region of 10–15% based on the amount of diene used. The physical properties, together with elemental analysis results, of the new fluorine-containing vinylcyclobutanes are reported in Table I.

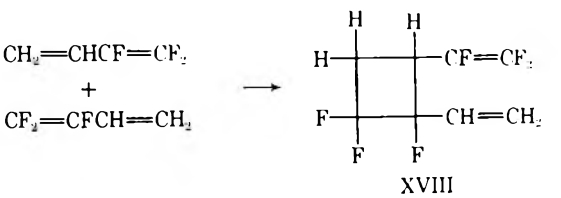
I with chlorotrifluoroethylene III yielded an equimolar mixture of *cis*- and *trans*-1-(1,1-difluorovinyl)-3,3,4-trifluoro-4-chlorocyclobutanes IV together with 1,2-dichlorohexafluorocyclobutane V. With 1,1-dichloro-2,2-difluoroethylene VI, I afforded 1-(1,1-difluorovinyl)-3,3-difluoro-4,4-dichlorocyclobutane VII as well as 1,1,2,2-tetrachlorotetrafluorocyclobutane VIII. No cycloaddition products arising from 1,2 addition were obtained in either of these reactions. No products arising from the dimerization of I were obtained.

II with tetrafluoroethylene IX gave both the 1:1 addition products, 1-vinylheptafluorocyclobutane X and 1-(trifluorovinyl)-3,3,4,4-tetrafluorocyclobutane XI, arising from 1,2 and 3,4 addition together with octafluorocyclobutane XII. With III, II afforded an equimolar mixture of *cis* and *trans* isomers of 1-vinyl-1,2,2,3,3,4-hexafluoro-4-chlorocyclobutane XIII and 1-(trifluorovinyl)-3,3,4-trifluoro-4-chlorocyclobutane XIV with some V. II and VI afforded 1-vinyl-1,2,2,3,3-pentafluoro-4,4-dichlorocyclobutane XV and 1-(trifluorovinyl)-3,3-difluoro-4,4-dichlorocyclobutane XVI together with some VIII. In the reaction of II with fluoro olefins some *trans*-1,4-divinylhexafluorocyclobutane XVII arising from the 1,2 cyclodimerization of II was obtained. A further higher boiling material



XVII

was obtained and tentatively identified as the 1,2:3,4-cyclodimerization product, 1-(trifluorovinyl)-3,3,4-trifluoro-4-vinylcyclobutane XVIII.



XVIII

Determination of Structure

The orientations of the new fluorine-containing vinylcyclobutanes were obtained on the basis of their nuclear magnetic resonance spectra (nmr). The ^1H nmr spectrum, although in every case giving a complex split-

(1) Part XII: P. Tarrant and H. Oliver, *J. Org. Chem.*, **31**, 1143 (1966).
(2) To whom all correspondence should be addressed.
(3) W. H. Sharkey, *Fluorine Chem. Rev.*, in press.
(4) R. E. Putnam, J. L. Anderson, and W. H. Sharkey, *J. Amer. Chem. Soc.*, **83**, 386 (1961).
(5) D. D. Coffman, P. L. Barrick, R. D. Cramer, and M. S. Raasch, *ibid.*, **71**, 490 (1949).

TABLE I
THE CYCLOADDITION PRODUCTS ARISING FROM THE REACTION BETWEEN FLUORO OLEFINS AND FLUORINE-CONTAINING BUTADIENES

Olefin[a]	Diene	Product	Bp, °C	$n^{22.5}D$	Mol wt[e]	Calcd,[d] % C	Calcd,[d] % H	Found,[d] % C	Found,[d] % H
CF_2=CFCl III	CH_2=CHCHCF_2 I	$CH_2CHCH{=}CF_2$ | | CF_2CFCl IV (*cis–trans*)	108–109	1.3726	206	34.86	1.94	35.47	2.23
CF_2=CCl_2 VI	I	$CH_2CHCH{=}CF_2$ | | CF_2CCl_2 VII	131–133	1.4102	222	32.29	1.78	32.34	1.94
CF_2=CF_2 IX	CF_2=CFCH=CH_2	$CF_2CFCH{=}CH_2$ | | CF_2CF_2 X	55[b]	1.3072		34.61	1.44	34.74	1.64
		$CH_2CHCF{=}CF_2$ | | CF_2CF_2 XI	93[b]	1.3350	208	34.61	1.44	35.45	1.92
III	II	$CF_2CFCH{=}CH_2$ | | CF_2CFCl XIII (*cis–trans*)	87.5[b]	1.3508	224	32.07	1.34	32.10	0.77
		$CH_2CHCF{=}CF_2$ | | CF_2CFCl XIV (*cis–trans*)	115.0[b]	1.3665	224	32.07	1.34	32.22	1.45
VI	II	$CF_2CFCH{=}CH_2$ | | CF_2CCl_2 XV	119[b]	1.3895		29.88	1.24	29.95	1.43
		$CH_2CHCF{=}CF_2$ | | CF_2CCl_2 XVI	141[b]	1.4018	240	29.88	1.24	29.84	1.42
VI	II	$CF_2CFCH{=}CH_2$ | | $CF_2CFCH{=}CH_2$ XVII (*trans*)	(112)[c]	1.3654	216	44.44	2.77	44.40	2.83

[a] A 1 mol excess used. [b] By capillary. [c] Polymerized at this temperature. [d] Analysis carried out by Peninsular ChemResearch, Inc., Gainesville, Fla. 32601, and by Galbraith Laboratories, Knoxville, Tenn. [e] From mass pattern.

ting pattern due to the H–H and F–H coupling, was utilized to indicate whether the cycloaddition which had taken place involved either the 1–2 or 3–4 carbon–carbon double bonds. It is now well established that nonconjugated olefinic proton frequencies fall between τ 4.3 and 5.4[6] and the cyclic proton frequency in cyclobutane is at τ 8.04 relative to tetramethylsilane (TMS).[7] Using these standards for comparison the orientations of the vinylcyclobutanes could be identified. In several cases the splitting pattern due to the individual protons could be assigned and these together with the other vinylcyclobutanes are listed in Table II.

TABLE II
^{1}H NMR FREQUENCIES[a] (τ VALUES)

Vinylcyclobutane	Vinylic hydrogen	Ring hydrogen
IV	5.62–6.18 (1 H)	6.54–7.26 (1 H)
		7.40–8.33 (2 H)
VII	5.35–5.89 (1 H)	6.32–6.82 (1 H)
		6.93–7.87 (2 H)
X	4.25–4.82	
XI		6.28–7.3 (1 H)
		7.36–8.04 (2 H)
XIII	4.2–4.82	
XIV		6.11–7.77
XV	4.07–4.68	
XVI		6.14–7.49
XVII	4.27–5.0	

[a] Nmr spectra were recorded as neat liquids with tetramethylsilane as the external reference.

The ^{19}F nmr spectra[8] were consistent with those expected from the proposed structures. The exocyclic trifluorovinyl group in XI, XIV, and XVI gave a characteristic AMX spectrum with further small coupling due to the fluorines and the hydrogens on the ring. The fluorine α to the ring always appeared upfield with respect to the two fluorines β to the ring, at +175–180 ppm from $CFCl_3$. The fluorine *trans* to the α fluorine occurred in the region +118–123 ppm from $CFCl_3$ while the β fluorine *cis* to the α fluorine was +98–105 ppm from $CFCl_3$.

The exocyclic difluoromethylene group in IV and VII comprised the AB part of an ABX pattern. The chemical shifts of the compound IV were +84.0 and +80.6 ppm from $CFCl_3$ while the chemical shifts due to VII were +82.1 and +84.8 ppm upfield from $CFCl_3$.

The difluoromethylene group in the ring system exhibited an AB quartet. Each half of the quartet coupled differently to the other hydrogens and fluorines in the ring. The chemical shifts due to this difluoromethylene group ranged from +97 to +135 ppm from $CFCl_3$.

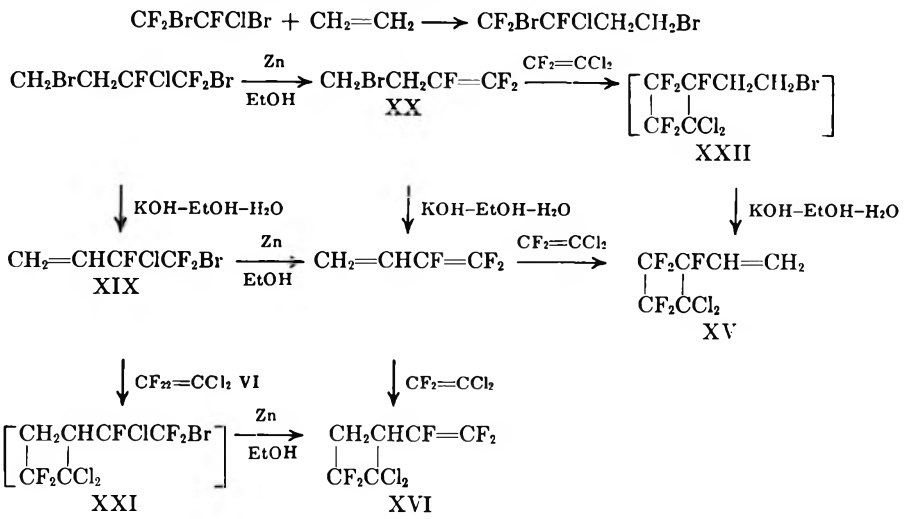
The ring chlorofluoromethylene group in IV, XIII, and XIV ranged from +110 to +142 ppm from $CFCl_3$. The coupling pattern in this case of course depended on the other fluorine and hydrogens in the ring, not only in bond distance but also in geometric relationship, that is whether the other species are *cis* or *trans* to the observed fluorine.

The fluorine α to the trifluorovinyl group in X, XIII, and XV appeared upfield from +171 to +192 ppm from $CFCl_3$. This was coupling not only with the other fluorines and hydrogens in the ring, but also with the exocyclic trifluorovinyl group.

Although the cyclodimerization reaction between fluoro olefins and fluorobutadienes led to the formation of fluorine-containing vinylcyclobutane, an alternative synthesis was carried out in one case to illustrate the generality of the method that could be used to identify the orientations of the products from the cyclodimeriza-

(6) R. T. Morrison and R. N. Boyd, "Organic Chemistry," 2nd ed, Allyn and Bacon, Inc., Boston, Mass., 1966, p 426.
(7) I. Fleming and D. H. Williams, *Tetrahedron*, **23**, 2747 (1967)
(8) Owing to the complexity of the spectrum a more detailed account will be published at a later date.

SCHEME I
SYNTHESES OF CYCLOBUTANES

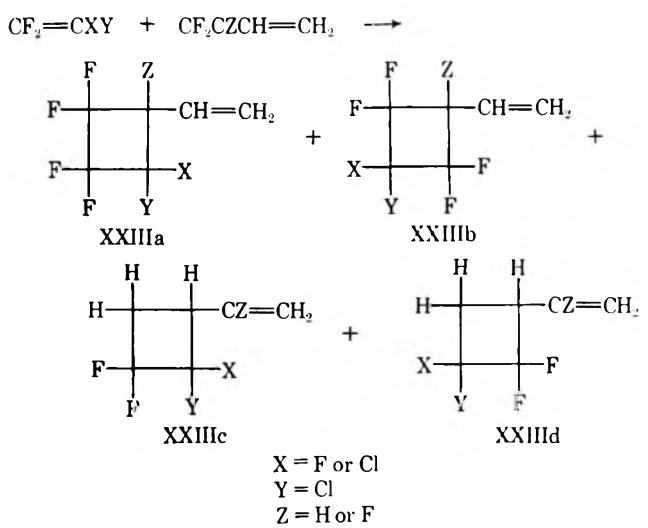


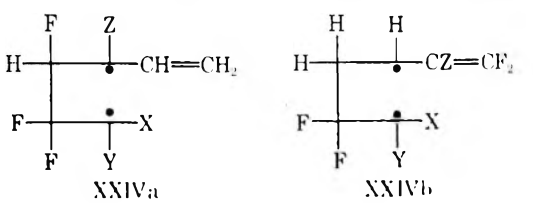
tion. This route, together with the original cyclodimerization reaction, is shown in Scheme I.

3-Chloro-3,4,4-trifluoro-4-bromobut-1-ene XIX on heating with a mole excess of VI gave XXI which was dehalogenated to give XVI. Similarly 1,1,2-trifluoro-4-bromobut-1-ene XX on heating with VI gave XXII which was dehydrobrominated to XVI.

Discussion

In an excellent study on the cyclodimerization of 1,1-dichloro-2,2-difluoroethylene with several butadienes, Bartlett[9] proposed that the structure of the product could be predicted by the rule that the most stable biradical intermediate determines the course of the reaction. In the codimerization reaction between unsymmetrically substituted fluoro olefins and fluorodienes it is theoretically possible that four 1:1 addition products could be formed (XXIIIa, b, c, or d) neglecting *cis-trans* isomers. The initial step in the cyclodimerization process is the formation of a single carbon–carbon bond between the diene and the fluoro olefin. As chlorine is able to stabilize a radical to a greater extent than fluorine,[10] it would be predictable that this initial step would take place between the difluoromethylene group on the fluoro olefin with a methylene group attached to the diene leaving the methylene group containing a chlorine atom free to stabilize the intermediate radical. This was shown to be the case. Only derivatives XXIIIa and XXIIIc arising from the intermediates XXIVa and XXIVb were obtained.





Coffman, *et al.*,[5] have shown that the addition of tetrafluoroethylene to 2-fluorobutadiene gives an equimolar mixture of vinylcyclobutanes arising from 1,2 and 3,4 cycloaddition. This indicates that the fluorine atom present at one of the radical sites has no effect on the mode of addition. We have, however, shown in our series of codimerization reactions that the presence of fluorine attached to the carbon atom in the 2 position has a pronounced effect, increasing the ratio of 1,2 to 3,4 addition products obtained. The results are tabulated in Table III.

TABLE III
TYPE OF ADDITION REACTION

Olefin	Diene	Percentage addition[a] 1,2	3,4
CF_2=CFCl III	CF_2=CHCH=CH_2 I		100
CF_2=CCl_2 VI	CF_2=CHCH=CH_2 I		100
CF_2=CF_2 IX	CF_2=CFCH=CH_2 II	26.2	73.8
CF_2=CFCl III	CF_2=CFCH=CH_2 II	27.5	72.5
CF_2=CCl_2 VI	CF_2=CFCH=CH_2 II	40.9	59.1

[a] Estimated from vapor phase chromatography.

(9) P. D. Bartlett, L. K. Montgomery, and B. Seidel, *J. Amer. Chem. Soc.*, **84**, 616 (1964).

(10) A. L. Henne and D. W. Kraus, *ibid.*, **76**, 1175 (1954). These authors showed that CCl_3Br added to CF_2=CFCl to give exclusively CCl_3CF_2-CFClBr. Since CCl_3Br additions involve attack of trichloromethyl radical on olefin, $CCl_3CF_2CFCl\cdot$ must be more stable than $CCl_3CFClCF_2\cdot$.

As indicated above, I gave with III and VI only products arising from 3,4 cycloaddition indicating that the difluoroallyl radical is stabilized much more effectively than the allyl radical. This behavior is

$$-CH_2\dot{C}HCH{=}CF_2 \longleftrightarrow -CH_2CH{=}C\dot{C}F_2 \cdot > -CF_2\dot{C}HCH{=}CH_2 \longleftrightarrow -CF_2CH{=}C\dot{C}H_2\cdot$$

not totally unexpected since fluorine atoms are known to stabilize radicals more readily than hydrogen as shown by the fact that molecules such as CCl_3Br, CF_2Br_2, and $CF_2BrCFClBr$ add to vinylidene fluorides to give exclusively products of the type $R_hCH_2CF_2Br$ where R_h is a perhaloalkyl group.[11] Since the mechanism of addition is accepted to involve the attack of a perhaloalkyl radical on the olefin it follows that $R_hCH_2CF_2\cdot$ is much more stable than $R_hCF_2CH_2\cdot$.

Haszeldine[12] has found that CF_3I adds to $CF_2{=}CH{-}CH_3$ to give $CF_2ICH(CF_3)CH_3$ which indicates that $CH_3(CF_3)CHCF_2\cdot$ is a more stable radical than $CH_3{-}\dot{C}HCF_2CF_3$, a result that shows two fluorine atoms to be more effective than a methyl group in stabilizing a radical. However, with replacement of the hydrogen situated on the carbon atom in the 2 position by fluorine in the diene, *i.e.*, with II, both 1,2 and 3,4 cycloaddition products were obtained. These results can be rationalized if it is postulated that the initial carbon–carbon single bond is formed by attack of the terminal CF_2 group of the olefin on the terminal CH_2 group of the diene as indicated by the high percentage of 3,4 addition products obtained over 1,2 addition products. However, in the case where the diradical can be stabilized by the presence of a fluorine atom as happens with II, then both

$$\begin{array}{l} CF_2CFCH{=}CH_2 \\ \quad\;\; | \quad | \\ CF_2CX_2 \end{array} \quad \text{and} \quad \begin{array}{l} CH_2CHCF{=}CF_2 \\ \quad\;\; | \quad\;\; | \\ CF_2CX_2 \end{array}$$

are formed. Since the latter is formed preferentially $\sim CH_2\dot{C}HCF{=}C\dot{F}_2$ must be a more stabile radical than $\sim CF_2\dot{C}FCH{=}CH_2$. These results parallel those of Bartlett who in the codimerization reaction of VI with chloroprene obtained more 1,2 cycloaddition than 3,4 addition.

Owing to the free rotation about the single bond in the diradical transition states XXIVa and XXIVb (where X = F; Y = Cl), odds are even for closure for the *cis* or *trans* structures. This was shown to be true for the addition of III to I and II. Although the individual isomers were not isolated, ^{19}F nmr spectra indicated that the ratio of *cis/trans* isomers was approximately equal.

One interesting result was the product arising from the dimerization of II. Only *trans*-1,4-divinylhexafluorocyclobutane was isolated besides a presumed 1,2:3,4 dimer. It is highly improbable that only the *trans* 1,2 dimer was formed; thus the *cis* derivative was formed but underwent further reaction typical of this type of compound.

(11) G. Sosnovsky, "Free Radical Reactions in Preparative Organic Chemistry," The MacMillan Co., New York, N. Y., 1964, Chapter 2.
(12) R. Haszeldine, *J. Chem. Soc.*, 3565 (1953).

Experimental Section

All boiling points are uncorrected. Infrared spectra were recorded on a Beckman IR-8 spectrometer. Analytical and preparative vapor phase chromatography was performed on F & M Models 700 and 775, respectively. ^1H nuclear magnetic resonance (nmr) spectra were obtained using a Varian A-60A spectrometer with tetramethylsilane as external reference. The ^{19}F nmr spectra were obtained using a Varian DP-60 spectrometer operating at 56.4 Mc. The chemical shifts were determined by placing an audiofrequency side band of the internal reference $CFCl_3$ at the peak position being measued. The coupling constants were measured graphically using the sideband technique. Molecular weights were obtained from the mass pattern recorded on Hitachi Perkin-Elmer RMU-6E mass spectrometer operating at an ionizing voltage of 70 eV. Refractive indices were measured using a Bausch and Lomb recorder.

The fluoro olefins were obtained from Peninsular ChemResearch, Inc., Gainesville, Fla., and were used without further purification. 1,1,2-Trifluorobutadiene was prepared by dehalogenation of 4-bromo-3-chloro-3,4,4-trifluoro-1-butene with zinc dust in ethanol.[13] 1,1-Difluorobutadiene was prepared[14] by dehydrobromination of $CF_2BrCH_2CH{=}CH_2$ using potassium hydroxide.

Reaction between Fluoro Olefin and Fluorobutadiene.—In a typical experiment a 130-ml stainless steel autoclave was charged with the diene (0.1 mol), the fluoro olefin (0.2 mol), and terpineol (1 g). The autoclave was then heated for 15 hr at 150–200° and then vented into a cold trap while hot. The mixture of products was then distilled and the individual products were further purified by preparative scale vpc. The cyclobutane, obtained from dimerization of the olefin, was identified by its infrared spectrum by comparison with that of an authentic sample.

Synthesis of XVI.—A stainless steel autoclave (130 ml) was charged with $CH_2{=}CHCFClCF_2Br$ (0.2 mol) and VI (0.2 mol) and heated for 36 hr at 200°. The autoclave was cooled and vented and the reaction products were then distilled. A fraction boiling between 65 and 75 (0.1 mm) (7 g) was obtained which was shown by analytical vpc to consist mainly of one component. Dehalogenation of this product using zinc dust in ethanol afforded after distillation a clear liquid, bp 140–142° (2.1 g). This compound was identified as XVI from a comparison of infrared spectra.

Synthesis of XV.—A stainless steel autoclave (130 ml) was charged with $CF_2{=}CFCH_2CH_2Br$ (0.2 mol) and VI (0.2 mol) and heated at 200–210° for 36 hr. After cooling, the autoclave was vented and the reaction product then distilled under reduced pressure. A fraction, bp 63–65° (2 mm) (8.0 g), was obtained which was shown by analytical vpc to consist mainly of one product. Treatment of this fraction with potassium hydroxide (5 g) in methanol (25 ml) and water (25 ml) for 2 hr at reflux temperature afforded, after washing well with water and distillation, a clear liquid, bp 119–120° (3.1 g). This was identified as XV from a comparison of infrared spectra.

Registry No.—*cis* IV, 18521-20-5; *trans* IV, 18521-21-6; VII, 18543-03-8; X, 18543-04-9; XI, 18543-05-0; *cis* XIII, 18521-22-7; *trans* XIII, 18521-23-8; *cis* XIV, 18521-24-9; *trans* XIV, 18521-25-0; XV, 18543-06-1; XVI, 18543-07-2; *trans* XVII, 18521-26-1.

Acknowledgments—We would like to express our thanks to C. Watkins for interpretation of ^{19}F nmr and to C. Watkins and W. S. Brey, Jr., for running the ^{19}F nmr spectra. Our thanks also are extended to Peninsular ChemResearch, Inc., for a sample of 1,1,2,2-tetrachlorotetrafluorocyclobutane.

(13) P. Tarrant and M. R. Lilyquist, *J. Amer. Chem. Soc.*, **77**, 3640 (1955).
(14) P. Tarrant and A. M. Lovelace, *ibid.*, **76**, 3466 (1954).

A Low-Pressure System for Producing Normal Aldehydes by Hydroformylation of α Olefins[1]

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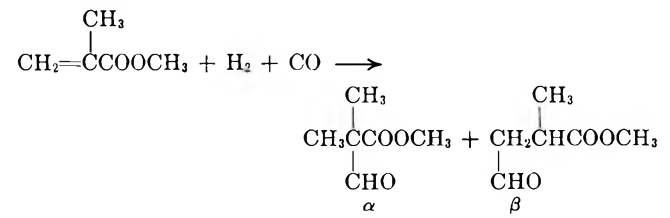
A new process is described for producing predominately normal aldehydes from α olefins with high efficiencies. The process consists of a rhodium-catalyzed, low-pressure hydroformylation in the presence of significant quantities of certain phosphorus ligands. The effect of various reaction parameters on the ratio of *n*- *vs.* isoaldehyde is reported. The results are consistent with a proposed mechanism which involves as the active catalyst a pentacoordinate rhodium complex, such as tris(triphenyl phosphite)rhodium carbonyl hydride, $[(C_6H_5O)_3P]_3Rh(CO)H$. Both trialkyl and triaryl phosphites are effective ligands. Of particular significance are the effects obtained by substituting electron-withdrawing and electron-donating groups in the *ortho* and *para* positions of the triaryl phosphites.

The hydroformylation of α olefins is successfully accomplished with cobalt catalysts at temperatures above about 100° and at pressures upward of 100 atm of synthesis gas. In general, aldehydes are obtained which may result from attachment of the carbonyl group at any of the positions on the carbon chain.[2] This is brought about by concomitant isomerization of the olefin and subsequent hydroformylation of the resulting internal olefin, in addition to the hydroformylation of the contained α olefin.[3] A number of experimental factors have been found which affect the distribution of the various aldehydes in the final product. Examples are pressure, temperature, solvent and H_2:CO ratios in the gas feed, among others. Piacenti and coworkers[4] demonstrated the effect of H_2:CO gas composition on the hydroformylation of pent-1-ene. Reaction of this olefin with 80 atm of hydrogen and 90 atm of carbon monoxide, at 100° and in the presence of cobalt carbonyl, produced *n*-hexanal, 2-methylpentanal, and 2-ethylbutanal in 76.8, 14.7, and 2.5% yields, respectively. Reaction under the same conditions of temperature and catalyst concentration, but with 80 atm of hydrogen and only 2.5 atm of carbon monoxide, produced these materials in 54.7, 24.3 and 3.7% yields. This work, along with other, leads to the conclusion that higher percentages of linear aldehydes are obtained at higher carbon monoxide partial pressures, in the cobalt-catalyzed reaction.

The metal catalyst has a marked effect upon the product distribution. It is known that rhodium is an extremely active catalyst for the hydroformylation of olefins.[5] It also was reported to produce an aldehyde product which contained predominately branched-chain isomers. Under our experimental conditions, the product produced by hydroformylation of oct-1-ene with rhodium catalyst at 70° and 2500 psi of 1:1 H_2:CO consisted of approximately equal amounts of *n*-nonanal and isomeric C_9 aldehydes.

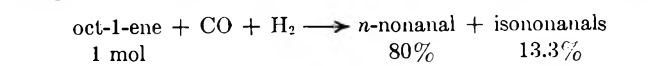
Falbe and Huppes[6] have examined factors which affect the rhodium-catalyzed hydroformylation of methyl methacrylate. The direction of addition to the α,β-double bond was affected by temperature (low temperatures gave α, high temperature β) and by the addition of tributylphosphine to the catalyst system (more α).



The hydroformylation of pent-1-ene with a rhodium carbonyl tri-*n*-butylphosphine complex catalyst at a temperature of 195° and total pressure of 450 psi has been reported by Slaugh and Mullineaux.[7] These workers obtained an aldehyde mixture which consisted of 72.1% *n*-hexanal and 27.9% branched-chain isomers. This result is similar to that of Osborn, Wilkinson, and Young,[8] who obtained a 70–20 product mixture with the use of a rhodium chloride–triphenylphosphine complex, and also similar to a result obtained in this investigation, *i.e.*, a 69–31 product percentage from the use of a rhodium–carbonyl–triphenyl phosphite complex.

Results and Discussion

We have found that under certain critical combinations of reaction parameters, very high percentages of linear aldehydes are obtained from the rhodium-catalyzed hydroformylation of α olefins. A typical example of conditions and results is temperature, 80°;



pressure of 1:1 H_2:CO, 80–100 psig; catalyst, 15 g of 5% Rh/C and 15 g $P(OC_6H_5)_3$; solvent, toluene. It should be emphasized that this set of experimental conditions, and many of those disclosed in the follow-

(1) Presented, in part, at the 154th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1967.

(2) This statement does not always apply to tetrasubstituted olefins [A. J. M. Keulemans, A. Kwantis, and Th. van Bavel, *Rec. Trav. Chim. Pays-Bas*, **67**, 298 (1948)], but since the olefins of this investigation are terminal, there is no contradiction.

(3) M. Johnson, *J. Chem. Soc.*, 4859 (1963).

(4) F. Piacenti, P. Pino, R. Lazzaroni, and M. Bianchi, *J. Chem. Soc., C*, 486 (1966).

(5) V. L. Hughes, U. S. Patent 2,880,241 (March 31, 1959).

(6) J. Falbe and N. Huppes, *Brennstoff-Chem.*, **48**, 46 (1967).

(7) L. H. Slaugh and R. D. Mullineaux, U. S. Patent 3,239,566 (March 8, 1966).

(8) J. A. Osborn, G. Wilkinson, and J. F. Young, *Chem. Commun.*, 17 (1965).

ing tables, are not necessarily optimum for making linear aldehydes. The intent of the experiments was to determine the effects of varying reaction conditions, and to relate these effects with a mechanistic model. It should also be noted that, although the examples described in this paper utilize rhodium on carbon as the metal catalyst source, the actual method of introduction is relatively unimportant. In any case the metal which dissolves is the actual catalyst; the rhodium on carbon was chosen for the sake of convenience. Preformed $HRh(CO)(PPh_3)_3$ acted in an identical manner; in this case a homogeneous, yellow solution was maintained throughout the reaction.

The product distribution was highly dependent on the total pressure of 1:1 H_2:CO gas. Some results are shown in Table I.

TABLE I
HYDROFORMYLATION OF OCT-1-ENE AT VARIOUS PRESSURES[a]

Psig (1:1 H_2:CO)	Reaction time, min	% aldehyde which is straight chain[b]
80–100	50	86
280–300	20	80
560–600	25	74
2500	25	69

[a] Octene (112 g), 5% Rh/C (15 g), triphenyl phosphite (15 g), toluene (200 ml), temperature 90°. [b] In these experiments, as well as those cited in tables following, the percentages are accurate to within 1%.

Even more striking are the results obtained with methyl methacrylate. The work of Falbe and Huppes[6] has demonstrated the controlled addition to the α-carbon atom with the catalyst system rhodium–tri-*n*-butylphosphine and with high pressure of hydrogen and carbon monoxide. The effects of incrementally lowering the pressure are shown in Table II.

TABLE II
HYDROFORMYLATION OF METHYL METHACRYLATE AT VARIOUS PRESSURES[a]

Psig (1:1 H_2:CO)	Reaction time, min	Ratio of β:α
2500		0.3:1[b]
450–470	180	2.0:1
220–240	124	5.2:1
110–114	110	24:1

[a] Methyl methacrylate (29.3 g), 5% Rh/C (1.3 g), triphenyl phosphite (1.2 g), toluene (146 g), temperature 100–110°. [b] The catalyst concentration was slightly different in this particular case, but not sufficiently so as to change the results.

Even at a low total pressure, variances in the partial pressures of the hydrogen and carbon monoxide from a ratio of 1:3 to a ratio of 3:1 produced significant changes in the product composition; the aldehyde produced was 79% straight chain in the former case and 90% in the latter.

The product distribution was also sensitive to the concentration of phosphorus ligand, although the effect leveled off at higher ligand concentrations. The results obtained by varying this reaction parameter are given in Table III.

All the prior discussion has been directed toward the effects of variables on the product composition with the use of a single phosphorus ligand, triphenyl phosphite.

TABLE III
HYDROFORMYLATION OF OCT-1-ENE WITH VARYING CONCENTRATIONS OF LIGAND[a]

$P(OC_6H_5)_3$, g	Reaction time, min	% aldehyde which is straight chain
0[b]	180	31
5.0	30	74
15.0	50	86
30.0	35	87
60.0	65	89

[a] Octene (112 g), 5% Rh/C (15 g), toluene (200 ml), temperature 90°, pressure 80–100 psig of 1:1 H_2:CO. [b] In the absence of phosphorus ligand, the reaction would not proceed at the cited conditions of temperature and pressure; slightly more severe conditions were required.

It was expected that changes in the nature of the phosphorus compound would also affect the results obtained, and this was proved to be the case.

The nature of the P(III) ligand was changed in two ways. The electronegativity of the group attached to P was changed; this would be expected to change the σ donor and π acceptor qualities of the phosphorus atom. The bulkiness of the phenyl groups in triphenyl phosphite was changed by attaching various groups in the *ortho* position(s); this would be expected to change the steric requirements of the R_3P ligand. The pronounced changes in products obtained in this manner are shown in Table IV.

TABLE IV
HYDROFORMYLATION OF OCT-1-ENE WITH VARIOUS TRISUBSTITUTED PHOSPHORUS LIGANDS[a]

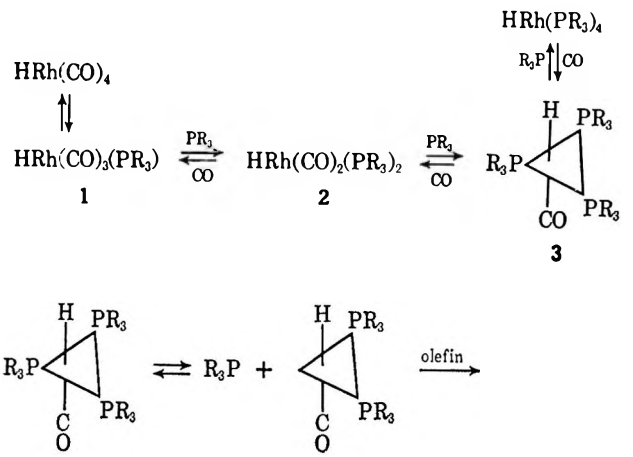
Nature of R in R_3P	Temp, °C	Reaction time, min	% aldehyde which is straight chain
n-Butyl	90	225	71
Phenyl	90	35	82
n-Butoxy	110	60	81
Phenoxy	90	50	86
o-Methylphenoxy	90	52	78
o,*o*-Dimethylphenoxy	90	80	47
o-Phenylphenoxy	90	95	52
p-Phenylphenoxy	90	70	85
p-Chlorophenoxy	90	55	93
p-Methoxyphenoxy	90	270	83

[a] Octene (112 g), toluene (200 ml), 5% Rh/C (10 g), R_3P (0.05 mol), pressure 80–100 psig of 1:1 H_2:CO.

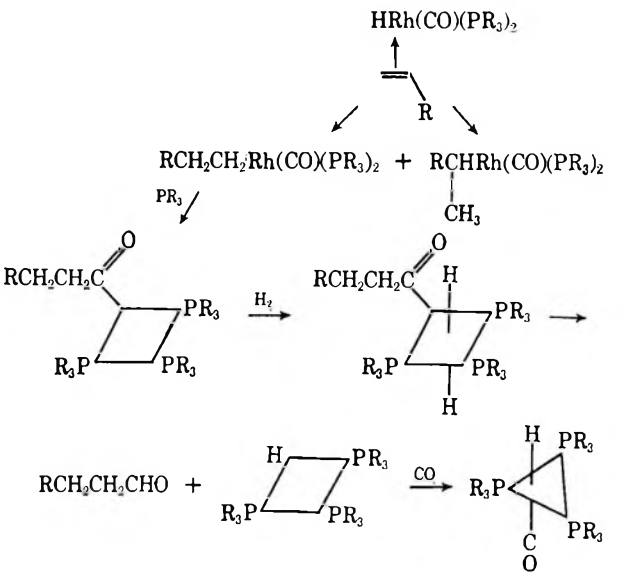
In view of the effects produced by changes in the reaction conditions, as noted in the preceding discussion, it seems clear that the product composition bears a direct relationship with the ability of the phosphorus ligand to compete successfully with carbon monoxide in a multisubstituted species.

In solution, all species of type **1**–**2**–**3** probably exist. The one which predominates is determined by carbon monoxide concentration (pressure), ligand concentration, and the nature of R_3P. High pressures of CO would result in a trend **3** → **2** → **1** whereas raising the relative concentration of R_3P would cause the opposite shift, **1** → **2** → **3**. The trend toward **3** would be favored if R_3P has good back-bonding ability, thus being able to prevent excess charge build-up on the Rh(I) atom. This explains the large difference between trialkylphosphine and triaryl phosphites. In those cases involving heavy steric interference, as exemplified

by tris(*o*-methylphenyl) phosphite, tris(*o*,*o*-dimethylphenyl) phosphite, and tris(*o*-phenylphenyl) phosphite, species **3** is in all probability nonexistent. Species **2** may even be open to question in such cases.



SCHEME I



It is further theorized that each species results in an individual reaction rate and a characteristic product distribution. The most significant one, probably **3**, gives a predominance of straight-chain aldehyde. The indications are that steric crowding is mainly responsible for the linear predominance, although electronic interactions may play a slight role.

Attempts were made to characterize species **1** and **2**. Species **3**, in which R = Ph, is a well-defined compound[9] and was useful as a catalyst in the present investigation. Subjecting **3** to simulated reaction conditions (100 psig 1:1 H_2:CO at 80° in cyclohexanone solvent) in the presence of incrementally decreasing amounts of triphenylphosphine caused a strengthening of the carbonyl ir absorption band(s) and shifted them to shorter wavelengths. The CO absorption band of the complex is weak at 1926 cm^{-1}. Heating as outlined above, in the presence of triphenylphosphine concentrations of 10–20 wt % in cyclohexanone, produced a strong doublet absorption at 1930–1960 cm^{-1}. A further decrease in concentration to 5–10 wt % triphenylphosphine resulted in a solution with a strong principal absorption at 1980 cm^{-1}. Both the increase in intensity and direction of shift are consistent with a change in species from **3** toward **1**.

The mechanism postulated for cobalt-catalyzed hydroformylations,[10] with some slight modifications, is reasonable for the pathway of this series of reactions (Scheme I).

The critical step, as concerns the relative amounts of *n*- and isoaldehydes formed, is the rearrangement of the π-bonded olefin to the σ-bonded *n*- or isoalkyl (step 3 above).

Falbe[11] has attributed the lower selectivity of rhodium, as compared to cobalt, to the larger size of the rhodium. This lessens the steric crowding of the individual ligands surrounding the central atom. However, as each carbon monoxide is successively replaced by the bulky P(III) ligand, the steric crowding and competition increases sharply. Thus even the hydroformylation of the strongly polarized methyl methacrylate, which is electronically controlled under normal circumstances, becomes sterically controlled in the presence of excess triphenyl phosphite. The tremendous reaction rate obtained in the rhodium-catalyzed hydroformylation, also attributed by Falbe to the lack of steric crowding around the larger rhodium atom, is also partially neutralized by excess phosphorus ligand.

Experimental Section

Materials.—Triphenyl phosphite and tributyl phosphite were used as purchased from Matheson Coleman and Bell. Triphenylphosphine and tributylphosphine were purchased from Carlisle Chemical Co. The tributylphosphine was redistilled under nitrogen before use. The triaryl phosphites were prepared by reaction of phosphorous trichloride with the appropriate substituted phenol in ether with N,N-dimethylaniline as the hydrogen chloride acceptor, as reported previously.[12] The crude triaryl phosphites were purified by vacuum distillation or by recrystallization, as appropriate. Such purification was necessary as the presence of amine hydrochloride has a deleterious effect on the reaction. Oct-1-ene was used as purchased from Phillips Petroleum Co. ("pure" grade).

General Procedure for Hydroformylations.—A 3-l. autoclave was charged with octene in toluene and with the appropriate amount of P(III) ligand and rhodium catalyst. The autoclave was sealed, placed in a rocking heater (American Instrument Co.), and flushed with carbon monoxide to remove the contained air. Hydrogen and carbon monoxide were added to give the desired pressure. Rocking was started and heat applied. The temperature was controlled at the desired temperature (usually 90°); reaction began at 75° in most cases. When the pressure had dropped to the lower limit of the desired range (80 psig in the 80–100-psig experiments), rocking was stopped while equal pressures of hydrogen and carbon monoxide were added in sufficient quantity to reach the upper pressure limit.

This same procedure has been conducted in a glass Fisher–Porter apparatus, with the contents being stirred magnetically. Thus the hydroformylation reaction may now be adapted to ordinary laboratory procedures, and it provides a very convenient

(9) (a) S. S. Bath and L. Vaska, *J. Amer. Chem. Soc.*, **85**, 3500 (1963); (b) S. J. LaPlaca and J. A. Ibers, *ibid.*, **85**, 3501 (1963).

(10) (a) R. F. Heck and D. S. Breslow, *ibid.*, **83**, 4023 (1961); (b) R. F. Heck, *Advan. Organometal. Chem.*, **4**, 243 (1966).

(11) J. Falbe, "Synthesen mit Kohlenmonoxide," Springer-Verlag, Berlin, 1967, p 4 ff.

(12) A. E. Arbuzov, G. Kamai, and L. V. Nesterov, *Chem. Abstr.*, **51**, 5720*f* (1957).

method for preparation of terminal aldehydes, from which acids, alcohols, amines, and other derivatives may easily be derived.

Analysis of Products. A. From Methyl Methacrylate.—The two aldehydes, methyl α-formyl isobutyrate and the corresponding β-formyl isomer, were separated by distillation in a 3-ft spinning band column. The former distilled at 50–53° (6–8 mm), the latter at 60–63° (7 mm). The α-isomer was characterized by a singlet aldehydic hydrogen at 9.7 ppm (relative to tetramethylsilane, spectrum obtained on a Varian A-60). The β isomer was characterized by a triplet at 9.8 ppm.

After the original separation and identification of the individual constituents, which provided authentic samples of both forms, most subsequent analyses were made directly on the crude reaction mixture, by vpc techniques. A Barber–Colman Model 20 instrument fitted with a hydrogen flame detector was used, with a 200-ft capillary column coated with Dow-Corning 550 silicone fluid, at an oven temperature of 100°. The α isomer was eluted first; aldehyde ratios were determined directly by the areas under the respective peaks. Aldehyde yields were determined by distillation in a few cases, although loss by polymerization was always encountered. A representative yield is 74% with <5% loss to methyl isobutyrate.

B. From Oct-1-ene.—As in the previous case, distillation was used to provide authentic reference samples of nonanals. The linear isomer distilled at 100° (37 mm), the isononanal(s) distilled a few degrees lower but pure samples of the latter were never obtained. The linear aldehyde was characterized by the triplet nmr absorption at 9.77 ppm; samples rich in α-methyloctanal showed a doublet at 9.65 in addition to the triplet.

In the earliest work, vpc analyses were made on the Barber–Colman Model 20 instrument fitted with the column and detector described in the previous section. At 100°, all of the individual isomeric aldehydes present were resolved. In cases in which the yield of *n*-aldehyde was comparatively low, as in the first example of Table III, three compounds were eluted rapidly in succession followed by the fourth after an appreciable time interval. The fourth peak was identified as being that for *n*-nonanal and in all likelihood the third was 2-methyloctanal, with the other two being 2-ethylheptanal and 2-propylhexanal.

For convenience sake, most analyses were conducted with the use of a Varian Aerograph Series 202 instrument. The column was 0.25 in. × 5 ft, packed with 20% Carbowax 20M on Gas Chrom P 60/80. The oven temperature was 160°, programmed to 225° after elution of hydrocarbon. This gave a rapid determination; all isoaldehydes were under one peak, which was followed immediately by the peak for the linear aldehyde.

The major by-product of the reaction is formed by isomerization of oct-1-ene to oct-2-ene. In a typical case the yield of *n*-nonanal was 80%, of 2-methyloctanal 13%, and 7% oct-2-ene. In the experiments involving methyl methacrylate, the major by-product was the hydrogenation product. In all cases the yields of aldehydes were in the range of 72–84%.

Registry No.—Oct-1-ene, 111-66-0; tris(triphenyl phosphite)rhodium carbonyl hydride, 18346-73-1; methyl methacrylate, 80-62-6.

The Enamine Chemistry of 2,3,4,6,7,12-Hexahydroindolo[2,3-*a*]quinolizine. I. Reaction with α,β-Unsaturated Aldehydes and Ketones[1]

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The reaction of 2,3,4,6,7,12-hexahydroindolo[2,3-*a*]quinolizine (2) with various electrophilic olefins has been investigated. With acrolein, the pentacyclic system **4a** is formed. Methyl vinyl ketone, on the other hand, undergoes cycloaddition to give the pentacyclic system **13**.

Our interest in the synthesis of compounds structurally related to the indole alkaloids eburnamine (**1a**) and vincamine (**1b**) led us to investigate the reaction of 2,3,4,6,7,12-hexahydroindolo[2,3-*a*]quinolizine (2) with various electrophilic agents. In this paper, we wish to describe the results of the reaction of compound 2 with acrolein and methyl vinyl ketone.

It was expected that compound 2 would behave like an enamine derived from a cyclic ketone and reaction would take place at C_1 of the quinolizine system. After the initial 1,4 addition to an electrophilic olefin, the charge on the transient species is dissipated either by proton transfer and generation of a substituted enamine or by cycloaddition.[2] However, in the case of compound 2, the indole nitrogen could react with the carbonyl group of the intermediate substituted enamine to form a pentacyclic system. In a similar situation, Wenkert and coworkers[3] reported that the intermediate obtained by addition of ethyl iodoacetate to the indole-enamine **3** cyclized on heating to give (after hydrogenation) epieburnamonine (**1c**).

The addition of acrolein to 2 in tetrahydrofuran–benzene solution was slightly exothermic; the product which precipitated in 82% yield was a monoadduct. It has been demonstrated that the reaction of enamines with acrolein can lead to aminodihydropyrans[4,5] (*cf.* compound **5**); however, the infrared spectrum of the adduct showed OH but no indole N–H or carbonyl absorption while the ultraviolet spectrum exhibited a maximum at 315 mμ characteristic of the conjugated system in 2,3,4,6,7,12-hexahydroindolo[2,3-*a*]quinolizines.[6] Thus it was apparent that the indole nitrogen had interacted with the aldehyde function to give the pentacyclic system **4a** wherein the newly formed ring is seven membered. Analogous results were obtained when crotonaldehyde or methacrolein were substituted for acrolein (compounds **4b** and **4c**) (Chart I).

(1) Presented in part at the First International Congress of Heterocyclic Chemistry, Albuquerque, N. M., June 12, 1967.

(2) For a review of the reactions of enamines with electrophilic olefins, see J. Szmuszkovics, *Advan. Org. Chem.*, **4**, 27 (1963).

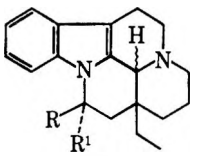
(3) E. Wenkert and B. Wickberg, *J. Amer. Chem. Soc.*, **87**, 1580 (1965).

(4) G. Optiz and I. Löschmann, *Angew. Chem.*, **72**, 523 (1960).

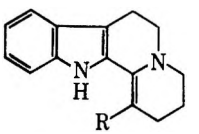
(5) R. N. Schut and T. M. H. Liu, *J. Org. Chem.*, **30**, 2845 (1965).

(6) (a) H. Zinnes, R. A. Comes, and J. Shavel, Jr., *J. Org. Chem.*, **30**, 105 (1965); (b) R. N. Schut and T. J. Leipzig, *J. Heterocycl. Chem.*, **3**, 101 (1966).

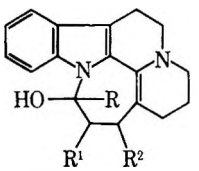
CHART I



1a, R = H; R¹ = OH; angular H β, equatorial
b, R = CO_2CH_3; R¹ = OH; angular H β, equatorial
c, RR¹ = O; angular H α, axial



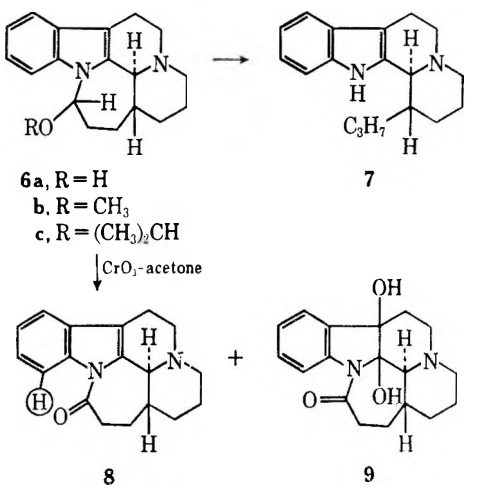
2, R = H
3, R = Et



4a, R = R¹ = R² = H
b, R = R¹ = H; R² = CH_3
c, R = R² = H; R¹ = CH_3
d, R = CO_2CH_3; R¹ = H; R² = C_6H_5
e, R = CH_3; R¹ = R² = H

5

SCHEME I



6a, R = H
b, R = CH_3
c, R = $(CH_3)_2CH$

7

8

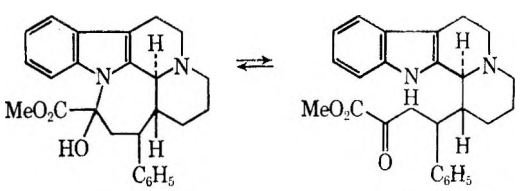
9

Catalytic reduction of **4a** in aqueous acidic medium proceeded rapidly with the uptake of 1 mol equiv of hydrogen. Absorption bands at 2755 and 2805 cm^{-1} in the infrared spectrum of the product indicated a *trans*-fused quinolizidine system (rings C and D).[7] Since axial protonation of the β-carbon atom of the enamine system in **4a** should predominate,[8] it follows that rings D and E must also be *trans* fused.[3] When anhydrous alcoholic solvents were used in the hydrogenation, N,O-acetals (*cf.* **6b** and **6c**) were formed. Under Wolff–Kishner reduction conditions ring opening of **6a** occurs and compound **7** is produced (Scheme I).[9]

Oxidation of **6a** with chromic acid–acetone proceeds in poor yield, giving two compounds in about equal amount. The first compound showed carbonyl absorption at 1700 cm^{-1} which was expected for structure **8**, since epieburnamonine (**1c**)[3] also shows carbonyl absorption in this region. An interesting feature of the nuclear magnetic resonance spectrum of **8** is the downfield shift of the indole-C_{11} proton (encircled) to 1.53 ppm. This shift has been noted for similar structures[10] and is apparently due to deshielding by the carbonyl group which is planar with respect to the indole portion of the molecule.

The other product from the oxidation of **6a** exhibited carbonyl absorption at 1650 cm^{-1}; the ultraviolet spectrum (λ_{max} 257 mμ) was not consistent for an indole but rather suggested the presence of an indoline system. The presence of broad absorption at 3400 cm^{-1} in the infrared spectrum as well as two D_2O exchangeable protons (OH) at 3.40 and 3.92 ppm in the nuclear magnetic resonance spectrum led to the assignment of structure **9** for the second oxidation product. This type of oxidation is not without precedent since treatment of 9-acetyl-1,2,3,4-tetrahydrocarbazole with nitric acid results in hydroxylation of the indole C_2–C_3 double bond.[11]

In order to obtain a compound more closely related to vincamine (**1b**), compound **2** was allowed to react with methyl benzylidenepyruvate. The expected adduct (**4d**) was formed in 63% yield. The double bond in **4d** was readily reduced catalytically or chemically (1 mol equiv uptake). However, since the OH absorption at 3520 cm^{-1} in the infrared spectrum of **4d** was considerably weaker and typical indole N–H absorption at 3470 cm^{-1} was now present in the spectrum of the hydrogenated product, it was assumed that ring opening had occurred to some extent (*cf.* **10** and **11**).



10 11

We next turned to the reaction of **2** with methyl vinyl ketone. There are three logical monoadducts which could be formed in this reaction: (1) the open chain compound **12**, (2) the pentacyclic system **4e** analogous to the acrolein reaction product, or (3) the pentacyclic system **13**. The latter pathway is, in fact, that taken in the reaction of methyl vinyl ketone with enamines of cyclic ketones.[12] For example, one of the postulated (but not isolated) intermediates (**14**) in the reaction of methyl vinyl ketone with the pyrrolidine enamine of cyclohexanone is formally analogous to **13** (Scheme II). The product actually isolated in that case was the pyrrolidine enamine of $\Delta^{1,9}$-2-octalone. The reaction of $\Delta^{1,9}$-dehydroquinolizidine with methyl vinyl ketone, however, did not lead to angular alkyla-

(7) (a) F. Bohlmann, *Ber.*, **91**, 2157 (1958); (b) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," John Wiley & Sons, Inc., New York, N. Y., 1965, p 326.

(8) We invoke here the argument used for preferential axial addition of a proton to an enol: E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp 241, 242.

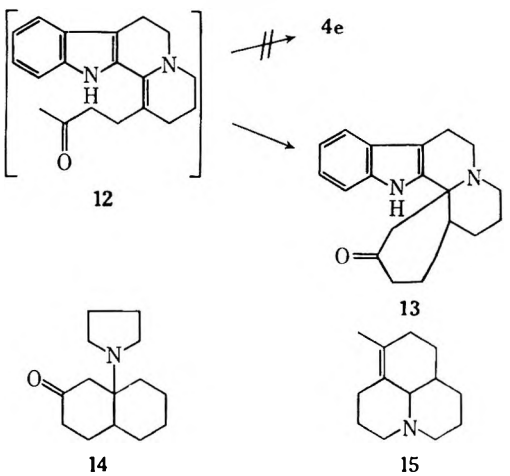
(9) The same type of reductive ring scission has been demonstrated for eburnamine: M. F. Bartlett and W. I. Taylor, *J. Amer. Chem. Soc.*, **82**, 5941 (1960).

(10) E. Winterfeldt, H. Radunz, and P. Strehlke, *Ber.*, **99**, 3750 (1966).

(11) B. Withkop, *J. Amer. Chem. Soc.*, **72**, 614 (1950).

(12) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *ibid.*, **85**, 207 (1963).

SCHEME II



tion.[13,14] Instead the tetrahydrojulolidine derivative **15** was obtained (after sodium borohydride reduction).

The infrared spectrum of the monoadduct obtained from the reaction of methyl vinyl ketone with **2** showed normal ketone carbonyl absorption at 1715 as well as the characteristic indole N–H absorption at 3470 cm^{-1}, thus excluding structure **4e**. The ultraviolet spectrum was consistent for that of a 2,3-disubstituted indole without extended conjugation. Since no uptake of hydrogen occurred on attempted catalytic reduction, it was concluded that the structure of the adduct must be represented by formulation **13**.

Experimental Section[15]

2,3,4,6,7,12-Hexahydro-1,12-(γ-hydroxy)trimethyleneindolo-[2,3-*a*]quinolizine (4a).—To a stirred solution of 22.4 g (0.10 mol) of **2**[5b] in 100 ml of THF was added dropwise 20 ml of acrolein in 50 ml of benzene over a 15-min period. Stirring was continued 3 hr at room temperature, then the product was collected and washed with benzene–ether: yield 22.8 g (82%); mp 183–185°. Two recrystallizations from acetone produced the analytical sample: mp 185–186°; uv max (MeOH, neutral) 232 mμ (ε 21,800), 315 (18,200); ir ($CHCl_3$) 3590 cm^{-1} (OH); nmr (DMSO, 10%), τ 2.3–3.6 (4, aromatic), 4.05 (2, –N–CHOH); shaking with D_2O produced one-proton peak at τ 3.92 (–N–CHO–).

Anal. Calcd for $C_{18}H_{20}N_2O$: 77.10; H, 7.19; N, 9.99. Found: C, 76.76; H, 7.27; N, 10.00.

2,3,4,6,7,12-Hexahydro-1,12-(α-methyl-γ-hydroxy)trimethyl-eneindolo[2,3-*a*]quinolizine (4b) was prepared from **2** and crotonaldehyde in the manner described above: yield 63%; mp 165–166° (acetone).

Anal. Calcd for $C_{19}H_{22}N_2O$: C, 77.51; H, 7.53; N, 9.52. Found: C, 77.52; H, 7.65; N, 9.45.

2,3,4,6,7,12-Hexahydro-1,12-(β-methyl-γ-hydroxy)trimethyl-eneindo[2,3-*a*]quinolizine (4c) was prepared from **2** and methacrolein; yield 82%; mp 171–173° (benzene).

Anal. Calcd for $C_{19}H_{22}H_2O$: C, 77.51; H, 7.53; N, 9.52. Found: C, 77.58; H, 7.81; N, 9.59.

2,3,4,6,7,12-Hexahydro-1,12(α-phenyl-γ-carbomethoxy-γ-hydroxy)trimethyleneindolo[2,3-*a*]quinolizine (4d).—A solution of 15.2 g (0.0792 mol) of methyl benzylidenepyruvate[16] in 60 ml of benzene was added to a stirred solution of 17.7 g (0.0792 mol) of **2** in 100 ml of dry THF over a 20-min period. The reaction mixture was stirred for 1 hr, then concentrated *in vacuo*. The residue was stirred with ether to give 20.7 g (63%) of tan solid, mp 110–112°. An analytical sample was prepared by recrystallization from ether–pentane: mp 114–115°; ir ($CHCl_3$) 3520 cm^{-1} (OH), 1730 (ester C=O); uv (MeOH, neutral) 213 mμ (ε 35,000), shoulder 227 (27,800), 305 (30,000) and 316 (26,000).

Anal. Calcd for $C_{26}H_{26}N_2O_3$: C, 75.33; H, 6.32; N, 6.76. Found: C, 75.04; H, 6.65; N, 6.71.

1,2,3,4,6,7,12,12b-Octahydroindolo-1,12-(γ-hydroxy)trimethyl-eneindolo[2,3-*a*]quinolizine (6a).—An 18.1-g sample (0.064 mol) of **4a** was dissolved in 125 ml of *i*-PrOH, 25 ml of 3.2 *N* HCl–*i*-PrOH and 50 ml of H_2O; 0.3 g of PtO_2 was added and the mixture was hydrogenated at 50 psi, room temperature. Hydrogen (1 mol equiv) was absorbed within 1 hr; no further uptake was observed. The catalyst was filtered and the filtrate was concentrated *in vacuo*. The residue was dissolved in 1500 ml of hot water and the solution was neutralized with 20% NaOH. The precipitate was collected, washed with water and dried to give 17.0 g of **6a**: yield 94%; mp 200–205°. An analytical sample was prepared by recrystallization from acetone–benzene–ether: mp 206–207°; ir ($CHCl_3$, 5%) 3590 cm^{-1} (OH), 2755, 2805 (12b axial H, *trans*-fused quinolizidine); nmr (DMSO, 10%) τ 3.81 (1, >NCHOH), 3.89 (1, >NCHOH).

Anal. Calcd for $C_{18}H_{22}N_2O$: C, 76.59; H, 7.86; N, 9.92. Found: C, 76.37; H, 7.78; N, 9.99.

1,2,3,4,6,7,12,12b-Octahydro-1,12(γ-methoxy)trimethylene-indolo[2,3-*a*]quinolizine (6b) was prepared as described above except that the hydrogenation was carried out under anhydrous conditions using methanol as solvent. The product was purified as the hydrochloride: yield 63%; mp 258–260° (methanol–ethyl acetate). The free base was generated using saturated $NaHCO_3$ solution and the white crystalline solid which formed was recrystallized from ether–pentane: mp 129–130°; ir ($CHCl_3$) no absorption at 3200–3600 cm^{-1}; 2755 cm^{-1} (12b axial H, *trans*-fused quinolizidine).

Anal. Calcd for $C_{19}H_{24}N_2O$: C, 76.99; H, 8.17; N, 9.45. Found: C, 76.99; H, 8.12; N, 9.36.[17]

1,2,3,4,6,7,12,12b-Octahydro-1,12(γ-2-propoxy)trimethylene-indolo[2,3-*a*]quinolizine (6c) was prepared in the same manner using 2-propanol as the solvent. The product was purified as the hydrochloride: yield 37%; mp 181–182° (ether–2-propanol). The free base was generated and recrystallized from ether–pentane, mp 153–154°.

Anal. Calcd for $C_{21}H_{28}N_2O$: C, 77.74; 8.70; N, 8.63. Found: C, 77.45; H, 8.64; 8.51.

Hydrogenation of 4d.—An 8.07-g sample of **4d** was dissolved in 50 ml of H_2O and 175 ml of 2-propanol containing 25 ml of 2 *N* HCl–2-propanol. Catalyst (0.3 g of PtO_2) was added and the mixture was hydrogenated at 50 psi and room temperature. The hydrogenation was complete within 2 hr (1 mol equiv uptake). The crude free base obtained (5.7 g) was chromatographed on 100 g of Florisil using 1 l. of acetone as eluent. The free base thus obtained was treated with ethereal oxalic acid to give 3.6 g of salt, mp 130–150°.

Anal. Calcd for $C_{26}H_{28}N_2O_3 \cdot (CO_2H)_2$: N (basic), 2.76; N (total), 5.53. Found: N (basic), 2.71;[18] N (total), 5.66.

The free base regenerated from the oxalate was an oily material; its infrared spectrum ($CHCl_3$) indicated a mixture of cyclic and open-chain forms **10** and **11** at 3520 (OH) and 3470 cm^{-1} (indole N–H).

1,2,3,4,6,7,12,12b-Octahydro-1,12-(γ-oxo)trimethyleneindolo-[2,3-*a*]quinolizine (8).—A 15.0-ml aliquot of chromic acid reagent[19] was added to 7.07 g of **6a** in 900 ml of acetone at 10°. The mixture was stirred at 10–15° for 10 min, then 30 g of Na_2CO_3 in 100 ml of H_2O was added. The inorganic salts were filtered and the filtrate was concentrated *in vacuo*. A chloroform extract of the residue was chromatographed on 150 g of

(13) F. Bohlmann and O. Schmidt, *Ber.*, **97**, 1354 (1964).

(14) F. Bohlmann, D. Schumann, and E. Bauerschmidt [*ibid.*, **100**, 542 (1967)] reported that angular substitution did occur in the Diels–Alder-type addition of 1-acetyl-1,3-butadiene to $\Delta^{1,9}$-dehydroquinolizidine.

(15) Melting points were taken on a Büchi melting point determination apparatus and are uncorrected. Infrared spectra were determined with a Perkin-Elmer Model 237 grating infrared spectrophotometer and ultraviolet spectra were recorded on a Perkin-Elmer Model 202 or Beckmann DB-G spectrophotometer. Nuclear magnetic resonance spectra were obtained with a Varian Model A-60 spectrometer and resonance peak positions are given in τ units, relative to tetramethylsilane at τ 10.

(16) E. D. Stecher and H. F. Ryder, *J. Amer. Chem. Soc.*, **74**, 4392 (1952)

(17) The Dumas method gave low values for this compound, therefore it was necessary to use the micro-Kjeldahl procedure.

(18) Basic nitrogen determined by titration with standard perchloric acid using acetic acid as solvent.

(19) C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

Florisil. Elution with chloroform gave 1.0 g of syrup which soon crystallized. After one recrystallization from acetone–ether, the product melted at 142–143°: ir ($CHCl_3$) 1700 cm^{-1} (indole N—C=O); nmr ($CDCl_3$) τ 2.5–2.9 (3, aromatic), 1.53 (1, indole C_{11}–H deshielded by C=O).

Anal. Calcd for $C_{18}H_{20}N_2O$: C, 77.10; H, 7.19; N, 9.99. Found: C, 76.76; H, 7.27; N, 10.17.

1,2,3,4,6,7,7a,12,12a,12b-Decahydro-7a,12-dihydroxy-1,12(γ-oxo)trimethyleneindolo[2,3-*a*]quinolizine (9).—Further development of the Florisil column described above using acetone as eluent gave 0.8 g of material which was purified by recrystallization from acetone: mp 244–245°; ir (KCl) 1650 (amide C=O); uv (MeOH) 212 mμ (ε 9800), 257 (10,900); nmr (pyridine-d_5), τ 3.40 (s, 1, C_{12}–OH), 3.92 (m, 1, C_{7a}–OH); shaking the pyridine solution with D_2O caused almost complete removal of these signals.

Anal. Calcd for $C_{18}H_{22}N_2O_3$: C, 68.76; H, 7.05; N, 8.91. Found: C, 68.61; H, 7.23; N, 9.01.

1,2,3,4,6,7,12,12b-Octahydro-1-propylindolo[2,3-*a*]quinolizine (7).—A mixture of 2.82 g (0.010 mol) of **6a**, 50 ml of ethylene glycol, 20 ml of hydrazine hydrate and 2 g of KOH was heated under a nitrogen atmosphere at 130–132° for 2 hr. The temperature was then raised to 180° and maintained for 1 hr. The thick solution was shaken with 500 ml of ether and the extract washed with 1 l. of cold water. The aqueous extracts were counter-extracted with ether and the combined extract then concentrated *in vacuo* to give 2.9 g of thick syrup. The material was chromatographed on 100 g of neutral alumina using chloroform as eluent. The product (1.69 g) was a yellow syrup which failed to crystallize; ir ($CHCl_3$) 3480 cm^{-1} (indole N–H); uv_{max} (MeOH) 227 mμ (ε 28,000), 283 (6400). Treatment of the free base with 0.6 g of oxalic acid in ether gave an ivory-colored salt (1.95 g) which after two recrystallizations from ether–methanol melted at 177–178° (bubbling); the salt resolidified and melted again at 244–245°.

Anal. Calcd for $C_{18}H_{24}N_2 \cdot (CO_2H)_2$; N, 7.82. Found: N, 7.69.

1,2,3,6,11,12,13,14,15,15a-Decahydro-13-oxo-5H-benz[*i*]indolo[2,3-*a*]quinolizine (13).—To a stirred solution of 11.2 g (0.050 mol) of **2** in 100 ml of dry THF was added a solution of 3.50 g (0.050 mol) of methyl vinyl ketone in 50 ml of benzene over a 30-min period. The solution was stirred for 5 hr, then the solvent was removed *in vacuo*. The crude product (10.7 g) was dissolved in a little $CHCl_3$ and chromatographed on 200 g of Florisil. Elution with USP ether and concentration of the fractions gave 3.9 g of material, which on stirring with anhydrous ether gave 1.4 g of crystalline product, mp 172–177°. Recrystallization from benzene–ether–hexane gave analytically pure **13**: mp 175–176°; ir ($CHCl_3$) 3470 cm^{-1} (indole N–H), 1715 (ketone C=O), no bands in the 2700–2800-cm^{-1} region; uv (MeOH, neutral) 226 mμ (ε 32,000), 283 (7900).

Anal. Calcd for $C_{19}H_{22}N_2O$: C, 77.55; H, 7.55; N, 9.52. Found: C, 77.46; H, 7.53; N, 9.43.

Acknowledgment.—The authors wish to thank Dr. Dale A. Stauffer and associates for the analytical services.

Registry No.—**2**, 5912-12-9; **4a**, 18039-47-9; **4b**, 18039-48-0; **4c**, 18067-03-3; **4d**, 18039-49-1; **6a**, 18031-30-6; **6b**, 18031-31-7; **6b**·HCl, 18031-32-8; **6c**, 18031-33-9; **6c**·HCl, 18031-34-0; **7**, 18039-51-5; **7** oxalate, 18031-35-1; **8**, 18031-36-2; **9**, 18031-37-3; **10** oxalate, 18031-38-4; **11** oxalate, 18031-39-5; **12**, 18039-50-4.

Steric Inhibition of Intramolecular Cyclizations by *ortho* Substituents. The Synthesis of 1H,3H-Thieno[3,4-c]thiophene, Its 2,2-Dioxide, and 5-Ethyl-5,6-dihydro-4H-thieno[3,4-*c*]pyrrole[1]

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During our study of the synthesis of anellated five-membered rings on thiophene, we discovered that some intramolecular cyclizations are adversely affected by *ortho* substituents in the aromatic ring. Reaction of 2,5-dibromo-3,4-bis(bromomethyl)thiophene with sodium sulfide furnished 4,6-dibromo-1H,3H-thieno[3,4-*c*]thiophene and ring closure of 2,5-dichloro-3,4-bis(chloromethyl)thiophene with sodium sulfide gave the 4,6-dichloro derivative. On the other hand, reaction of 2,5-dichloro-3,4-bis(chloromethyl)thiophene with ethylamine in acetonitrile does not form a thienopyrrole derivative, while cyclization to 5-ethyl-5,6-dihydro-4H-thieno[3,4-c]pyrrole was successful when the chlorine atoms on the thiophene nucleus of the tetrachloride were removed prior to the reaction with ethylamine. Our explanation of the steric inhibition of intramolecular cyclization by *ortho* substituents is given.

In an earlier publication[2] we have described the synthesis of 1H,3H-thieno[3,4-*c*]thiophene (**4**) by ring closure of dimethyl 3,4-bis(bromomethyl)thiophene-2,5-dicarboxylate with sodium sulfide, followed by removal of the carbomethoxy groups. In view of the current interest in thienothiophenes,[3,4] we wish to describe here an improved preparation of thienothiophene **4**. Cyclization of 2,5-dibromo-3,4-bis(bromomethyl)thiophene (**1**)[5] with sodium sulfide gave 4,6-dibromo-1H,3H-thieno[3,4-*c*]thiophene (**2**) in 60% yield; the latter could be reduced to 1H,3H-thieno-[3,4-*c*]thiophene (**4**) in 75% yield (Scheme I). The cyclization reaction also yielded the dimeric compound 1,3,7,9-tetrabromo-4H,6H,10H,12H,dithieno[3,4-*c*:3′,4′-*h*][1,6]dithiecin (**3**) in 18% yield. Oxidation of sulfide **2**, followed by zinc in acetic acid reduction, furnished 1H,3H-thieno[3,4-*c*]thiophene 2,2-dioxide (**6**) in 60% over-all yield.

As we have described, reaction of methyl 2,3-bis-

(1) Abstracted in part from the Doctoral Thesis of D. J. Z., Groningen, 1967.

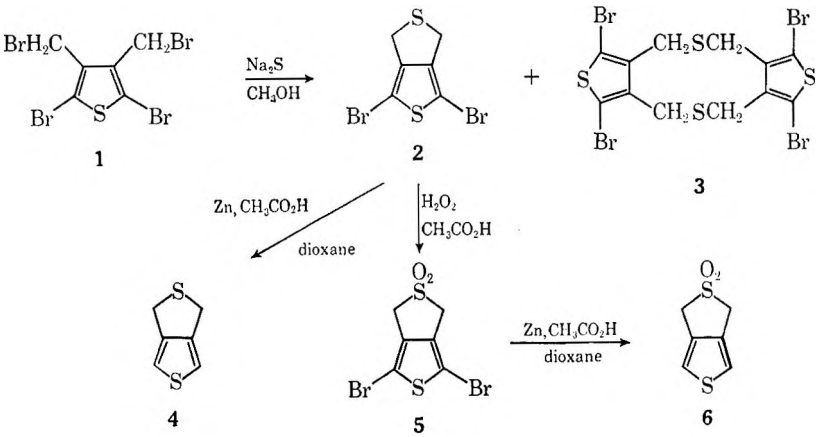
(2) H. Wynberg and D. J. Zwanenburg, *J. Org. Chem.*, **29**, 1919 (1964).

(3) H. Wynberg and D. J. Zwanenburg, *Tetrahedron Lett.*, 761 (1967).

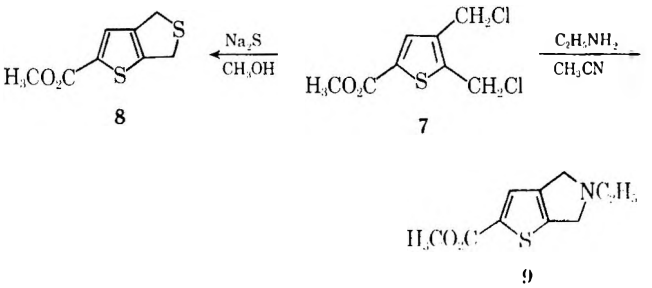
(4) M. P. Cava and N. M. Pollack, *J. Amer. Chem. Soc.*, **89**, 3639 (1967).

(5) D. J. Zwanenburg and H. Wynberg, *Rec. Trav. Chim. Pays-Bas*, in press.

SCHEME I

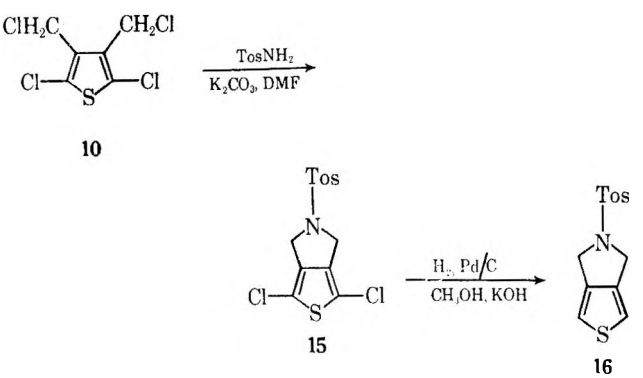


(chloromethyl)thiophene-5-carboxylate (**7**) with sodium sulfide in methanol or with ethylamine in acetonitrile gives the thienothiophene **8**[6] and the thienopyrrole **9**,[7] respectively.



In view of the results of the ring-closure reactions with sodium sulfide, and of the formation of a thienopyrrole derivative in the reaction of **7** with ethylamine, we tried to synthesize 1,3-dichloro-5-ethyl-5,6-dihydro-4H-thieno[3,4-*c*]pyrrole by ring closure of 2,5-dichloro-3,4-bis(chloromethyl)thiophene (**10**)[8,9] with ethylamine in acetonitrile, using about the same conditions as were used in the synthesis of the thienopyrrole **9**. The attempts to prepare a thienopyrrole derivative by cyclization of tetrachloride **10** with ethylamine were unsuccessful, however. Two products were isolated, namely, 1,3,7,9-tetrachloro-5,11-diethyl-5,6,11,12-tetrahydro-4H,10H-dithieno[3,4-*c*:3′,4′-*h*][1,6]diazecine (**11**) and the open compound 2,5-dichloro-N,N′-diethyl-3,4-bis(aminomethyl)thiophene (**12**) (Scheme II). Similar results were found for the reaction of 2,5-dichloro-3,4-bis(iodomethyl)thiophene (**13**) and ethylamine in acetonitrile. The bis(iodomethyl) compound **13** was prepared from the reaction of the tetrachloride **10** with sodium iodide in acetone. The open compound **12** was further characterized by the formation of the ditosylate after reaction with *p*-tolylsulfonylchloride.

Whereas reaction of the tetrachloride **10** with ethylamine did not furnish a thienopyrrole derivative, ring closure of the tetrachloride **10** with *p*-toluenesulfonamide in dimethylformamide and potassium carbonate[10,11] as base did furnish 1,3-dichloro-5-tosyl-5,6-dihydro-4H-thieno[3,4-*c*]pyrrole (**15**). Subsequent catalytic dechlorination furnished 5-tosyl-5,6-dihydro-4H-thieno[3,4-*c*]pyrrole (**16**).



Discussion

The striking differences in the behavior of tetrachloride **10** and dichloride **7** toward ethylamine can be rationalized by a working hypothesis in which a SN2 transition state[12,13] leads to the thienopyrrole ring

(6) D. J. Zwanenburg, H. de Haan, and H. Wynberg, *J. Org. Chem.*, **31**, 3363 (1966).

(7) D. J. Zwanenburg, J. Feyen, and H. Wynberg, *Rec. Trav. Chim.*, **86**, 589 (1967).

(8) 2,5-Dichloro-3,4-bis(chloromethyl)thiophene (**10**) was synthesized in 75% yield from 2,5-dichlorothiophene using chloromethyl methyl ether and stannic chloride (see Experimental Section).

(9) Cyclization of tetrachloride **10** with sodium sulfide in methanol furnished in 48% yield the 4,6-dichloro analog of **2**.

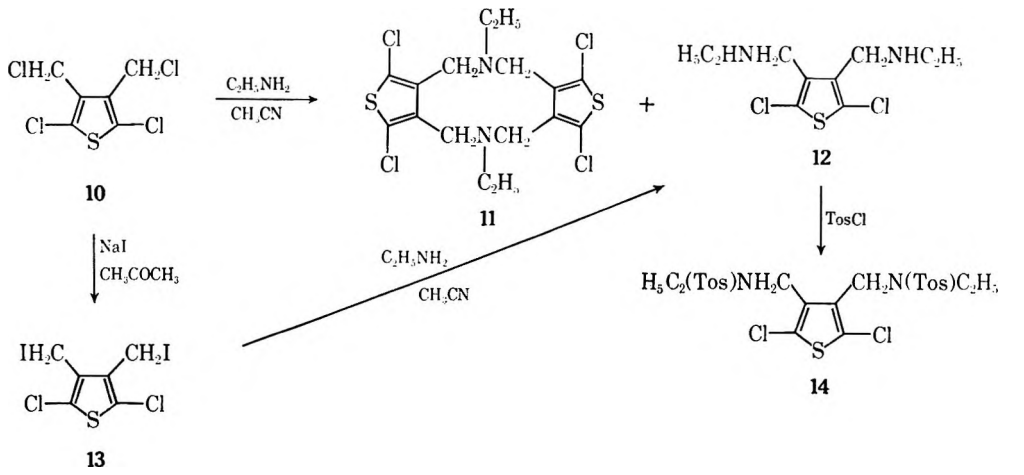
(10) This reaction was first carried out in ethanol with sodium hydroxide as base, in analogy with the reaction of *o*-xylylene dibromide and *p*-toluenesulfonamide giving 2-tosyl-1,3-dihydroisoindole[11] in 48% yield. Under these conditions thienopyrrole **15** was obtained in only 6% yield. From the nmr spectrum of the reaction mixture it appeared that a reaction had taken place between tetrachloride **10** and the solvent.

(11) J. Bornstein, S. C. Lashua, and A. P. Boiselle, *J. Org. Chem.*, **22**, 1255 (1957).

(12) Östman[13] has provided strong experimental evidence for the SN2 character of the reaction of 2- and 3-thenyl chloride with lithium chloride in dimethylformamide. Naturally our working hypothesis—namely, whether all of these cyclization reactions are truly SN2, or whether an SN1-type mechanism also plays a role—needs further investigation. Preliminary experiments indicate that the polarity of the solvent plays a role in some of these reactions, suggesting the need for detailed kinetic work.

(13) B. Östman, *J. Amer. Chem. Soc.*, **87**, 3163 (1965).

Scheme II



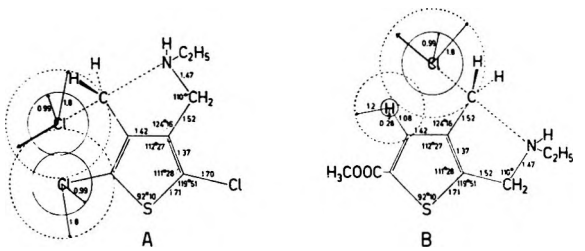
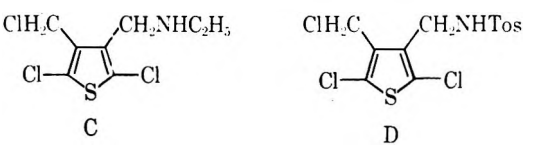


Figure 1.—An approximation of the transition states for the reactions of ethylamine with 2,5-dichloro-3,4-bis(chloromethyl)-thiophene (**10**) and methyl 2,3-bis(chloromethyl)thiophene-5-carboxylate (**7**), respectively, to the corresponding thienopyrrole derivatives. The angles and distances of the thiophene nucleus are of Bak and coworkers.[15] For the distances C_{Ar}–Cl, C_{Ar}–C, C–Cl, C–N and the angles CCN, CCCl are taken the values[16] of chlorobenzene, toluene, 1,2-dichloroethane, diethylamine diethylamine and 1,2-dichloroethane, respectively. The solid circles are the covalent radii of Cl and H respectively, and the dotted circles are the van der Waals radii of these atoms.

system. In Figure 1, an approximation of the transition states is given.[14] The figure clearly suggests that in the ring closure of tetrachloride **10** with ethylamine the leaving chloride anion suffers considerable steric hindrance from the chlorine atom attached to the thiophene nucleus. Crucial to our argument is the reasonable assumption that the entire ring-closure sequence must occur in the plane of the aromatic ring. Steric factors of this nature are not involved in the case of dichloride **7**; the hydrogen atom in this case is so small that there is no steric hindrance for the leaving chloride anion. The energy of activation in case A will be much greater, due to the steric hindrance, than in case B. On the other hand, in the transition state of the reaction of the $-CH_2NHC_2H_5$ group in the intermediate C with a $-CH_2Cl$ group of a second molecule, there will be less steric hindrance, because in this case the nitrogen has the opportunity also to attack the $-CH_2Cl$ group from above and below. The energy of activation in the dimerization reaction consequently will be smaller than those in the cyclization reaction



to a five-membered ring. Likewise, the energy of activation for the reaction of intermediate C with a molecule of ethylamine will be smaller than those for the cyclization reaction to a five-membered ring. Also, the intramolecular cyclization of the intermediate C to a five-membered ring does not occur by reason of the high energy of activation.

The fact that a reaction between tetrachloride **10** and *p*-toluenesulfonamide furnished a thienopyrrole derivative is not in contradiction with the given explanation, for the nucleophilicity of the anion of the $-NHSO_2C_6H_4CH_3$ group in intermediate D is considerably greater than the nucleophilicity of the $-NHC_2H_5$ group in the intermediate C.[15] For the same reason the reaction of tetrachloride **10** with sodium sulfide does furnish a five-membered ring, for the $-CH_2S^-$ group is also a strong nucleophile.

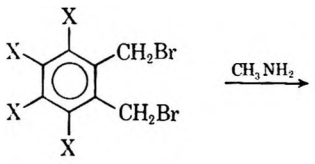
Evidence from the Literature.—In the literature several ring-closure reactions, which support our explanation of steric inhibition of intramolecular cyclizations, are described. Rosen and coworkers[16] obtained only a 5% yield of the isoindoline derivative **18** (X = Cl) in the reaction of 1,2-bis(bromomethyl)-3,4,5,6-tetrachlorobenzene (**17**, X = Cl) with methylamine. The main product (52%) in this reaction was the diazecine derivative **19** (X = Cl). A reaction of 1,2-bis(bromomethyl)benzene (**17**, X = H) with methylamine, however, gives isoindole **18** (X = H) in 56% yield.[17]

(14) The assumption of the transition state B, in which the chloromethyl group in the 2 position has reacted with ethylamine prior to that in which the chloromethyl group in the 3 position has reacted, is based on the work of Östman.[13] B. Bak, D. Christensen, L. Hansen-Nygaard, and J. Rastrup-Anderson, *J. Mol. Spectrosc.*, **7**, 58 (1961). "Tables of Interatomic Distances and Configuration in Molecules and Ions," L. E. Sutton, Ed., The Chemical Society, Burlington House, W.1., London, 1958.

(15) For a discussion on nucleophilicity and activation parameters see J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," John Wiley & Sons, Inc., New York, N. Y., 1963, pp 62, 243.

(16) W. E. Rosen, V. P. Toohey, and A. C. Shabica, *J. Amer. Chem. Soc.*, **80**, 935 (1958).

(17) G. Wittig, H. Tenhaeff, W. Schock, and G. Koenig, *Ann.*, **572**, 1 (1951).



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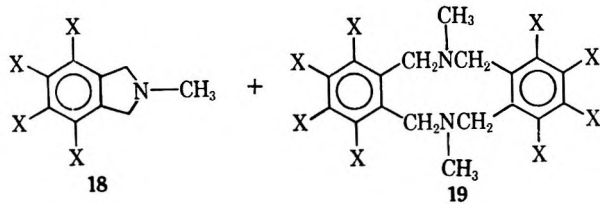
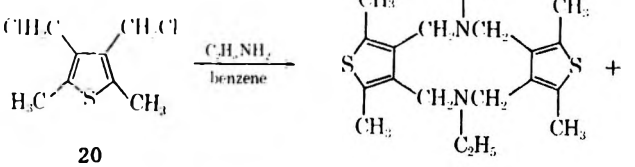


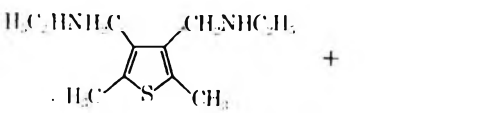
18 19

Gol'dfarb and Kondakova[18] obtained no formation of a thienopyrrole derivative in the reaction of several primary amines with 3,4-bis(chloromethyl)-2,5-dimethylthiophene (**20**). In the reaction of **20** with ethylamine in benzene, a mixture of products, as indicated in Scheme III, was obtained. On treatment

SCHEME III



20 21



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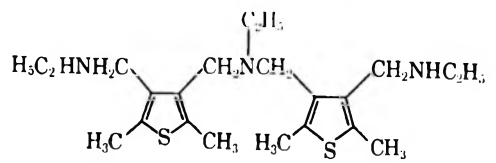


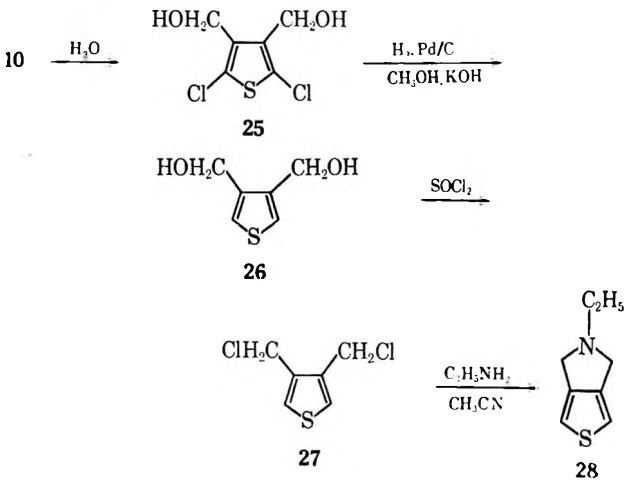
23

of 2,5-di-*t*-butyl-3,4-bis(chloromethyl)thiophene (**24**) with ethylamine in benzene, Gol'dfarb and Litvinov[19] obtained N,N'-diethyl-3,4-bis(aminomethyl)-2,5-di-*t*-butylthiophene in 99% yield. No thienopyrrole derivative could be detected.

The low yield of **18** (X = Cl) in the reaction of **17** (X = Cl) with methylamine and the fact that no thienopyrrole derivatives were found in the reactions of **20** and **24** with primary amines are in accordance with our results obtained in the reaction of tetrachloride **10** with ethylamine. These results are a support of our explanation "steric inhibition of intramolecular cyclizations by *ortho* substituents."

Further Experimental Evidence.—Convincing experimental support for our proposal that appropriate *ortho* substituents can inhibit SN2 cyclization in aromatic systems was found in the observation that cyclization was successful when the chlorine atoms on the thiophene nucleus in **10** were removed *prior* to the reaction with ethylamine. Thus reaction of 3,4-bis(chloromethyl)thiophene (**27**) with ethylamine furnished 5-ethyl-5,6-dihydro-4H-thieno[3,4-*c*]pyrrole (**28**) in 49% yield (Scheme IV). The formation of thieno-

SCHEME IV



25 26 27 28

pyrrole **28** from the reaction of **27** with ethylamine proves that the chlorine atoms on the thiophene nucleus in tetrachloride **10** are responsible for the fact that no thienopyrrole is formed in the reaction of **10** with ethylamine. It cannot be an electron-withdrawing inductive effect of the chlorine atoms, for then the reaction of 3,4-bis(chloromethyl)-2,5-dimethylthiophene (**20**) with ethylamine should furnish a thienopyrrole derivative. Therefore, steric effects of the chlorine atoms at the thiophene nucleus are responsible for the fact that no thienopyrrole derivative is formed in the reaction of **10** with ethylamine.

Reaction of Methyl 2,3-Bis(chloromethyl)-4-methylthiophene-5-carboxylate (30) with Ethylamine.—The reaction of methyl 2,3-bis(chloromethyl)-4-methylthiophene-5-carboxylate (**30**) with ethylamine in acetonitrile was investigated in order to study a reaction of ethylamine with a 2,3-bis(chloromethyl)thiophene derivative having a substituent in the *ortho* position to a CH_2Cl group. In **30**, there is a considerable steric hindrance to the leaving chloride anion from the methyl group at the 4 position, when ethylamine first attacks the $-CH_2Cl$ group in the 2 position. On the other hand, little or no steric hindrance will occur by prior attack of ethylamine at the $-CH_2Cl$ group in the 3 position.

Compound **30** was synthesized by chloromethylation of methyl 3-methylthiophene-2-carboxylate (**29**)[20,21] using chloromethyl methyl ether and zinc chloride as catalyst (Scheme V). Reaction of **30** with ethylamine in acetonitrile gave methyl 5-ethyl-3-methyl-5,6-dihydro-4H-thieno[2,3-*c*]pyrrole-2-carboxylate (**31**, 37%), dimethyl 5,11-diethyl-3,7-dimethyl-4,5,6,10,11,12-hexahydrodithieno[2,3-*c*:3',2'-*h*][1,6]diazecine-2,8-dicar-

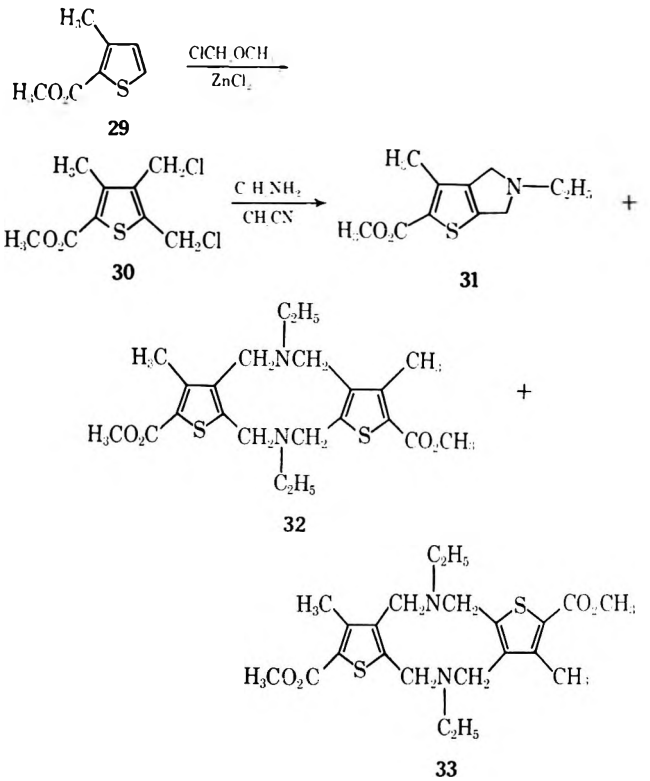
(18) Ya. L. Gol'dfarb and M. S. Kondakova, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*,, 501 (1961).

(19) Ya. L. Gol'dfarb and V. P. Litvinov, *ibid.*, 343 (1963); *Chem. Abstr.*, **59**, 582 (1963).

(20) H. Wynberg and J. de Wit (unpublished results in this laboratory) synthesized **29** *via* a Grignard reaction of 2-bromo-3-methylthiophene.[21]

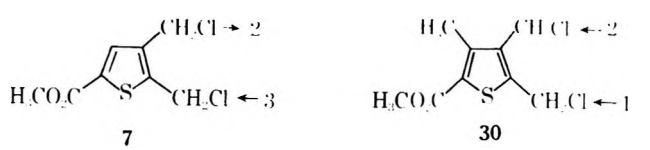
(21) R. M. Kellogg, A. P. Schaap, E. T. Harper, and H. Wynberg, *J. Org. Chem.*, **33**, 2902 (1968).

Scheme V



boxylate (**32**, 4%)[22] and dimethyl 5,11-diethyl-3,9-dimethyl-4,5,6,10,11,12-hexahydrodithieno[2,3-*c*:2′,3′-*h*][1,6]diazecine-2,8-dicarboxylate (**33**, 3%).[23]

The 37% yield of thienopyrrole **31** was a surprise to us, for we assumed prior attack of ethylamine at the $-CH_2Cl$ group in the 2 position of **30**. Steric hindrance in the intramolecular ring closure reaction should then inhibit the formation of thienopyrrole **31**. The relatively high yield of thienopyrrole **31** suggests prior attack of ethylamine at the $-CH_2Cl$ group in the 3 position of **30** and cyclization of this intermediate to the thienopyrrole can occur because there is no steric hindrance involved in this case. We then decided to determine the relative reactivity of the $-CH_2Cl$ groups in methyl 2,3-bis(chloromethyl)-4-methylthiophene-5-carboxylate (**30**) as well as in methyl 2,3-bis(chloromethyl)thiophene-5-carboxylate (**7**). A reaction of **30** and **7**, respectively, was carried out with sodium iodide in acetone as solvent and the reaction was followed with nmr spectroscopy (see Experimental Section for details). The relative reactivities of the $-CH_2Cl$ groups are indicated in the formulas. The data show that in **7** the $-CH_2Cl$ group in the 2 position is the more reactive group, whereas in **30** it is the $-CH_2Cl$ group in the 3 position which is most reactive. With these data, the results obtained in the reaction of **30** with ethylamine become clear; because of the greater relative reactivity of the $-CH_2Cl$ group in the 3 position, most of the ethylamine reacts with this group first and formation of the thienopyrrole **31** will occur.



Experimental Section

All melting points are corrected. The boiling points are uncorrected. Nmr spectra were determined on a Varian A-60, using tetramethylsilane (TMS, τ 10) as internal standard, uv spectra in 95% alcohol using a Zeiss P.M.Q. II, and ir spectra on a Unicam S.P. 200 spectrofotometer. Microanalyses were carried out in the analytical section of our department under the direction of Mr. W. M. Hazenberg.

4,6-Dibromo-1H,3H-thieno[3,4-*c*]thiophene (2).—A warm solution of 8.6 g (0.020 mol) of 2,5-dibromo-3,4-bis(bromomethyl)-thiophene (**1**) in 600 ml of methanol and a solution of 2.0 g (0.025 mol) of sodium sulfide[6] in 100 ml of methanol were added to 250 ml of boiling methanol, during 3 hr. The precipitate in the reaction mixture was collected (see below), the filtrate was concentrated to about 200 ml and 400 ml of water was added. The precipitate was collected and crystallized from methanol giving 3.6 g (60%) of thienothiophene **2**: mp 67–68°; uv max 252.5 mμ (ϵ 9300); nmr (30% in CCl_4) τ 6.20 (s, ArCH_2S–).

Anal. Calcd for $C_6H_4Br_2S_2$ (300.06): C, 24.02; H, 1.34; Br, 53.27; S, 21.37. Found: C, 24.2, 24.1; H, 1.4, 1.4; Br, 53.4, 53.3; S, 20.9, 20.9.

The precipitate (1.7 g) from above was crystallized from pyridine–water (10:1) giving 1.1 g (18%) of 1,3,7,9-tetrabromo-4H,6H,10H,12H-dithieno[3,4-*c*:3′,4′-*h*][1,6]dithiecin (**3**), mp 275° dec.

Anal. Calcd for $C_{12}H_8Br_4S_4$: C, 24.02; H, 1.34; Br, 53.27; S, 21.37; mol wt, 600.12. Found: C, 24.3, 24.2; H, 1.2, 1.2; Br, 53.4, 53.5; S, 21.2, 21.3; mol wt (mass spectroscopy[24]), 596 (based upon ^{32}S and ^{79}Br).

The solubility of this compound was too low for determination of the nmr and uv spectra.

1H,3H-Thieno[3,4-*c*]thiophene (4).—To a solution of 4.5 g (0.015 mol) of thienothiophene **2** in 45 ml of dioxane was added 5.9 g (0.09 g-atom) of zinc powder and 7.2 g (0.12 mol) of acetic acid. The reaction mixture was stirred and refluxed for 24 hr and the solids were removed by filtration of the warm solvent. The filtrate was concentrated and extracted with ether. The ether solution was extracted with Na_2CO_3 solution, dried ($CaCl_2$), concentrated, and sublimed [55° (0.2 mm)] giving 1.6 g (75%) of thienothiophene **4**: mp 60–62° [from petroleum ether (bp 40–70°)]. This compound was identical (ir spectrum and mixture melting point) with one earlier reported.[2]

4,6-Dibromo-1H,3H-thieno[3,4-*c*]thiophene 2,2-Dioxide (5).—A solution of 4.0 g (0.013 mol) of 4,6-dibromo-1H,3H-thieno-[3,4-*c*]thiophene (**2**) in 200 ml of acetic acid was heated at 90° with 4.6 g (0.04 mol) of a 30% H_2O_2 solution for 0.5 hr. The reaction mixture was cooled to 50° and 200 ml of water was added. After cooling to 0°, the precipitate was collected and crystallized from carbon tetrachloride giving 3.95 g (89.5%) of sulfone **5**: mp 182–182.5°; uv max 250 mμ (ϵ 9200), 263 sh (8200); ir (KBr) 1320 and 1128 cm^{-1} (SO_2); nmr (10% in $CDCl_3$) τ 5.78 (s, ArCH_2SO_2–).

Anal. Calcd for $C_6H_4Br_2O_2S_2$ (332.06): C, 21.70; H, 1.21; Br, 48.13; S, 19.32. Found: C, 21.8, 21.7; H, 1.2, 1.2; Br, 48.4, 48.6; S, 19.4, 19.0.

1H,3H-Thieno[3,4-*c*]thiophene 2,2-Dioxide (6).—To a solution of 3.32 g (0.010 mol) of **5** in 30 ml of dioxane was added 3.90 g (0.060 g-atom) of zinc powder and 4.8 g (0.080 mol) of acetic acid. The mixture was stirred and refluxed for 24 hr, and after filtration the filtrate was concentrated. Water was added to the residue, the precipitate was collected and crystallized from carbon tetrachloride giving 1.2 g (69%) of sulfone **6**: mp 164–165°;

(22) This structure was assigned to compound **32**, and not the alternative structure (dimethyl 5,11-diethyl-3,9-dimethyl-4,5,6,10,11,12-hexahydrodithieno[2,3-c:2′,3′-*h*][1,6]diazecine-2,8-dicarboxylate), on the basis of its nmr spectrum (see Experimental Section), which shows for the N-ethyl groups two quartets and two triplets for CH_2 and CH_3, respectively.

(23) This structure was assigned on the basis of the nmr spectrum (see Experimental Section). The CH_2 and CH_3 of the N-ethyl groups show one quartet and one triplet, respectively.

(24) We are indebted to Dr. C. Bokhoven, States Mines, The Netherlands, for the mass spectrometric molecular weight determination.

uv max 244 mμ (ε 6400); ir (KBr) 1320 and 1130 cm^{-1} (SO_2); nmr (5% in $CDCl_3$) τ 2.72 (s, 2, thiophene aromatic), 5.73 (s, 4, Ar**CH$_2$**SO$_2$–).

Anal. Calcd for $C_6H_6O_3S_2$ (174.24): C, 41.35; H, 3.48; S, 36.80. Found: C, 41.0, 41.2; H, 3.4, 3.4; S, 36.2, 36.4.

2,5-Dichloro-3,4-bis(chloromethyl)thiophene (10).—The title compound was prepared recently by Winn and Bordwell[25] by chloromethylation of 2,5-dichlorothiophene using chloromethyl methyl ether in carbon disulfide and tin tetrachloride in 73.8% yield. We obtained tetrachloride **10** in 75% yield by the following procedure.

A solution of 76.5 g (0.5 mol) of 2,5-dichlorothiophene in 500 ml of chloromethyl methyl ether (Fluka, T 52107, n^{20}D 1.397) was cooled in an ice-salt mixture to −5°. Tin tetrachloride (130 g, 0.5 mol) was added in 1.5 hr, keeping the temperature at 0 to −5°. After the addition of $SnCl_4$, the reaction mixture was stirred for 1 hr at 0°, for 2.5 hr at room temperature and boiled for 1 hr. The dark solution was cooled to room temperature and poured with stirring onto 1500 g of crushed ice. The ethereal extract was washed with water, dried (Na_2SO_4), concentrated and distilled giving 93.8 g (75%) of **10**: bp 85° (0.2 mm); mp 40–41° (from petroleum ether, bp 40–60°) [lit.[25] bp 137–145° (2.0 mm), mp 41–42°]; uv max 214 mμ (ε 19,600), 257 (5300); nmr (20% in CCl_4) τ 5.38 (s, Ar**CH$_2$**Cl).

Reaction of 2,5-Dichloro-3,4-bis(chloromethyl)thiophene (10) with Ethylamine.—A solution of 25.0 g (0.1 mol) of tetrachloride **10** in 500 ml of acetonitrile (dried with $CaCl_2$ and distilled, bp 81–82°, n^{20}D 1.3445) and a solution of 13.5 g (0.3 mol) of ethylamine (waterfree, Fluka 50241) in 500 ml of acetonitrile were added to 500 ml of acetonitrile during 30 hr. Stirring was continued for another 90 hr. A precipitate was formed in the reaction mixture. The acetonitrile was removed *in vacuo*, after which the residue was taken up in 300 ml of 2 *N* NaOH solution and 400 ml of ether. The ether solution was extracted with 4 *N* HCl solution. The HCl solution was cooled to about 0° and neutralized with 4 *N* NaOH solution. The separated oil solidified upon standing. The precipitate (23.8 g) was collected[26] and treated with 150 ml of cold methanol in a mortar. The remaining solid was filtered off (for the filtrate, see below). The light brown solid (5.9 g), mp 101–103.5°, was crystallized from methanol giving 5.5 g (27%) of dithienodiazecine **11**: mp 102.5–103.5°; uv max 245 mμ (ε 15,100); ir (KBr) no NH absorption at about 3300 cm^{-1}; nmr (10% in CCl_4) τ 6.27 (s, 8, Ar**CH$_2$**N–), 7.45 (q, 4, J = 7 Hz, N**CH$_2$**CH$_3$), 8.95 (t, 6, J = 7 Hz, NCH$_2$**CH$_3$**).

Anal. Calcd for $C_{16}H_{18}Cl_4N_2S_2$: C, 43.25; H, 4.09; Cl, 31.92; N, 6.31; mol wt, 444.28. Found: C, 43.6, 43.4; H, 4.2, 4.1; Cl, 31.5, 31.6; N, 6.6, 6.3; mol wt (in benzene), 447, 451.

The filtrate (see above) was concentrated *in vacuo* and distilled giving 4.8 g (20%) of secondary amine **12**: bp 106–116° (0.5 mm); mp 80–81° (from petroleum ether, bp 40–60°, cooling to −60°); uv max 246.5 mμ (ε 6500); ir (KBr) 3300 cm^{-1} (NH); nmr (20% in CCl_4) τ 6.35 (s, 4, Ar**CH$_2$**NH–), 7.40 (q, 4, J = 7 Hz, RNH-**CH$_2$**CH$_3$), 8.38 (s, 2, –**NH**–), 8.93 (t, 6, J = 7 Hz, RNHCH$_2$-**CH$_3$**).

Anal. Calcd for $C_{10}H_{16}Cl_2N_2S$ (267.22): C, 44.94; H, 6.04; Cl, 26.54; N, 10.48. Found: C, 44.7, 44.9; H, 6.1, 6.0; Cl, 26.5, 26.6; N, 10.8, 10.6.

2,5-Dichloro-N,N′-diethyl-N,N′-ditosyl-3,4-bis(aminomethyl)thiophene (14) was obtained in 85% yield from **12**, using *p*-toluenesulfochloride in the usual manner: mp 128.5–130°; uv max 233 mμ (ε 27,200); ir (KBr) 1345, 1310, 1115 cm^{-1} (SO_2); nmr (10% in CCl_4) τ 2.39 (d, 4, J = 8 Hz, tosyl aromatic), 2.77 (d, 4, J = 8 Hz, tosyl aromatic), 5.66 (s, 4, Ar**CH$_2$**N–), 6.86 (q, 4, J = 7 Hz, –N**CH$_2$**CH$_3$), 7.60 (s, 6, –C$_6$H$_4$**CH$_3$**), 9.07 (t, 6, J = 7 Hz, –NCH$_2$**CH$_3$**).

Anal. Calcd for $C_{24}H_{28}Cl_2N_2O_4S_3$ (575.59): C, 50.08; H, 4.90; N, 4.87. Found: C, 50.1, 50.1; H, 4.9, 5.0; N, 5.1, 5.3.

The reaction of tetrachloride **10** and ethylamine has been carried out several times. The rate of addition was varied from 0 to 30 hr. Dithienodiazecine **11** and the secondary amine **12** always were obtained in about 27 and 20% yield, respectively. No 1,3-dichloro-5-ethyl-5,6-dihydro-4H-thieno[3,4-c]pyrrole could be detected.

2,5-Dichloro-3,4-bis(iodomethyl)thiophene (13).—A solution of 30.0 g (0.12 mol) of tetrachloride **10** and 39.6 g (0.264 mol) of sodium iodide in 300 ml of acetone was stirred for 3 hr at room temperature. The reaction mixture was concentrated and the residue was crystallized from petroleum ether (bp 40–60°) giving 36.7 g (70%) of iodide **13**: mp 93.5–94.5°; uv max 242 mμ (ε 21,400); nmr (10% in CCl_4) τ 5.62 (s, Ar**CH$_2$**I). The compound is unstable.

Anal. Calcd for $C_6H_4Cl_2I_2S$ (432.87): C, 16.64; H, 0.93; I, 58.63. Found: C, 16.8, 16.6; H, 0.9, 0.9; I, 58.7, 58.6.

Reaction of 2,5-Dichloro-3,4-bis(iodomethyl)thiophene (13) with Ethylamine.—A solution of 10.8 g (0.025 mol) of iodide **13** in 250 ml of acetonitrile and a solution of 3.4 g (0.075 mol) of ethylamine (Fluka 50241) were added to 250 ml of acetonitrile during 4 hr. After stirring overnight the reaction mixture was worked up as described for the reaction of the tetrachloride **10** with ethylamine. Two products were isolated, namely, the secondary amine **12** in 57% yield and the dithienodiazecine **11** in 6% yield. No thienopyrrole derivative could be detected.

1,3-Dichloro-5-tosyl-5,6-dihydro-4H-thieno[3,4-c]pyrrole (15).—A solution of 10.0 g (0.04 mol) of tetrachloride **10** and 6.85 g (0.04 mol) of *p*-toluenesulfonamide in 500 ml of dimethylformamide [distilled from $CaCl_2$, bp 47.0–47.5° (15 mm), n^{20}D 1.4305; lit.[27] bp 153° (760 mm), n^{25}D 1.4269] was dropped in 6 hr into a stirred suspension of 150 g (1.08 mol) of K_2CO_3 in 750 ml of dimethylformamide. The temperature during the addition was about 100–110°. After the addition was complete, the reaction mixture was kept at 100–110° for 0.5 hr. The brown reaction mixture was filtered and the solid on the filter was washed with dimethylformamide and with ether. The ether–DMF solution was concentrated *in vacuo*. The residue was treated with water and the remaining solid was crystallized from ethanol (decolorizing charcoal), giving 6.7 g (48%) of 1,3-dichloro-5-tosyl-5,6-dihydro-4H-thieno[3,4-c]pyrrole (**15**): mp 176–177.5°; uv max 233 mμ (ε 18,500); ir (KBr) 1340, 1150 cm^{-1} (SO_2); nmr (10% in $CDCl_3$) τ 2.25 (d, 2, J = 8 Hz, tosyl aromatic), 2.67 (d, 2, J = 8 Hz, tosyl aromatic), 5.72 (s, 4, Ar**CH$_2$**N–), 7.58 (s, 3, –C$_6$H$_4$**CH$_3$**).

Anal. Calcd for $C_{13}H_{11}Cl_2NO_2S_2$: C, 44.81; H, 3.19; N, 4.03; mol wt, 348.27. Found: C, 45.1, 44.9; H, 3.3, 3.2; N, 4.1, 4.0; mol wt (in ethyl acetate), 344, 346.

5-Tosyl-5,6-dihydro-4H-thieno[3,4-c]pyrrole (16).—To a solution of 10.0 g (0.029 mol) of **15** in 2.2 l. of warm methanol, a suspension of 8.0 g of 10% palladium on charcoal in 250 ml of methanol, in which was dissolved 6.2 g (0.20 mol) of KOH, was added. The reaction mixture was stirred and heated under reflux. A slow stream of hydrogen was bubbled through the reaction mixture. After a reaction time of 74 hr[28] the hot reaction mixture was filtered and the filtrate was concentrated *in vacuo* to a volume of 10 ml. Water and ether were added to the residue. The ethereal extract was dried (Na_2SO_4) and concentrated after which the residue was crystallized from 95% ethanol, giving 3.2 g (40%) of **16** as white crystals: mp 124.5–125.5°; uv max 232 mμ (ε 18,500); ir (KBr) 1150, 1330 cm^{-1} (–SO_2–); nmr (10% in $CDCl_3$) τ 2.26 (d, 2, J = 8 Hz, tosyl aromatic), 2.71 (d, 2, J = 8 Hz, tosyl aromatic), 3.15 (s, 2, thiophene aromatic), 5.63 (s, 4, Ar**CH$_2$**N–), 7.61 (s, 3, –C$_6$H$_4$**CH$_3$**).

Anal. Calcd for $C_{13}H_{13}NO_2S_2$ (279.38): C, 55.89; H, 4.70; N, 5.02. Found: C, 56.3, 56.1; H, 4.7, 4.7; N, 5.0, 4.9.

2,5-Dichloro-3,4-bis(hydroxymethyl)thiophene (25).—A mixture of 5.0 g (0.02 mol) of tetrachloride **10** and 100 ml of water was refluxed for 6 hr. The warm reaction mixture was filtered and cooled, giving 3.0 g (70%) of the dihydroxy derivative **25**: mp 105–106°; uv max 248 mμ (ε 6700); ir (KBr) 3350 cm^{-1} (OH); nmr (4% in $CDCl_3$) τ 5.42 (broad s, 4, Ar**CH$_2$**OH), τ 6.33 (broad s, 2, CH$_2$**OH**); nmr (10% in CD_3COCD_3) τ 5.44 (m).

Anal. Calcd for $C_6H_6Cl_2O_2S$ (213.08): C, 33.82; H, 2.84; S, 15.04. Found: C, 34.0, 33.7; H, 2.9, 2.9; S, 15.2, 14.8.

3,4-Bis(hydroxymethyl)thiophene (26).—To a suspension of 4.0 g of 10% palladium on charcoal in 100 ml of methanol, in which was dissolved 4.0 g (0.07 mol) of KOH, 4.0 g (0.019 mol) of **25** was added. The reaction mixture was stirred and refluxed, while a slow stream of hydrogen was bubbled through the mixture. After a reaction time of 40 hr,[29] the mixture was filtered, the filtrate concentrated and the residue was extracted with acetone. The acetone was removed by distillation and the residue was taken up in dry ether. The ether solution was cooled until −60° giving 1.2 g (44%) of 3,4-bis(hydroxymethyl)thiophene (**26**): mp 65–66°; uv max 236 mμ (ε 5300), 239 (5300); ir

(25) M. Winn and F. G. Bordwell, *J. Org. Chem.*, **32**, 1610 (1967).

(26) The filtrate, extracted with ether, did not give organic material.

(27) Houben-Weyl, "Methoden der organischen Chemie," Band 1/2, 4th ed, Georg Thieme Verlag, Stuttgart, 1959, p 831.

(28) The reaction was followed with tlc (silica gel, solvent benzene).

(29) The reaction was followed with tlc (silica gel, solvent ethyl acetate).

(KBr) 3300 cm^{-1} (OH); nmr (10% in CD_3COCD_3) τ 2.71 (s, 2, thiophene aromatic), 5.37 (s, 4, $ArCH_2OH$), 5.67 (broad s, 2, $ArCH_2OH$).

Anal. Calcd for $C_6H_8O_2S$ (144.18): C, 49.97; H, 5.59; S, 22.24. Found: C, 50.2, 50.3; H, 5.6, 5.6; S, 22.3, 21.9.

3,4-Bis(chloromethyl)thiophene (27).—To a solution of 2.5 g (0.017 mol) of 3,4-bis(hydroxymethyl)thiophene (**26**) in 50 ml of chloroform, 2.5 ml of pyridine was added. In a nitrogen atmosphere, a solution of 6.0 g (0.05 mol) of thionyl chloride in 10 ml of chloroform was added at such a rate that the reaction mixture boiled. After the addition the mixture was refluxed for 0.5 hr. After cooling, the reaction mixture was poured into 400 g of ice–water and stirred for 20 min. The chloroform layer was separated and washed with 50 ml of 1 *N* HCl solution, 50 ml of 10% Na_2CO_3 solution and 50 ml of water. The chloroform solution was dried ($CaCl_2$), concentrated, and distilled giving 2.0 g (65%) of 3,4-bis(chloromethyl)thiophene (**27**): bp 98° (2.2 mm); mp 51–53° [from petroleum ether (bp 40–60°)]; uv max 230 mμ sh (ε 5200); ir (KBr) no OH absorption; nmr (10% in CCl_4) τ 2.72 (s, 2, thiophene aromatic), 5.34 (s, 4, $ArCH_2Cl$).

Anal. Calcd for $C_6H_6Cl_2S$ (181.09): C, 39.80; H, 3.33; Cl, 39.19. Found: C, 39.5, 39.9; H, 3.4, 3.3; Cl, 38.9.

5-Ethyl-5,6-dihydro-4H-thieno[3,4-c]pyrrole (28).—A solution of 1.27 g (0.007 mol) of 3,4-bis(chloromethyl)thiophene (**28**) and 0.94 g (0.021 mol) of waterfree ethylamine in 300 ml of acetonitrile was stirred for 100 hr at room temperature. The acetonitrile was removed by distillation *in vacuo*. A mixture of 30 ml of 2 *N* NaOH solution and 40 ml of ether was added to the residue. The ethereal extract was extracted with 2 *N* HCl solution. The acidic extract was neutralized with 4 *N* NaOH solution (temperature about 0°). The basic solution was extracted with ether. The ethereal extract was dried (Na_2SO_4), concentrated, and distilled giving 0.5 g (49%) of thienopyrrole **28**: bp 81° (2.0 mm); $n^{20}D$ 1.5510; uv max 242.5 mμ (ε 6200), 232.5 sh (5900); ir (neat) no NH absorption at about 3300 cm^{-1}; nmr (10% in CCl_4) τ 3.28 (s, 2, thiophene aromatic), 6.37 (s, 4, $ArCH_2N$), 7.29 (q, 2, J = 7 Hz, $-NCH_2CH_3$), 8.87 (t, 3, J = 7 Hz, NCH_2CH_3).

Anal. Calcd for $C_8H_{11}NS$: C, 62.70; H, 7.23; S, 20.93; mol wt, 153.24. Found: C, 62.5, 62.5; H, 7.2, 7.4; S, 20.6, 20.7; mol wt (in benzene), 157, 159.

Methyl 2,3-Bis(chloromethyl)-4-methylthiophene-5-carboxylate (30).—A solution of 14.7 g (0.094 mol) of methyl 3-methylthiophene-2-carboxylate (**29**) in 100 ml of chloromethyl methyl ether was added in 35 min to a boiling solution of 13.6 g (0.1 mol) of $ZnCl_2$ in 350 ml of chloromethyl methyl ether. After the addition the reaction mixture was refluxed for 4.5 hr. After cooling, the reaction mixture was poured into 1.5 l. of ice–water and stirred for 45 min. The precipitate was collected and washed with water, 0.1 *N* NaOH solution and again with water. The solid was taken up in ether. The ethereal extract was dried (Na_2SO_4) and concentrated. The residue was crystallized from petroleum ether (bp 40–60°) giving 19.5 g (82%) of dichloride **30**: mp 98.5–99.5°; uv max 218 mμ (ε 14,200), 270 (ε 13,400); nmr (10% in CCl_4) τ 5.27 (s, 2, CH_2Cl 2 position), 5.47 (s, 2, CH_2Cl 3 position), 6.17 (s, 3, $COOCH_3$), 7.44 (s, 3, $ArCH_3$).

Anal. Calcd for $C_9H_{10}Cl_2O_2S$ (253.15): C, 42.70; H, 3.98; Cl, 28.01. Found: C, 42.8, 42,6; H, 4.2, 3.9; Cl, 28.0, 27.8.

Reaction of Methyl 2,3-Bis(chloromethyl)-4-methylthiophene-5-carboxylate (30) with Ethylamine.—A solution of 7.6 g (0.03 mol) of dichloride **30** and 4.05 g (0.09 mol) of ethylamine in 800 ml of acetonitrile was stirred for 8 days. A precipitate was formed in the reaction mixture. The acetonitrile was removed *in vacuo*, after which the residue was taken up in 125 ml of 2 *N* NaOH solution and 170 ml of ether. The ether solution was extracted with 4 *N* HCl solution. The HCl solution was cooled to about 0°, neutralized with 4 *N* NaOH solution and extracted with ether. The ethereal extract was dried (Na_2SO_4), concentrated and treated with cold methanol giving 0.2 g (3%) of diazecine **33** (for the filtrate, see below): mp 218–219° (from CCl_4); uv max 269 mμ (ε 22,300); ir (KBr) no NH absorption at about 3300 cm^{-1}; nmr (15% in $CDCl_3$) τ 6.15 (s, 6, $COOCH_3$), 6.13 (s, 4, $ArCH_2N$), 6.64 (s, 4, $ArCH_2N$), 7.08 (q, 4, J = 7 Hz, NCH_2CH_3), 7.42 (s, 6, $ArCH_3$), 8.72 (t, 6, J = 7 Hz, NCH_2CH_3).

Anal. Calcd for $C_{22}H_{30}O_4N_2S_2$: C, 58.64; H, 6.71; N, 6.22; mol wt, 450.64. Found: C, 58.5, 58.5; H, 6.6, 6.7; N, 6.1, 6.1; mol wt (mass spectroscopy), 450.

The filtrate (see above) was concentrated and distilled giving 2.5 g (37%) of thienopyrrole **31**: bp 128° (0.2 mm); uv max 258 mμ (ε 11,000), 286 (8900); ir (neat) no HN absorption at about 3300 cm^{-1}; nmr (10% in CCl_4) τ 6.19 (m, 4, $-ArCH_2N(Et)CH_2-$), 6.21 (s, 3, $COOCH_3$), 7.24 (q, 2, J = 7 Hz, NCH_2CH_3), 7.61 (s, 3, $ArCH_3$), 8.87 (t, 3, J = 7 Hz, NCH_2CH_3).

Anal. Calcd for $C_{11}H_{15}O_2NS$: C, 58.64; H, 6.71; N, 6.22; mol wt, 225.32. Found: C, 58.5, 58.5; H, 6.7, 6.8; N, 6.1, 6.2; mol wt (mass spectroscopy), 225.

The residue in the distillation flask was treated with methanol (decolorizing charcoal) and cooled until −30°, giving 0.25 g (4%) of the dithienodiazecine **32**: mp 142–143° (from CH_3OH); uv max 261 mμ (ε 22,300), 270 sh (21,400); ir (KBr) no NH absorption at about 3300 cm^{-1}; nmr (15% in $CDCl_3$) τ 6.07 (s, 4, $ArCH_2N$), 6.21 (s, 6, $COOCH_3$), 6.29 (s, 4, $ArCH_2N$), 6.90–7.45 (two partially overlapping quadruplets 4, NCH_2CH_3), 7.54 (s, 6, $ArCH_3$), 8.60–8.90 (two triplets partially falling over each other, 6, NCH_2CH_3).

Anal. Calcd for $C_{22}H_{30}O_4N_2S_2$: C, 58.64; H, 6.71; N, 6.22; mol wt, 450.64. Found: C, 58.5, 58.6; H, 6.8, 6.7; N, 6.2, 6.2; mol wt (mass spectroscopy), 450.

Determination of the Relative Reactivities of the $-CH_2Cl$ Groups in Dichlorides 7 and 30, Respectively. A. Methyl 2,3-Bis(chloromethyl)thiophene-5-carboxylate (7).—The following reaction mixtures were prepared: I, 1.2 g (5.0 mmol) of **7** in 12 ml of acetone; II, solution I plus 0.375 g (2.5 mmol) of NaI; III, solution II plus 0.375 g (2.5 mmol) of NaI; IV, solution III plus excess NaI. Nmr spectra (sweep width 50 cps) were run of the solutions I, II, III and IV, after filtration (NaCl is insoluble in acetone). In solutions II and III there are four compounds, namely, methyl 2,3-bis(chloromethyl)thiophene-5-carboxylate (**7**, J in Table I), methyl 3-chloromethyl-2-iodomethylthiophene-5- carboxylate (K), methyl 2-chloromethyl-3-iodomethylthiophene-5-carboxylate (L) and methyl 2,3-bis(iodomethyl)thiophene-5-carboxylate (M). The chemical shifts[30] in cycles per second relative to TMS (0 cps) of the CH_2Cl and CH_2I groups are determined and tabulated in Table I. J_2 means $CH_2(Cl)$ group of J in the 2 position, K_2 means $CH_2(I)$ group of K in the 2 position, etc. The differences in chemical shifts of $J_2 - J_3$, $K_2 - K_3$, etc., in all spectra are about the same, but the chemical shifts relative to TMS of, for instance, the CH_2Cl groups in J in the different spectra are not the same, due to differences in the solvent medium. The data between brackets, behind the chemical shifts, are the relative area of the peaks for each spectrum. From these relative areas, we can determine the relative reactivity of the CH_2Cl groups in the 2 and 3 position, respectively, as (6 + 18):(6 + 10) = 3:2 (for solution II) and as (17 + 18):(17 + 7) = 3:2 (for solution III).

Table I

Data from the Nmr Spectra of Solutions I, II, III, and IV

	Chemical shifts of solutions, cps (area)			
CH_2X	I	II	III	IV
J_2	295.2 (1)	298.2 (31)	298.1 (7)	
J_3	280.7 (1)	283.9 (31)	283.5 (7)	
$J_2 - J_3$	14.5	14.3	14.6	
K_2		292.7 (18)	292.6 (18)	
K_3		280.1 (18)	279.9 (18)	
$K_2 - K_3$		12.6	12.7	
L_2		295.0 (10)	294.7 (7)	
L_3		274.3 (10)	273.7 (7)	
$L_2 - L_3$		20.7	21.0	
M_2		290.4 (6)	290.1 (17)	292.3 (1)
M_3		271.3 (6)	270.6 (17)	273.1 (1)
$M_2 - M_3$		19.1	19.5	19.2

B. **Methyl 2,3-Bis(chloromethyl)-4-methylthiophene-5-carboxylate (30).**—The following solutions (reaction mixtures) were prepared: V, 1.26 g (5.0 mmol) of **30** in 13 ml of acetone; VI, solution V plus 0.375 g (2.5 mmol) of NaI; VII, solution VI plus 0.375 g (2.5 mmol) of NaI; VIII, solution VII plus excess NaI. Nmr spectra (sweep width 50 cps) were run of solutions V, VI, VII and VIII, after filtration. In solutions VI and VII, there are four compounds, namely, methyl 2,3-bis(chloromethyl)-4-methylthiophene-5-carboxylate (**30**, indicated as N in Table II), methyl 3-chloromethyl-2-iodomethyl-4-methylthiophene-5-car-

(30) All signals are doublets with J = 0.5 Hz.

TABLE II

DATA FROM THE NMR SPECTRA OF SOLUTIONS V, VI, VII AND VIII

	Chemical shifts of solutions, cps (area)			
CH_2X	V	VI	VII	VIII
N_2	303.6 (1)	299.3 (30)	301.1 (9)	
N_3	288.6 (1)	284.3 (30)	286.4 (9)	
$N_2 - N_3$	15.0	15.0	14.7	
O_2		293.7 (7)	295.6 (5)	
O_3		282.2 (7)	284.3 (5)	
$O_2 - O_3$		11.5	11.3	
P_2		296.3 (19)	298.0 (24)	
P_3		272.4 (19)	274.7 (24)	
$P_2 - P_3$		23.9	23.3	
Q_2		291.4 (3)	293.4 (15)	297.2 (1)
Q_3		270.1 (3)	272.5 (15)	276.1 (1)
$Q_2 - Q_3$		21.3	20.9	21.1

boxylate (O), methyl 2-chloromethyl-3-iodomethyl-4-methylthiophene-5-carboxylate (P) and methyl 2,3-bis(iodomethyl)-4-methylthiophene-5-carboxylate (Q). The chemical shifts[31] in cycles per second, relative to TMS (0 cps) of the CH_2Cl and CH_2I groups are determined and tabulated in Table II. The meaning of the letters N_2, N_3, etc., is analogous to those in A.

From the relative area (in brackets, behind the chemical shifts) the relative reactivity of the CH_2Cl groups in the 2 and 3 position, respectively, of **30** can be determined as (3 + 7):(3 + 19) = 1:2 (for solution VI) and as (15 + 5):(15 + 24) = 1:2 (for solution VII).

(31) All signals are singlets.

Registry No.—**2**, 18354-60-4; **3**, 18354-61-5; **4**, 250-35-1; **5**, 18354-63-7; **6**, 18354-64-8; **10**, 10095-90-6; **11**, 18354-66-0; **12**, 18354-67-1; **13**, 18354-68-2; **14**, 18354-69-3; **15**, 18354-70-6; **16**, 18354-71-7; **25**, 18354-72-8; **26**, 18354-73-9; **27**, 18448-62-9; **28**, 18354-74-0; **30**, 18354-75-1; **31**, 18354-76-2; **32**, 18354-77-3; **33**, 18354-78-4.

Acknowledgment.—We thank Mr. K. Hovius for help in the syntheses of several compounds described in this article.

The Synthesis of 1H,3H-Thieno[3,4-*c*]furan. Another Example of Steric Inhibition of Intramolecular Cyclization by *ortho* Substituents[1]

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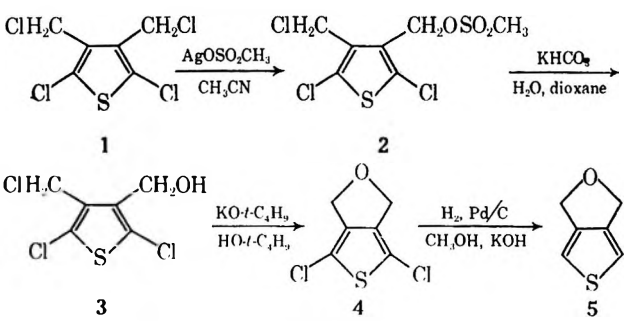
For the synthesis of 1H,3H-thieno[3,4-*c*]furan (**5**), it was found necessary to prepare 2,5-dichloro-3-chloromethyl-4-hydroxymethylthiophene (**3**). Cyclization, with potassium *t*-butoxide as base, and catalytic dechlorination furnished the title compound **5**. Attempts to synthesize 4,6-dichloro-1H,3H-thieno[3,4-*c*]furan (**4**) by treatment of the hydroxy chloride **3** with sodium hydroxide in water–dioxane were unsuccessful and bis(2,5-dichloro-3-hydroxymethyl-4-thenyl) ether (**9**) was obtained. This is another example of steric inhibition of intramolecular cyclization by *ortho* substituents.

In continuation of our studies of the synthesis and properties of anellated five-membered rings on thiophene,[2-7] we wish to describe the synthesis of 1H,3H-thieno[3,4-*c*]furan (**5**).

Reaction of 2,5-dichloro-3,4-bis(chloromethyl)thiophene (**1**)[6] with 0.5 equiv of silver methanesulfonate[8] in acetonitrile gave the mesylate of 2,5-dichloro-3-chloromethyl-4-hydroxymethylthiophene (**2**) in 55% yield. Treatment of a solution of mesylate **2** in water–dioxane with potassium hydrogen carbonate furnished 2,5-dichloro-3-chloromethyl-4-hydroxymethylthiophene (**3**) in 82% yield (Scheme I). Ring closure of hydroxy chloride **3** to 4,6-dichloro-1H,3H-thieno[3,4-*c*] furan (**4**) was effected in 25% yield, using potassium *t*-butoxide in *t*-butyl alcohol. Catalytic dechlorination of **4** furnished 1H,3H-thieno[3,4-*c*]furan (**5**), mp 53–54°, in 45% yield.

SCHEME I



In the reaction of tetrachloride **1** with 0.5 equiv of silver methanesulfonate, dimesylate **6** was isolated as a by-product in 9% yield (Scheme II). Dimesylate **6** was obtained in 71% yield on treatment of tetrachloride **1** with more than 2 equiv of silver methanesulfonate. Reaction of dimesylate **6** with potassium carbonate in water–dioxane gave 2,5-dichloro-3,4-bis(hydroxymethyl)thiophene (**7**) in 87% yield. The same product was obtained in 65% yield on boiling dimesylate **6** with water. Dihydroxy compound **7** was obtained in 70% yield on treatment of tetrachloride **1** with boiling water.[6] The last-mentioned reactions normally give the dihydroxy analogs, in contrast to the reaction

(1) Abstracted in part from the doctoral dissertation of D. J. Z., Sept 8, 1967, Groningen.

(2) H. Wynberg and D. J. Zwanenburg, *J. Org. Chem.*, **29**, 1919 (1964).

(3) D. J. Zwanenburg, H. de Haan, and H. Wynberg, *ibid.*, **31**, 3363 (1966).

(4) H. Wynberg and D. J. Zwanenburg, *Tetrahedron Lett.*, 761 (1967).

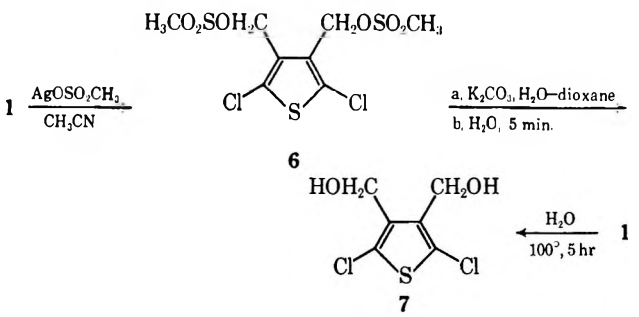
(5) D. J. Zwanenburg, J. Feyen, and H. Wynberg, *Rec. Trav. Chim. Pays-Bas*, **86**, 589 (1967).

(6) D. J. Zwanenburg and H. Wynberg, *J. Org. Chem.*, **34**, 335 (1969).

(7) Doctoral dissertation of D. J. Z.

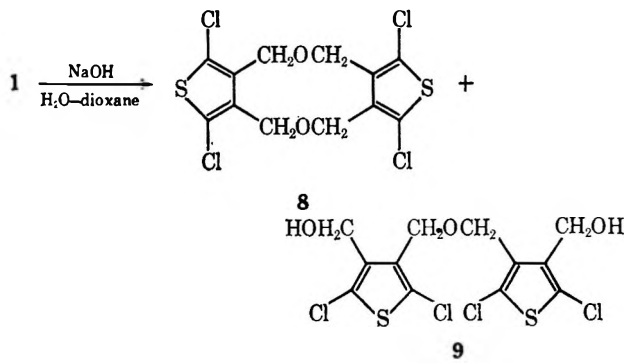
(8) W. D. Emmons and A. F. Ferris, *J. Amer. Chem. Soc.*, **75**, 2257 (1953).

Scheme II

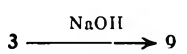


of 3,4-bis(chloromethyl)-2,5-dimethylthiophene with water at 70–80°. Gol'dfarb and Kondakova[9] obtained 1,3,7,9-tetramethyl-4H,6H,10H-dithieno[3,4-*c*]:-[3′,4′-*f*]oxocin in 51% yield in the last reaction.

Reaction of tetrachloride **1** with sodium hydroxide in water–dioxane gave two products, namely, 1,3,-7,9-tetrachloro-4H,6H,10H,12H-dithieno[3,4-*c*:3′,4′-*h*]-[1,6]dioxecin (**8**) and bis(2,5-dichloro-3-hydroxymethyl-4-thenyl) ether (**9**).



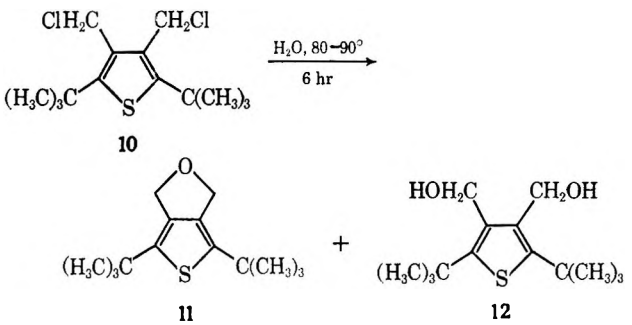
Attempts to cyclize hydroxy chloride **3** to thienofuran **4** using sodium hydroxide in water–dioxane were unsuccessful. Instead, ether **9** was obtained in 49% yield.



Discussion

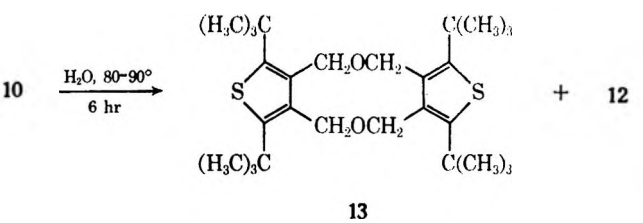
Reaction of 2,5-dichloro-3chloromethyl-4-hydroxymethylthiophene (**3**) with potassium *t*-butoxide in *t*-butyl alcohol furnished thienofuran **4**, whereas reaction of **3** with sodium hydroxide in water–dioxane did not. In the last case, sodium hydroxide is not basic[10,11] enough to abstract a proton from the OH group in **3**. The formation of intermolecular products (**8** and **9**) or intramolecular product **4** as a function of reaction conditions indicates that the two reaction paths are sensitive to a number of factors which are not readily unraveled. The intramolecular alcoholysis of **3** to a thienofuran is sterically inhibited by the chlorine atoms at the nucleus of thiophene and other reactions take place. This is another example of steric inhibition of intramolecular cyclization by *ortho* substituents.[6] In the reaction of **3** with potassium *t*-butoxide, the base[10] abstracts a proton from the OH group in **3** to form anion $-CH_2O^-$. The steric hindrance of the chlorine atoms at the thiophene nucleus can be overcome with this highly nucleophilic anion.

The Reaction of 2,5-Di-*t*-butyl-3,4-bis(chloromethyl)-thiophene (10) with Water.—Gol'dfarb and Kondakova obtained a product with mp 220–221° and 2,5-di-*t*-butyl-3,4-bis(hydroxymethyl)thiophene (**12**) in the reaction of 2,5-di-*t*-butyl-3,4-bis(chloromethyl)thiophene (**10**) with water.[9] Gol'dfarb and Kondakova



assigned structure **11** to the compound with mp 220–221° on the basis of the elemental analysis and the reaction with thionyl chloride, giving dichloride **10**.

The formation of thienofuran **11** in the reaction of dichloride **10** with the weakly nucleophilic water seemed unlikely to us. We repeated the reaction of dichloride **10** with water using the method described by Gol'dfarb and Kondakova.[9] Our results were in accordance with those of the Russian authors. The compound with mp 220–221° was found to have a molecular weight of 478 and 476. Therefore, structure **11**, claimed by Gol'dfarb and Kondakova, cannot be correct. The spectral properties (nmr and ir spectra, see Experimental Section), the elemental analysis and the molecular weight are in accordance with the structure 1,3,7,9-tetra-*t*-butyl-4H,6H,10H,12H-dithieno[3,4-*c*:3′,4′-*h*][1,6]dioxecin (**13**). The "structure proof" of Gol'dfarb and Kondakova holds of course for the dimeric structure **13** as well; with thionyl chloride, the latter will give dichloride **10**, as would compound **11**.



Experimental Section

All melting points are corrected. The boiling points are uncorrected. Nmr spectra were determined on a Varian A-60, using tetramethylsilane (TMS, τ 10) as internal standard, uv spectra in 95% alcohol using a Zeiss P.M.Q. II, ir spectra on a Unicam S.P. 200, and mass spectra on MS-9 mass spectrometer. Microanalyses were carried out in the analytical section of our department under the direction of Mr. W. M. Hazenberg.

Mesylate of 2,5-Dichloro-3-chloromethyl-4-hydroxymethylthiophene (2).—A solution of 20.3 g (0.10 mol) of silver methanesulfonate[8] in 250 ml of anhydrous acetonitrile was added to a boiling solution of 50.0 g (0.20 mol) of 2,5-dichloro-3,4-bis-(chloromethyl)thiophene (**1**)[6] in 500 ml of anhydrous acetonitrile, during 2 hr. After the addition the reaction mixture was re-

(9) Ya. L. Gol'dfarb and M. S. Kondakova, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1208 (1956).

(10) The pK_a values[11] of benzyl alcohol, *t*-butyl alcohol and water are 18, 19 and 15.7, respectively.

(11) D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965, p 4.

fluxed for 2 hr. After cooling, the reaction mixture was filtered, concentrated *in vacuo* and extracted with benzene. The benzene solution was concentrated and the residue was extracted with hot petroleum ether (bp 60–80°). The petroleum ether solution was treated with charcoal and concentrated to a volume of 500 ml. After cooling to −20°, 15.4 g of monomesylate **2** was obtained: mp 58–59°; uv max 257 mμ (ε 5700); ir (KBr) 1360 and 1175 cm^{-1} ($ROSO_2R$); nmr (10% in CCl_4) τ 4.84 (s, 2, $ArCH_2OSO_2CH_3$), 5.43 (s, 2, $ArCH_2Cl$), 7.03 (s, 3, $-OSO_2CH_3$).

Anal. Calcd for $C_7H_7Cl_3O_3S_2$ (309.62): C, 27.16; H, 2.26; S, 20.72. Found: C, 27.1, 27.3; H, 2.2, 2.5; S, 20.9, 20.9.

The petroleum ether filtrate was concentrated to 250 ml and cooled to −80° giving 27.5 g of the starting material **1**.

The residue which remained behind after the petroleum ether extraction was crystallized from carbon tetrachloride giving 3.1 g, mp 83–85°, of the dimesylate of 2,5-dichloro-3,4-bis(hydroxymethyl)thiophene (**6**, see below). The yield of **2** and **6**, based on recovered **1**, was 55 and 9%, respectively.

2,5-Dichloro-3-chloromethyl-4-hydroxymethylthiophene (3).—A solution of 13.9 g (0.045 mol) of mesylate **2** in 225 ml of dioxane and 150 ml of water was warmed up to the boiling point. Potassium hydrogen carbonate was added until the CO_2 liberation stopped. The reaction mixture was refluxed for 15 min. After cooling the solution was saturated with NaCl and extracted with ether. The ethereal extract was dried ($CaCl_2$) and concentrated. The residue was purified by column chromatography (silica gel, tube 40 cm long and 2.4 cm diameter, eluent benzene). After 0.1 g of mesylate **2**, 8.5 g (82%) of 2,5-dichloro-3-chloromethyl-4-hydroxymethylthiophene (**3**) was obtained: mp 79–80° (from petroleum ether, bp 60–80°); uv max 251 mμ (ε 5900); ir (KBr) 3300 cm^{-1} (OH); nmr (10% in $CDCl_3$) τ 5.37 (s, 2, CH_2OH), 5.39 (s, 2, CH_2Cl), 7.56 (broad s, 1, OH).

Anal. Calcd for $C_6H_5Cl_3OS$ (231.52): C, 31.11; H, 2.18; Cl, 45.95. Found: C, 31.1, 31.4; H, 2.3, 2.3; Cl, 45.6, 45.6.

4,6-Dichloro-1H,3H-thieno[3,4-*c*]furan (4).—A solution of 9.3 g (0.04 mol) of hydroxy chloride **3** in 200 ml of anhydrous *t*-butyl alcohol and a solution of 2.3 g (0.06 g-atom) of potassium in 200 ml of anhydrous *t*-butyl alcohol were added to 400 ml of boiling *t*-butyl alcohol during 3 hr, in a nitrogen atmosphere. After the addition, the reaction mixture was stirred and boiled for 2 hr, and concentrated *in vacuo*. The residue was taken up in ether and water. The ethereal extract was dried ($CaCl_2$) and concentrated. The residue was purified by column chromatography (silica gel, tube 40 cm long and 2.4 cm diameter, eluents CCl_4 and benzene) giving 1.95 g (25%) of thienofuran **4**: mp 48–49°, after sublimation [30° (0.1 mm)]; uv max 247 mμ (ε 10,000); ir (KBr) 1130 cm^{-1} ($-CH_2OCH_2-$); nmr (10% in CCl_4) τ 5.36 (s, $ArCH_2O-$).

Anal. Calcd for $C_6H_4Cl_2OS$: C, 36.94; H, 2.07; S, 16.43; mol wt, 195.06. Found: C, 36.9, 36.8; H, 2.1, 2.1; S, 16.4, 16.3; mol wt (in ethyl acetate), 202, 203.

1H,3H-Thieno[3,4-*c*]furan (5).—To a suspension of 1.8 g of 10% Pd/C in 50 ml of methanol was added a solution of 1.1 g (5.7 mmol) of **4** and 1.8 g (32 mmol) of KOH in 50 ml of methanol. The reaction mixture was refluxed and a slow stream of hydrogen was bubbled through the mixture. After a reaction time of 22 hr a suspension of 0.5 g of 10% Pd–C in 50 ml of methanol was added to the reaction mixture and hydrogen was bubbled through the mixture for another 18 hr. The reaction mixture was filtered and concentrated *in vacuo*. The residue was taken up in water and ether. The ethereal solution was dried ($CaCl_2$) and concentrated. The residue was crystallized from petroleum ether (bp 40–60°) at low temperature (−70°) giving 320 mg (45%) of 1H,3H-thieno[3,4-*c*]furan (**5**): mp 53–54°; uv max 244 mμ (ε 6600); nmr (10% in CCl_4) τ 3.26 (s, 2, thiophene aromatic), 5.26 (s, 4, $ArCH_2O-$).

Anal. Calcd for C_6H_6OS (126.17): C, 57.11; H, 4.78; S, 25.42. Found: C, 57.1; H, 4.9; S, 24.6.

Dimesylate of 2,5-Dichloro-3,4-bis(hydroxymethyl)thiophene (6).—To a solution of 20.4 g (0.1 mol) of silver methanesulfonate[8] in 100 ml of anhydrous acetonitrile was added 10.0 g (0.04 mol) of 2,5-dichloro-3,4-bis(chloromethyl)thiophene (**1**). The solution was stirred for 3 hr at room temperature and refluxed for 1 hr. After cooling, the reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was extracted with benzene. The benzene solution was concentrated and the residue was crystallized from carbon tetrachloride giving 10.5 g (71%) of the unstable dimesylate **6**: mp 85–86°; uv max 256 mμ (ε 5800); ir (KBr) 1350 and 1190 cm^{-1} ($ROSO_2R$); nmr (20% in $CDCl_3$) τ 4.75 (s, 2, $ArCH_2O-$), 6.92 (s, 3, OSO_2CH_3).

Anal. Calcd for $C_8H_{10}Cl_2O_6S_3$ (369.26): C, 26.02; H, 2.72; S, 26.05. Found: C, 25.9, 25.9; H, 2.8, 2.8; S, 25.5, 25.5.

2,5-Dichloro-3,4-bis(hydroxymethyl)thiophene (7).—A solution of 3.7 g (0.01 mol) of dimesylate **6** in 75 ml of water and 75 ml of dioxane was refluxed for 5 min and 2.1 g (0.02 mol) of Na_2CO_3 was added in 5 min. The reaction mixture was boiled for 5 min and after cooling saturated with NaCl. The reaction mixture was extracted with ether. The ethereal extract was dried ($CaCl_2$) and concentrated. The residue was crystallized from carbon tetrachloride giving 1.85 g (87%) of the dihydroxy compound **7**: mp 107–107.5°; uv max 248 mμ (ε 6700); ir (KBr) 3350 cm^{-1} (OH); nmr (4% in $CDCl_3$) τ 5.42 (broad s, 4, CH_2OH), 6.33 (broad s, 2, CH_2OH); nmr (10% in CD_3COCD_3) τ 5.36–5.52 (m).

Anal. Calcd for $C_6H_6Cl_2O_2S$ (213.08): C, 33.82; H, 2.84; S, 15.04. Found: C, 34.0, 33.7; H, 2.9, 2.9; S, 15.2, 14.8.

The dihydroxy compound **7** was obtained in 65% yield on boiling 2.0 g (5.4 mmol) of dimesylate **6** with 75 ml of water for 5 min. The hot reaction mixture was filtered and after cooling 0.75 g (65%) of **7**, mp 106–107°, was obtained.

Reaction of 2,5-Dichloro-3,4-bis(chloromethyl)thiophene (1) with Sodium Hydroxide in Water–Dioxane.—A solution of 3.2 g (0.08 mol) of NaOH in 100 ml of water and 100 ml of dioxane was added to a stirred, boiling solution of 10.0 g (0.04 mol) of tetrachloride **1** during 8 hr. After the addition the reaction mixture was refluxed and stirred for 15 hr. After cooling the precipitate was collected (for the filtrate, see below) and crystallized from chloroform giving 3.0 g (38%) of the dithienodioxecin **8**: mp 270–271°; uv max (CH_2Cl_2)[12] 246 mμ (ε 14,400); ir (KBr) 1090 cm^{-1} (CH_2OCH_2), nmr (5% in pyridine) τ 5.49 (s, $ArCH_2O-$).

Anal. Calcd for $C_{12}H_8Cl_4O_2S_2$: C, 36.94; H, 2.07; S, 16.43; mol wt, 390.12. Found: C, 36.9, 36.7; H, 2.1, 2.1; S, 16.3, 16.3; mol wt (mass spectroscopy), 388 (on basis of ^{32}S and ^{35}Cl).

The filtrate was poured into water. The precipitate (3.0 g) was collected and crystallized from $CHCl_3$ giving 0.85 g (10%) of ether **9**: mp 179.5–180.5°; uv max 247.5 mμ (ε 12,400); ir (KBr) 3350 (OH) and 1070 cm^{-1} ($-CH_2OCH_2-$); nmr (10% in pyridine) τ 5.17 (s, 4, CH_2OH), 5.23 (s, 4, $-CH_2OCH_2-$).

Anal. Calcd for $C_{12}H_{10}Cl_4O_3S_2$: C, 35.30; H, 2.49; Cl, 34.75; S, 15.71; mol wt, 408.16. Found: C, 35.0, 35.2; H, 2.4, 2.5; Cl, 35.0, 35.2; S, 15.7, 15.6; mol wt (in ethyl acetate), 397, 408.

In the $CHCl_3$ mother liquors, **9** and **4** could not be detected (tlc, silica gel, eluent benzene).

Reaction of 2,5-Dichloro-3-chloromethyl-4-hydroxymethylthiophene (3) with Sodium Hydroxide in Water–Dioxane.—A solution of 1.15 g (0.005 mol) of hydroxy chloride **3** in 25 ml of water and 25 ml of dioxane was added in 2.5 hr to a boiling solution of 0.40 g (0.01 mol) of NaOH in 25 ml of water and 25 ml of dioxane. After the addition the reaction mixture was boiled for 1 hr. After cooling in ice the precipitate was collected and crystallized from carbon tetrachloride giving 0.5 g (49%) of ether **9**: mp 179–180°. In the mother liquor no thienofuran **4** could be detected.

Reaction of 2,5-Di-*t*-butyl-3,4-bis(chloromethyl)thiophene (10) with Water According to Gol'dfarb and Kondakova.[9]—A stirred mixture of 5.0 g (0.017 mol) of 2,5-di-*t*-butyl-3,4-bis(chloromethyl)thiophene (**10**)[13] and 70 ml of water was heated at 80–90° for 6 hr. After the work-up as described by Gol'dfarb and Kondakova[9] 0.8 g of dihydroxy compound **12**, mp 167–169° (lit.[9] mp 167–169°), and 0.5 g of a colorless solid, mp 220–221°, were obtained. The spectral data and the elemental analysis are in accordance with dithienodioxecin **13**: ir (KBr) 1090 cm^{-1} (CH_2OCH_2); nmr (10% in CCl_4) τ 5.40 (s, 4, $ArCH_2O-$), 8.58 (s, 18, $C(CH_3)_3$).

Anal. Calcd for $C_{28}H_{44}O_2S_2$: C, 70.53; H, 9.31; S, 13.45; mol wt, 476.78. Found: C, 70.9, 70.8; H, 9.3, 9.2; S, 13.2, 13.3; mol wt (in ethyl acetate), 478, 476.

Registry No.—**2**, 18366-66-0; **3**, 18366-67-1; **4**, 18366-68-2; **5**, 250-34-0; **6**, 18366-70-6; **7**, 18354-72-8; **8**, 18366-72-8; **9**, 18366-73-9; **13**, 18366-74-0.

Acknowledgment.—We thank Mr. K. Hovius for help in the syntheses of several compounds described in this article.

(12) Uv spectrum of thienofuran **4** in CH_2Cl_2, 248 mμ (ε 10,200).

(13) Ya. L. Gol'dfarb and M. S. Kondakova, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 495 (1956).

Bromination, Deuteration, and Lithiation of the Dithienyls[1]

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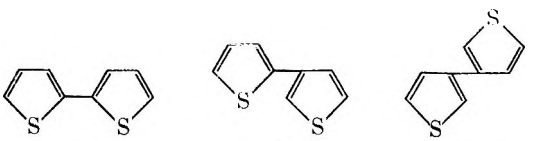
Reaction of 2,2′-dithienyl (**1**), 2,3′-dithienyl (**2**), and 3,3′-dithienyl (**3**) with 2 equiv of NBS in chloroform–acetic acid leads to the formation in virtually quantitative yield of 5,5′-dibromo-2,2′-dithienyl (**4**), 2′,5-dibromo-2,3′-dithienyl (**5**) and 2,2′-dibromo-3,3′-dithienyl (**7**), respectively. Reaction of **2** and **3** with excess NBS in CCl_4 for long periods leads to formation of 2′,5,5′-tribromo-2,3′-dithienyl (**6**) and 2,2′,5,5′-tetrabromo-3,3′-dithienyl (**8**), respectively. Reduction of the bromodithienyls to the respective deuterio compounds is described. The nmr spectra of **1** and **3** have been analyzed and that of **2** has been partially solved. Exchange in refluxing deuterioacetic acid with **1** leads to exchange at the 5,5 positions, with **2** to exchange at the 2′ and 5 positions, and with **3** to exchange at the 2,2′ positions. Exchange reactions with *n*-butyllithium have been carried out with **1**, **2**, and **3**; all α positions undergo exchange. Results of electrophilic substitution are compared with predictions obtained from extended Pariser–Parr–Pople calculations.

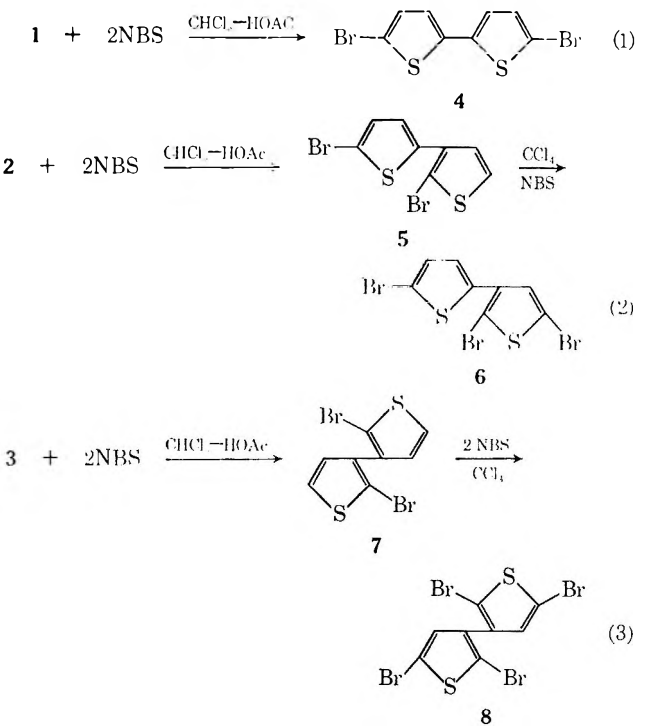
Our interest in the mechanisms of substitution reactions of thiophenes[2] led us to investigate the behavior of 2,2′-dithienyl (**1**), 2,3′-dithienyl (**2**), and 3,3′-dithienyl (**3**) in some detail. We report here the first *complete* analyses of the kinetically controlled products of electrophilic bromination and deuteration with **1**, **2**, and **3** together with a brief study of hydrogen–lithium exchange reactions with these biaryls.



1 **2** **3**

Results

We established previously that the brominations of a number of 3-substituted thiophenes proceed with high selectivity giving the corresponding 2-bromo derivatives, the products of kinetic control. These brominations, especially with 3-aryl- and alkyl-substituted thiophenes, are complicated by concomitant acid-catalyzed rearrangements induced by hydrogen bromide released during reaction. Not surprisingly, similar difficulties are met with upon attempted direct bromination of **2** and **3** resulting in complex product mixtures.[3] Fortunately, these problems can be circumvented by use of the brominating agent N-bromosuccinimide (NBS) in mixed chloroform–acetic acid solvent.[2] Under these conditions **1**, **2**, and **3** react smoothly and essentially quantitatively within a matter of minutes at room or slightly elevated temperatures with 2 equiv of NBS to give 5,5′-dibromo-2,2′-dithienyl (**4**), 2′,5-dibromo-2,3′-dithienyl (**5**), and 2,2′-dibromo-3,3′-dithienyl (**7**), respectively (eq 1–3).[4] Succinimide (not shown) is a reaction product easily removed upon work-up. Other reaction conditions and longer times were used to form 2′,5′,5-tribromo-2,3′-dithienyl (**6**) and 2,2′,5,5′-tetrabromo-3,3′-dithienyl (**8**) (eq 2 and 3).



All products obtained from brominations of **1**, **2**, and **3** were identified by analysis of the nmr spectra.[5] Structure assignments were considered to be virtually unambiguous but, because instability[6] prevented elemental analyses of the previously unknown derivatives **5**, **6**, **7**, and **8**, we chose to confirm these structures further by reduction with zinc and deuterioacetic acid to the corresponding stable deuterated dithienyls. This reduction is known to proceed with bromothiophenes without accompanying rearrangement.[2,7] Con-

(1) A preliminary account of some of the results contained herein was presented at the Second IUPAC Symposium on Photochemistry, Enschede, The Netherlands, July 1967.

(2) R. M. Kellogg, A. P. Schaap, E. T. Harper, and H. Wynberg, *J. Org. Chem.*, **33**, 2902 (1968).

(3) (a) N. Gjös and S. Gronowitz, *Acta Chem. Scand.*, **21**, 2893 (1967). See ref 2 for a detailed discussion of this problem. (b) No particular difficulties are experienced with 2,2′-dithienyl (**1**) and indeed bromination products from this compound have long been known; see, for example, W. Steinkopf, "Die Chemie des Thiophens," Verlag Th. Steinkopf, Leipzig, 1941, pp 141–149, and references contained therein.

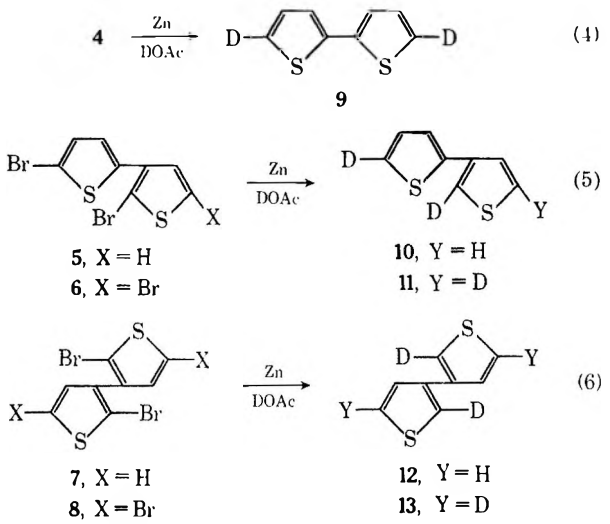
(4) Because of obvious separation difficulties no exhaustive effort was made to isolate monobromides although this is probably possible. All reactions were followed by glpc under conditions where monobromides could be observed. Dibromides appeared at a very early stage in the reaction and with **2** monobromide peaks of similar heights were observed which remained in nearly constant ratio during the course of reaction.

(5) See, for example, the discussion by S. Gronowitz, *Advan. Heterocyclic Chem.*, **1**, 1 (1963).

(6) Bromination products **5**, **6**, **7**, and **8** were indefinitely stable at −20° but began to discolor seriously within 1 hr at room temperature. In one case an old sample of **5**, after standing at room temperature, suddenly decomposed with near explosive violence; large quantites of hydrogen bromide were liberated.

(7) B. Bak, *J. Org. Chem.*, **21**, 797 (1956).

version of **4**, **5**, **6**, **7**, and **8** into, respectively, 5,5′-dideuterio-2,2′-dithienyl (**9**), 2′,5-dideuterio-2,3′-dithienyl (**10**), 2′,5,5′-trideuterio-2,3′-dithienyl (**11**), 2,-2′-dideuterio-3,3′-dithienyl (**12**), and 2,2′,5,5′-tetradeuterio-3,3′-dithienyl (**13**) proceeded smoothly and in good yield (eq 4–6). Analysis of the nmr spectra completely substantiated the original structure assignments of the bromine-substituted precursors (see Experimental Section).



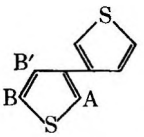
In addition to confirming the structural assignments of the bromo precursors an analysis of the nmr spectra of these deuterated derivatives allowed a complete solution of the nmr spectra of **1** and **3** as well as a partial analysis of that of **2**.[8] The ABC spectrum of **1** was first approximated as ABX and the parameters measured from 5,5′-dideuterio-2,2′-dithienyl (**9**) were used to adjust these ABX approximations. These approximate values were substituted in an ABC matrix equation and minor changes in spectral parameters were continously incorporated until the generated and experimentally obtained ABC spectra matched. The spectrum of **3** in deuterioacetone solvent is of the ABB′ type and is readily solved as described for 3-phenylthiophene;[9] the spectrum collapses to a singlet in CCl_4 solution. The spectrum of **2** is not sufficiently resolved to allow complete analysis of the overlapping ABC spectra; noteworthy, however, is the solvent sensitivity of the spectrum of **2** and deuterated derivatives **10** and **11** wherein the 4′,5′-protons collapse to a singlet in CCl_4 solution but are resolved in C_3D_6O. This is of considerable help in spectral analyses of partially deuterated derivatives. All obtainable parameters for **1**, **2**, and **3** are shown; parameters are applicable for a 10% solution of the respective compound in C_3D_6O.

We had previously discovered that many substituted thiophenes readily undergo deuterium–hydrogen exchange in refluxing deuterioacetic acid[2] and wished to

$J_{AB} = 1.2$ Hz; $\nu_B - \nu_A = 7.1$ Hz $J_{B'C'} = 5.0$ Hz; $\nu_{C'} - \nu_{B'} = 8.2$ Hz

$J_{BC} = 3.4$ Hz; $\nu_C - \nu_A = 18.8$ Hz $J_{BC} = 3.6$ Hz; $\nu_C - \nu_B = 15.9$ Hz

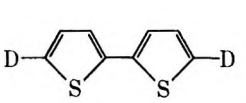
$J_{AC} = 5.0$ Hz



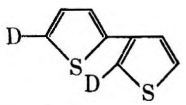
$J_{AB} + J_{AB'} = 4.3$ Hz[9]

$\nu_B - \nu_A = \nu_{B'} - \nu_A = 11.2$ Hz

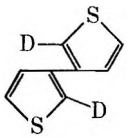
use this reaction as a second model of an electrophilic substitution reaction with the dithienyls. With the nmr spectral analyses in hand such an investigation became experimentally feasible. The results of deuterium–hydrogen exchange reactions with **1**, **2**, and **3** carried out for 5 hr in refluxing deuterioacetic acid are as shown; exchange occurred exclusively at the positions indicated.[10] Recovery of material was at least 80% and usually nearly quantitative. The amount and position of deuterium substitution were determined by



5,5′, *ca.* 60% exchange



5, 22%; 2′, 40% exchange



2,2′, *ca.* 60% exchange

analysis of nmr spectra of exchanged products taken both in CCl_4 and C_3D_6O. The partially deuterated compounds were then allowed to react with 2 equiv NBS and the dibromides obtained were shown to be identical with those obtained from non-deuterated materials; exchange is therefore established to occur only at the positions substituted by bromine.[11] From consideration of spectra and integration ratios the amounts of exchange were determined.

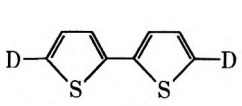
A brief study of hydrogen–lithium exchange reactions with **1**, **2**, and **3** was carried out; the dithienyls were treated with *n*-butyllithium, warmed to room temperature, and quenched with D_2O. Recovery of starting materials was 97% or better. Determination of the position and amount of substitution was similar to that described above and the results are as shown; exchange was confined to the positions shown.

(8) Nmr techniques with arylthiophenes wherein deuterium labeled compounds are used in obtaining certain nmr spectral parameters have been described: R. M. Kellogg and H. Wynberg, *J. Amer. Chem. Soc.*, **89**, 3495 (1967).

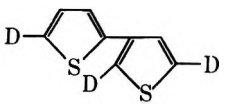
(9) Solution of the spectra gives only the combined value $J_{AB} + J_{AB'}$ while $J_{BB'}$ is not measurable. From the spectrum of 2,5′-dideuterio-3,3′-dithienyl obtained as a product of photolysis from **10**,[1] $J_{AB'}$ has been measured as 1.2 Hz requiring therefore that $J_{AB} = 3.1$ Hz. This agrees well with the spectrum of 3-phenylthiophene.[8]

(10) No conflict exists between these exchange reactions and the structure proofs of the bromodithienyls carried out by reduction with zinc in refluxing deuterioacetic acid. Exchange undoubtedly takes place in the latter reaction but is a "blind" deuterium–deuterium exchange leading to no *observable* products other than those obtained by direct bromine–deuterium substitution.

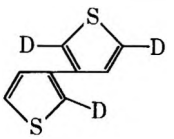
(11) We were concerned whether bromination might lead to loss of deuterium at a position other that being substituted. This point has been checked specifically with 2,5-dideuterio-3-phenylthiophene which gives *only* 2-bromo-5-deuterio-3-phenylthiophene upon bromination; no deuterium loss from the 5 position is observable: R. M. Kellogg, J. J. C. Vermeer, and H. Wynberg, unpublished results.



5,5′, 92% exchange



5, *ca.* 40%; 2′, *ca.* 40%, 5′, 33% exchange

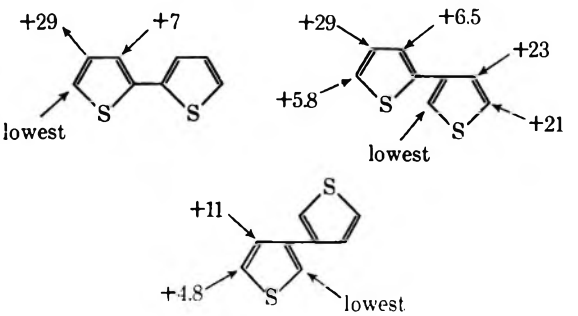


2,2′, 38%; 5,5′, 7% exchange

Discussion

The electrophilic brominations[12] and deuterations of the dithienyls proceed with high selectivity in the 5,5′ positions of **1**, the 2′,5 positions of **2**, and 2,2′ positions of **3**.[13,14] Since virtually all the starting material is accounted for as products there exists little chance that other isomers might have been missed. Electrophilic substitution in thiophenes is expected to be favored at positions adjacent to sulfur consistent with the 5,5′-substitution in **1**; the situation becomes, however, more interesting with **2** and **3** where three and four α positions are available, respectively.

The observed positions for substitution have been compared with those predicted from extended Pariser–Parr–Pople molecular orbital calculations. The relative activation energies (in kilocalories per mole) involved in electrophilic substitution at various positions were determined and the results of these calculations are as illustrated.[15] One is encouraged to see that the calculated positions of highest reactivity are the same as those found experimentally. The most notable discrepancy is the predicted reactivity of the 3,3′ positions in **1** and the 3 position of **2** while no electrophilic bromination or deuteration occur at these positions. The 3,3′ positions of **1** are reported, however, to be substituted when the 5,5′ positions are blocked.[3b] These results[16] must, of course, be treated with appropriate caution but it would appear that the positions at which substitution occur are governed primarily by energetic considerations and steric factors which *a priori* might be expected to be important with **2** and **3** do not play a major role in bromination or deuteration. These results are in contrast to those with biphenyl where *para* is highly favored over *ortho* substitution; this has been rationalized by one set of authors in terms of steric factors affecting the transition state.[17]



The lithium–hydrogen exchange experiments are not readily interpreted since no acceptable model mechanism for this reaction exists.[5] Second, one is not at all sure whether the products obtained in this case are those of kinetic control. The results obtained represent a more complete analysis of product distribution than that previously reported using carbonation as the quenching technique.[14] The present results, especially with **2** and **3**, agree well with experiments recently carried out with 3-phenylthiophene wherein substitution at the 2 and 5 positions has been observed both after quenching with deuterioacetic acid and by direct nmr spectral examination of the lithium compounds.[18]

Experimental Section

Melting points and boiling points are uncorrected. Deuterium oxide (99.7 atom %) was obtained from Carl Roth (Karlsruhe). Nuclear magnetic resonance (nmr) spectra were measured with a Varian A-60 instrument with tetramethylsilane (TMS) as an internal standard. Spectra were taken at 500-, 250- and 100-cps sweep widths and integrations were done two times going from low to high field and two times from high to low field and the average values were used. Gas–liquid partition chromatography (glpc) was done with an F & M Model 810 gas chromatograph equipped with hydrogen flame detectors. Compounds cited without reference were either prepared by standard procedures or were available in stock.

5,5′-Dibromo-2,2′-dithienyl (4) was prepared from the reaction of 2,2′-dithienyl (420 mg, 2.53 mmol) in 15 ml of a 50:50 (v/v) mixture of chloroform and acetic acid to which NBS (900 mg, 5.05 mmol) was added. Reaction started instantly at room temperature and the solution was warmed briefly to ensure complete conversion. The reaction mixture was taken up in CS_2 (used only with **4** because of its insolubility in other organic solvents), was washed with KOH solution until basic, washed once with H_2O, and was dried over $MgSO_4$. Removal of the solvent left 786 mg (96%) of **4**: mp 149–151° (lit.[14] mp 146–147.5°); nmr (CS_2) δ 6.78 (d, 2, J = 3.6 Hz, 4 H[19]), 6.92 (d, 2, J = 3.6 Hz, 3 H).

(12) A possible mechanism for the electrophilic brominations of thiophenes by NBS as well as evidence that the products obtained are kinetically controlled has been discussed.[2]

(13) 2,2′-Dithienyl (**1**) has received some investigation wherein halogenations,[3] nitration,[3,14] acetylations,[3] mercurations,[3] and sulfonations[3] have been examined. In virtually all cases the 5,5′ positions are most reactive. Investigation of 2,3′-dithienyl (**2**) has been confined to acetylation by Wynberg, *et al.*, where substitution at the 5 position was observed.[14] 3,3′-Dithienyl (**3**) appears not to have been studied seriously.

(14) H. Wynberg and A. Bantjes, *J. Amer. Chem. Soc.*, **82**, 1447 (1960); see also H. Wynberg, A. Logothetis, and D. VerPloeg, *ibid.*, **79**, 1972 (1957).

(15) These results were obtained with a program written by the Department of Structural Chemistry of the University of Groningen. We are grateful to Professor E. Wiebenga and Mr. E. J. Bouwhuis of this department for making results available to us. Parameters used and the approaches to building molecular orbitals were essentially those described by A. J. H. Wachters and D. W. Davies, *Tetrahedron*, **20**, 2841 (1964). Relative activation energies are those derived from assumptions of the changes involved concomitant with adjustment from sp^2 to sp^3 hybridization at a particular position upon addition of an arbitrary electrophile. Calculations were carried out both for *cis* and *trans* conformations of **1**, **2**, and **3** but energy differences were insignificant. The values given are for the *trans* conformations (sulfurs oriented in opposite directions).

(16) The positions of electrophilic substitution can, of course, be predicted correctly by the cruder expedient of considering the longest conjugated system which may be formed by addition of an electrophile; see, for example, H. Hogeveen, *Rec. Trav. Chim. Pays-Bas*, **85**, 1072 (1966).

(17) H. C. Brown and L. M. Stock, *J. Amer. Chem. Soc.*, **84**, 1238 (1962); for arguments that the effect derives from electronic factors, see R. C. Neuman, Jr., *ibid.*, **84**, 3025 (1962), and R. Baker, R. W. Bott, and C. Eaborn, *J. Chem. Soc.*, 2136 (1963).

(18) N. Gjös and S. Gronowitz, *Arkiv Kemi*, in press. We are grateful to Professor Gronowitz for providing us with a copy of this manuscript prior to publication; see also S. Gronowitz and A. Bugge, *Acta Chem. Scand.*, **22**, 59 (1968).

(19) These assignments are assumed by analogy to other systems.

5,5′-Dideuterio-2,2′-dithienyl (9) was prepared by reduction of 4 (280 mg, 0.77 mmol) with Zn (0.8 g, 12.2 mg-atoms) in a mixture of redistilled acetic anhydride (2 ml) and deuterium oxide (2 ml). The mixture was put in a flame-dried erlenmeyer equipped with magnetic stirring bar, reflux cooler, and drying tube. The reaction mixture was refluxed 5.5 hr after which time excess water was added and the Zn was filtered off and was thoroughly washed with ether. The reaction mixture was extracted three times with ether, the ether layer was neutralized by washing repeatedly with $KHCO_3$ solution, was washed once with water, and was dried over $MgSO_4$. Removal of the ether left 87 mg (67% yield) of 9: nmr (C_3D_6O) δ 7.00 (d, 2, J = 3.4 Hz, 4 H), 7.20 (d, 2, J = 3.4 Hz, 3 H), (CCl_4) δ 6.90 (d, 2, J = 3.4 Hz, 4 H), 7.07 (d, 2, J = 3.4 Hz, 3 H). The doublets at δ 7.00 and 6.90 in C_3D_6O and CCl_4, respectively, were broadened by coupling to the deuterium atoms in the 5 positions.[20]

2′,5-Dibromo-2,3′-dithienyl (5) was prepared from the reaction of 2,3′-dithienyl (420 mg, 2.53 mmol) with NBS (900 mg, 5.05 mmol) in 16 ml of a 50:50 (v/v) mixture of chloroform–acetic acid. After reaction and work-up as described above there was obtained 771 mg (94%) of 5: mp 46–47°; nmr (C_3D_6O) δ 7.13 (d, 1, J = 4.0 Hz, 4 H), 7.21 [d, 1, J = 5.8 Hz, 4′ H (absorption buried under other peaks)], 7.30 (d, 1, J = 4.0 Hz, 3 H), 7.42 (d, 1, J = 5.8 Hz, 5′ H), (CCl_4) δ 6.91 (d, 1, J = 3.8 Hz, 4 H), 6.92 (d, 1, J = 5.8 Hz, 4′ H), 7.08 (d, 1, J = 3.8 Hz, 3 H), 7.17 (d, 1, J = 5.8 Hz, 5′ H). The nmr spectrum in C_3D_6O owing to overlapping gave only six resolved peaks under all conditions while in CCl_4 at expanded sweep width and high instrument sensitivity all four sets of doublets could be observed.

2′,5-Dideuterio-2,3′-dithienyl (10) was prepared from the reduction of 5 (745 mg, 2.3 mmol) with Zn (2.0 g, 30.6 mg-atoms) in acetic anhydride (5.5 ml) and deuterium oxide (6.5 ml). After reaction and work-up as described above there was obtained 250 mg (65%) of 10: nmr (C_3D_6O) δ 7.04 [d (broadened by coupling to deuterium), 1, J = 3.5 Hz, 4 H], 7.30 (d, 1, J = 3.5 Hz, 3 H), 7.35 (d, 1, J = 5.0 Hz, 4′ H), 7.49 [d (slightly deuterium broadened), 1, J = 5.0 Hz, 5′ H], (CCl_4) δ 6.90 [d (deuterium broadened), 1, J = 3.5 Hz, 4 H], 7.06 (d, 1, J = 3.5 Hz, 3 H), 7.20 (s, 2, 4′,5′ H).

2′,5,5′-Tribromo-2,3′-dithienyl (6) was obtained from the reaction (*ca.* 50 hr) of 2,3′-dithienyl (100 mg, 0.62 mmol) with NBS (500 mg, 2.8 mmol) in 5 ml of CCl_4 containing a trace of water–acetone.[21] Work-up of the reaction mixture (washed with aqueous KOH and water, dried over $MgSO_4$) gave 102 mg (40%) of 6: mp 54.0–55.3°; nmr (C_3D_6O) δ 6.60 (d, 1, J = 4.0 Hz, 4 H), 6.72 (d, 1, J = 4.0 Hz, 3 H), 6.82 (s, 1, 4′ H).

2′,5,5′-Trideuterio-2,3′-dithienyl (11) was obtained by treatment of 6 (72 mg, 0.18 mmol) with excess Zn and deuterioacetic acid under conditions previously described to give 24 mg (79%) of 11: nmr (C_3D_6O) δ 7.03 [d, 1, J = 3.5 Hz, 4 H (broadened by deuterium coupling)], 7.29 (d, 1, J = 3.5 Hz, 3 H), 7.37 [s, 1, 4′ H (broadened by deuterium coupling)].

2,2′-Dibromo-3,3′-dithienyl (7) was prepared from the reaction of 3,3′-dithienyl (420 mg, 2.53 mmol) with NBS (900 mg, 5.05 mmol) in 16 ml of a 50:50 (v/v) mixture of chloroform–acetic acid; reaction was complete within a few minutes at room temperature. Work-up gave 825 mg (101%) of 7: mp 78–79°; nmr (C_3D_6O) δ 7.15 (d, 2, J = 5.7 Hz, 4,4′ H) and 7.62 (d, 2, J = 5.7 Hz, 5,5′ H).

2,2′-Dideuterio-3,3′-dithienyl (12) was prepared by the reduction of 7 (1.19 g, 3.67 mmol) with Zn (2.4 g, 37 mg-atoms) in a mixture of acetic anhydride (7 ml) and deuterium oxide (7 ml). After work-up 560 mg (91%) of 12 was obtained; nmr spectra in both C_3D_6O and CCl_4 consisted of singlets. Treatment of the obtained 12 with 2 equiv of NBS gave 2,2′-dibromo-3,3′-dithienyl identical with that prepared from nondeuterated material.

2,2′,5,5′-Tetrabromo-3,3′-dithienyl (8) was prepared from the reaction of 3,3′-dithienyl (1.00 g, 6.02 mmol) with NBS (4.2 g, 23.6 mmol) in 30 ml of CCl_4. After 152 hr the reaction was stopped and the mixture was worked up to yield 1.0 g (34%) of 8: mp 133–136°; nmr spectra in both C_3D_6O and CCl_4 consisted of one singlet.

2,2′,5,5′-Tetradeuterio-3,3′-dithienyl (13) was prepared by the reduction of 8 (777 mg, 1.61 mmol) with zinc (2.44 g, 34.4 mg-atoms) in a mixture of acetic anhydride (7.5 ml) and deuterium oxide (9 ml); the mixture was refluxed 5 hr. Work-up gave 200 mg (73%) of 13: nmr spectra in CCl_4 and C_3D_6O consisted of singlets.

Deuterium exchange with the dithienyls was carried out by treating the appropriate dithienyl (125 mg, 0.755 mmol) in a mixture of acetic anhydride (2 ml) and D_2O (2.25 ml) for 5 hr. The solutions were quenched with water and extracted with ether; the ether layer was neutralized with $NaHCO_3$ solution, washed with water, and dried over $MgSO_4$. Evaporation of the solvent left the exchanged dithienyl in 80–100% yield. The nmr spectra of the exchanged products were taken in CCl_4 and C_3D_6O and compared with the dideuterio compounds already prepared. The exchanged compounds were then allowed to react with 2 equiv of NBS to give dibromides which were shown to be identical with those obtained from nondeuterated dithienyls. This indicates that deuteration and bromination occur at identical positions. By detailed examination of the nmr spectra of the exchanged materials the amount of deuterium exchange at the reactive positions could be determined.

Lithium exchange experiments with dithienyls were carried out with the appropriate dithienyl (664 mg, 4.0 mmol) in 20 ml of dry ether. *n*-BuLi (8–9 mmol *ca.* 1.0 *M* in ether solution) was added at 0° under an N_2 atmosphere. The mixtures became turbid and then clear. After standing *ca.* 10 min the reaction mixtures were quenched with 5 ml of D_2O. The solutions were filtered, washed, and dried to give the dithienyl in not less than 97% yield. Nmr spectra in CCl_4 and C_3D_6O were taken after which the deuterated materials were brominated with 2 equiv of NBS. The spectra of the dibromides were examined to determine the amounts and location of the deuterium remaining. Careful examination of all spectra allowed the assignments given.

Registry No.—1, 492-97-7; 2, 2404-89-9; 3, 3172-56-3; 4, 4805-22-5; 5, 18592-84-2; 6, 18592-85-3; 7, 18592-86-4; 8, 18592-87-5; 9, 18592-88-6; 10, 18592-89-7; 11, 18592-90-0; 12, 18592-91-1; 13, 18592-92-2.

Acknowledgment.—The authors thank Mr. J. Buter for aid with certain experimental problems met within the course of this work.

(20) For a discussion of this phenomenon in deuteriothiophenes, see R. A. Hoffman and S. Gronowitz, *Arkiv Kemi*, **16**, 45 (1959).

(21) This method was used for a number of reactions before the catalytic effects of acetic acid were noted. The tribromination in chloroform–acetic acid did not, however, go well in our hands.

Chemistry of Thienopyridines. III. Syntheses of the Thieno[2,3-*b*]- and Thieno[3,2-*b*]pyridine Systems. Direct Substitution into the Former System[1a,2,3]

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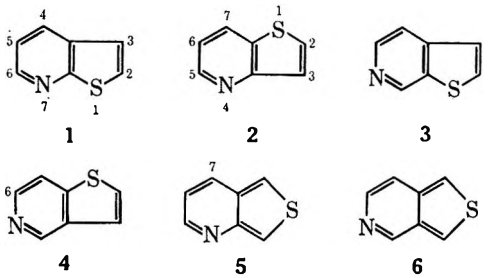
Condensation–cyclization reactions of 2- and 3-thienylammonium hexachlorostannates were used in practical syntheses of thieno[2,3-*b*]pyridine (**1**), thieno[3,2-*b*]pyridine (**2**), and their derivatives. Malondialdehyde tetraethyl acetal (MDTA) reacted with these salts to give **1** and **2** (44 and 77% yields, respectively). Acetoacetaldehyde dimethyl acetal reacted (with attendant loss of acetone) to form monoacetyl derivatives, wherein the substituent is located β to the nitrogen atom. Methyl vinyl ketone led to mixed (α and γ) monomethyl compounds. Some 1,3-diketones and 1,3-ketoaldehydes also reacted. Structures of the monomethyl derivatives were established by direct comparison with the products of reaction of vinylmethylpyridines and methylethylpyridines with hydrogen sulfide at 630°. The salts of 4- and 5-amino-2-acetylthiophene also reacted with MDTA to form 2-acetyl derivatives of **1** and **2**. Nmr data are reported and correlated with structures of the various thienopyridine compounds. Bromination of **1** gave the 2,3-dibromo derivative, while reaction of **1** with deuteriosulfuric acid gave fastest D–H exchange at C-3 and slower exchange at C-2. Reaction of **1** with methyllithium led to products expected from lithiation at C-2 and from addition to the C=N moiety. These results are consistent with calculated reactivity indices and expectations as based on data for the quinoline and benzo[*b*]thiophene systems.

Of the six theoretically possible parent thienopyridine compounds, **1**–**6**, only **1**–**4** have been previously synthesized, albeit in low yields (1–6% from available starting materials).[3-7] Chemical interest in the thienopyridine system arises from the fact that a thiophene ring (susceptible to facile electrophilic substitution, but resistant to nucleophilic substitution)[8] is fused to a pyridine ring (susceptible to facile nucleophilic substitution, but resistant to electrophilic substitution).[9,10] Pharmacological interest in these systems stems from their isosterism with quinoline and isoquinoline rings. The present paper is concerned with syntheses of systems **1** and **2** and direct substitution into the former system.



1 **2** **3**

4 **5** **6**

In the extensive studies of Steinkopf and coworkers on the reactions of thiophene[11] it was discovered that the mononitrothiophenes can be readily reduced to the corresponding aminothiophenes, but these reduction products are exceptionally easily oxidized and/or polymerized by air. Fortunately, they found that the aminothiophenes can be handled and stored as the relatively stable crystalline salts of hexachlorostannic(IV) acid.[12] As noted in an earlier paper[2] the low yield of **1** from Skraup reaction on the amine salt (under oxidizing conditions) is, thus, not surprising and leads one to investigate the possibilities of formation of the pyridinoid ring under nonoxidative conditions—in particular, under dehydrative conditions. Thus Emerson, Holly and Klemm[2] found that acetylacetone reacts with the 2-thienylammonium salt in the presence of concentrated sulfuric acid at room temperature to give **1c**. Similar condensations with other β-diketones and β-ketoaldehydes were not successful in their hands, however. More recently, Zhiryakov and Abramenko reported reactions of both aminothiophene salts with methyl vinyl ketone (MVK) in the presence of ethanolic ferric chloride–zinc chloride[13] and with acetoacetaldehyde diethyl acetal (ADEA) in the presence of ethanolic zinc chloride.[14] They assigned monomethylthienopyridine structures to their isolated products, but without experimental verification of such structures.[15] We have reinvestigated these reactions and extended and modified them so as to provide the first practical syntheses for the parent compounds **1** and **2**, as well as generally applicable syntheses for derivatives (of proven structures) of them.[15a]

(1) (a) This investigation was supported by research grant No. CA-5969 from the National Cancer Institute and by research contract No. DA-49-193-MD-2998 from the U. S. Army Medical Research and Development Command. For papers I and II in this series see ref 2 and 3, respectively. (b) Research Assistant, 1963–1965; NDEA Predoctoral Fellow, 1965–1966. (c) NATO Postdoctoral Fellow, 1966–1967; Research Associate, 1967. (d) Research Assistant, 1964–1967. (e) NSF Undergraduate Research Participant, summer 1967.

(2) W. S. Emerson, F. W. Holly, and L. H. Klemm, *J. Amer. Chem. Soc.*, **63**, 2569 (1941).

(3) L. H. Klemm and D. Reed, *J. Org. Chem.*, **25**, 1816 (1960).

(4) W. Steinkopf and G. Lützkendorf, *Ann.*, **403**, 45 (1914).

(5) David R. McCoy, unpublished results from this laboratory.

(6) C. Hansch, W. Carpenter, and J. Todd, *J. Org. Chem.*, **23**, 1924 (1958).

(7) W. Herz and L. Tsai, *J. Amer. Chem. Soc.*, **75**, 5122 (1953).

(8) S. Gronowitz, *Advan. Heterocycl. Chem.*, **1**, 43, 69 (1963).

(9) R. A. Barnes, "Pyridine and Its Derivatives," Part 1, E. Klingsberg, Ed., Interscience Publishers, New York, N. Y., 1960, pp 12–29.

(10) H. D. Hartough and S. L. Meisel, "Compounds with Condensed Thiophene Rings," Interscience Publishers, New York, N. Y., 1954, pp 427–432.

(11) W. Steinkopf, "Die Chemie des Thiophens," Theodor Steinkopff, Leipzig, Germany, 1941.

(12) W. Steinkopf and G. Lützkendorf, *Ann.*, **403**, 17 (1914).

(13) V. G. Zhiryakov and P. I. Abramenko, *Zh. Vses. Khim. Obshchestva im. D. I. Mendeleeva*, **5**, 707 (1960); *Chem. Abstr.*, **55**, 11416 (1961).

(14) V. G. Zhiryakov and P. I. Abramenko, *Khim. Geterotsikl. Soedin., Akad. Nauk Latv. SSR*, 334 (1965); *Chem. Abstr.*, **63**, 13231 (1965); *Chem. Heterocycl. Compounds (USSR)*, **1**, 219 (1965). The abstract and the English translation of this article are inconsistent in many details. It is presumed that the authors did not use the Pb double salt (such as is reported in the abstract).

(15) As noted later, it appears that ref 13 and 14 contain several erroneous structural assignments.

(15a) NOTE ADDED IN PROOF.—Practical syntheses of **2** and **3** from 2- and 4-vinylpyridines, respectively, have recently been achieved: L. H. Klemm, J. Shabtai, D. R. McCoy, and W. K. T. Kiang, *J. Heterocycl. Chem.*, in press.

Thiophene was nitrated directly to 2-nitrothiophene[16] (which contained 15% of the 3 isomer) and was also converted into 3-nitrothiophene (which contained 5% of the 2 isomer) by a previously reported multistep procedure.[17,18] Each nitro product was reduced with tin and hydrochloric acid to the corresponding bis-(thienylammonium) hexachlorostannate(IV),[4] readily convertible into a thienopyridine mixture (44% in the former case, 77% in the latter) by treatment *in situ* with ethanol, zinc chloride, and malondialdehyde tetraethyl acetal (MDTA) at 85°. The ease of direct nitration of thiophene makes the synthesis of thieno-[2,3-*b*]pyridine (**1**) by this method experimentally facile. On the other hand, despite the higher yield of thieno[3,2-*b*]pyridine (**2**) in the MDTA reaction, the arduous synthesis of 3-nitrothiophene by the reported method makes the over-all production of **2** experimentally difficult. It is better perhaps, especially if one is interested in both isomers, to separate **2** from the product mixture which results from the synthesis of **1**. Thus isomer **1** is easily freed from **2** by extraction of the mixture with a limited excess of 0.05 *M* HCl, in which **2** is considerably more soluble.[19] The **2**-enriched extract is then separable by liquid–solid chromatography with alumina onto which **2** is more strongly adsorbed.[20]

In analogous fashion the isomeric products from nitration of 2-acetylthiophene, *i.e.*, 4-nitro-2-acetylthiophene (**7**) and 5-nitro-2-acetylthiophene (**8**),[21,22] were reduced and cyclized to **2c** and **1i**, respectively, in over-all yields of *ca.* 10% each. Mixtures of **1i** and **2c** were also separable by acid extraction and chromatography on alumina, wherein the [3,2-*b*] isomer again showed a higher basicity.

The mechanism of the MDTA reaction has not been investigated. Formally it may be visualized as a combination of stepwise hydrolysis of MDTA (effectively to malondialdehyde) plus a sequence of Schiff's base formation with the amine salt (1:1) and then cyclodehydrative substitution (SE reaction) into the thiophene ring.

Treatment of the 2-amine salt with acetylacetone and zinc chloride in dioxane at 90° gave **1c** (45% yield). Similarly, **1d** (32% yield) and 5,6,7,8-tetrahydrothieno[2,3-*b*]quinoline (**1h**, 5% yield) were obtained by reactions of 3-methylpentane-2,4-dione and 2-hydroxymethylenecyclohexanone, respectively, with the 2-amine salt. Also, reaction of acetylacetone with the salt of 2-amino-5-acetylthiophene gave **1k** (42%).

Comparison of the nmr spectra of **1** and **2** with the spectral characteristics for the heteroring protons of quinoline and benzo[*b*]thiophene shows that it is possible to ascribe, on a reasonable basis, a particular part of the total spectrum to each of the five protons present in either **1** or **2**. These assignments for the parent compounds are corroborated by spectral data for various derivatives for which structures are clearly established by their methods of synthesis. Complete data on chemical shifts and coupling constants for all thienopyridine compounds reported in this paper are given in Tables I and II. No long-range splitting effects are apparent in the spectrum of **1**, but the spectrum of **2** shows long-range coupling between H-2 and H-6 and also between H-3 and H-7.

Repetition of the studies of Zhiryakov and Abramenko gave results inconsistent with many of their reports. Thus, in our study, reaction of the 2-amine salt with MVK[13] gave two products, **1a** (as reported) in 15% yield and **1b** (not reported) in 10% yield. These isomers were readily separable by vpc on Carbowax 20M, on which **1a** (less steric hindrance to H bonding from the stationary phase) shows higher retentivity (*cf.* tlc data on alumina).[20] Tentative assignments of our structures, as based on microanalyses and chromatographic results, were corrborated by nmr spectra wherein **1a** shows signals at $\delta > 8.2$ (present also in the spectrum of **1**, but not in that of **1b**) ascribable to the presence of an aromatic proton α to the pyridinoid N atom. Confirmation of these structural assignments was provided by high-temperature (630°) reactions of hydrogen sulfide with substituted pyridines in a flow system. Thus 3-ethyl-4-methylpyridine plus H_2S gave a low yield (1%) of **1a** (only thienopyridine found) while 2-methyl-5-vinylpyridine or 2-methyl-5-ethylpyridine gave the expected isomeric pair of methylthienopyridines **1b** (2%, by preferential cyclization into the 6 position of the pyridine ring) and **4a** (0.3%, by cyclization into the 4 position of the pyridine ring).[23] Also obtained from the latter reaction were small amounts of the parent compounds (from demethylation)[24] **1** (0.5%) and **4** (0.1%).[25]

Reaction of the 3-amine salt with MVK gave **2a** (9%, not reported by Zhiryakov and Abramenko)[13] and **2b** (41%, previously reported).[13] Structures were assigned by the same methods as used in the **1** series. Thus **2b** showed greater retentivity than **2a** in vpc and tlc,[20,26] **2b** and **2** (but not **2a**) showed nmr signals at $\delta > 8.2$, and **2a** (0.9%) plus **2** (0.4%) were also obtained from reaction of 2-methyl-6-vinylpyridine with H_2S. The melting point of our **2b** picrate was 12° higher than that reported by the Russian workers. Moreover, we found no evidence for the formation of the 7-methyl derivative of **5**, reported by them.[13] It might be noted that the methylthienopyridine isomer which forms in the larger amount (from either the 2- or the 3-amine salt) results (at least in a formal sense) from initial Michael addition of the amino group to the α-vinylketo system rather than from Schiff's base formation.

(16) V. S. Babasinian, "Organic Syntheses," Coll. Vol. II, John Wiley & Sons, Inc., New York, N. Y., 1943, p 466.

(17) W. Steinkopf and T. Höpner, *Ann.*, **501**, 174 (1933).

(18) H. Burton and W. A. Davy, *J. Chem. Soc.*, 525 (1948).

(19) Compare 2-methylmercaptopyridine, pK_a 3.62, with 3-methylmercaptopyridine, pK_a 4.45: A. Albert, "Physical Methods in Heterocyclic Chemistry," Vol. I, A. R. Katritzky, Ed., Academic Press, New York, N. Y., 1963, Chapter 1.

(20) L. H. Klemm, C. E. Klopfenstein, and H. P. Kelly, *J. Chromatog.*, **23**, 428 (1966).

(21) I. J. Rinckes, *Rec. Trav. Chim.* **52**, 538 (1933).

(22) The structure of **8** follows from its synthesis[21] from 5-nitro-2-thienoic acid, which (in turn) produces 2-nitrothiophene on decarboxylation [I. J. Rinckes, *ibid.*, **51**, 1134 (1932)]. Similar interconversions[21] show that **7** is in the 3-nitrothiophene series and, hence, must be either 3-nitro-2-acetyl- or 4-nitro-2-acetylthiophene. The small coupling constant (J = 1.6 Hz) for the aromatic AB system in **7** is consistent with the structural assignment as given (*meta* protons present).

(23) C. Hansch and W. Carpenter, *J. Org. Chem.*, **22**, 936 (1957).

(24) C. D. Hurd and J. I. Simon [*J. Amer. Chem. Soc.*, **84**, 4519 (1962)] found that picolines undergo some demethylation at 700° but do not give methyl migration at that temperature.

(25) Compound **4** is more readily obtained from H_2S and 3-vinylpyridine.[5]

(26) As expected in tlc on alumina the R_f value of **2** lies between that of **2a** and that of **2b**.[20]

TABLE I

NUCLEAR MAGNETIC RESONANCE DATA FOR THIENO[2,3-*b*]PYRIDINES[a]

Compd	Substituent(s)	Chemical shift, δ					Coupling constant, Hz				Other signals
		H-2	H-3	H-4	H-5	H-6	$J_{2,3}$	$J_{4,5}$	$J_{4,6}$	$J_{5,6}$	
1	None	7.40	7.08	7.85	7.10	8.46	5.9	8.1	1.6	4.5	
1a	4-Me	7.37	7.12		6.86[b]	8.34	6.0			4.5	2.35 (s, CH_3)[b]
1b	6-Me	7.33	7.10	7.80	7.12		6.0	8.0			2.60 (s, CH_3)
1c	4,6-DiMe	7.27	7.08		6.77		6.0				2.39, 2.51[c]
1d	4,5,6-TriMe	7.16	6.97				6.0				2.10, 2.30, 2.44[d]
1e	2-Et		6.82	7.78	7.12	8.53		8.1	1.7	4.5	1.30 (t, J = 7.6, CH_2CH_3)[e]
1f	5-Et[f]	7.41	7.10	7.79		8.38	6.0		1.8		1.22 (t, J = 7.5, CH_2CH_3)[g]
1g	6-*n*-Bu	7.27	7.03	7.76	6.98		6.0	8.2			0.92 [t, J = 6, $(CH_2)_3CH_3$][h]
1h	5,6-$(CH_2)_4$	7.23	6.92	7.43			6.0				1.5–2.1 [m, $-CH_2CH_2CH_2CH_2-$][i]
1i	2-Ac		7.84	8.17	7.36	8.79		8.2	1.8	4.5	2.60 (s, CH_3CO)
1j	5-Ac[f]	7.60	7.35	8.58		9.10	6.0		1.9		2.69 (s, CH_3CO)
1k	4,6-DiMe-2-Ac[f]		7.89		7.03						2.63 (s, CH_3CO, $2CH_3$)[j]
1l	2-D		7.11	7.90	7.12	8.45		8.0	1.7	4.6	
1m	3-D	7.41		7.92	7.14	8.46		8.0	1.7	4.6	
1n	2,3-DiD			7.90	7.14	8.45		8.0	1.7	4.6	
1o	2,3-DiBr			7.86	7.23	8.46		8.0	1.8	4.6	

[a] Unless otherwise indicated the solvent is CCl_4. Integrated areas of the signals were consistent with structural assignments. The multiplicity in the spectral pattern for each aromatic proton is 2^n, where n is the number of spin–spin couplings indicated for that proton. [b] Slightly split by coupling (J = 0.8 Hz) of H-5 with CH_3. [c] Singlets, $2CH_3$, probably at C-4 and C-6, respectively. [d] Singlets, $3CH_3$, probably at C-5, C-4, and C-6, respectively. [e] Also 2.86 (q, J = 7.6, CH_2CH_3). [f] Solvent $CDCl_3$. [g] Also 2.68 (q, J = 7.5, CH_2CH_3). [h] Also 1.1–2.0 (m, $CH_2CH_2CH_2CH_3$) and 2.83 (t, J = 7.5, $CH_2CH_2CH_2CH_3$). [i] Also 2.5–3.2 (m, $-CH_2CH_2CH_2CH_2-$). [j] Slightly split singlet.

TABLE II

NUCLEAR MAGNETIC RESONANCE DATA FOR THIENO[3,2-*b*]PYRIDINES[a]

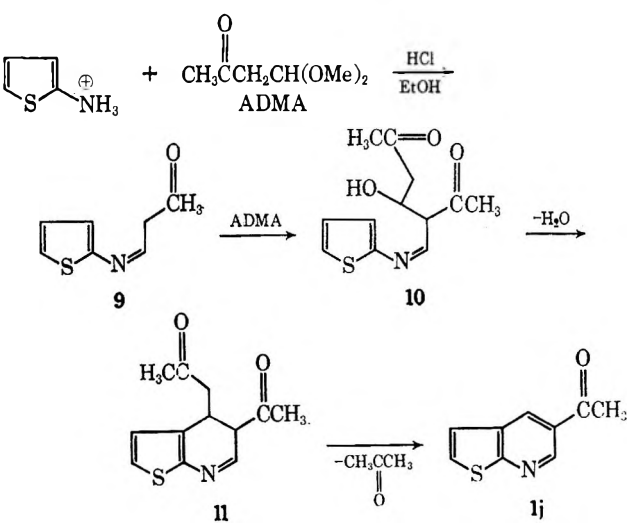
Compd	Substituent	Chemical shift, δ					Coupling constant, Hz						Methyl signals, δ
		H-2	H-3	H-5	H-6	H-7	$J_{2,3}$	$J_{2,6}$	$J_{3,7}$	$J_{5,7}$	$J_{6,7}$	$J_{8,7}$	
2	None	7.68	7.51	8.64	7.12	8.08	6.1	0.4	0.8	4.8	1.6	8.8	
2a	5-Me	7.59	7.41		6.98	7.92	5.8	0.5	0.7			8.4	2.61 (s, CH_3)
2b	7-Me	7.60	7.48	8.45	6.88[b]		5.6	0.4		5.0			2.45[b]
2c	2-Ac[c]		8.22	8.88	7.45	8.33			<1	4.5	1.5	7.8	2.72 (s, CH_3CO)[d]
2d	6-Ac[c]	7.97	7.58	9.22		8.70	5.8		0.9		2.1		2.69 (s, CH_3CO)
2e	6-Et	7.59[e]	7.59[e]	8.60		7.86	*e*		<1		2		*f*

[a] See footnote *a*, Table I. [b] Slightly split by coupling (J = 0.8 Hz) of H-6 with CH_3. [c] Solvent $CDCl_3$. [d] In CCl_4 the acetyl singlet falls at δ 2.67. [e] Unresolved singlet. [f] 2.62 (q, J = 7.5 Hz, CH_3CH_2), 1.16 (t, J = 7.5 Hz, CH_3CH_2).

When the 2- or 3-amine salt was heated with excess acetoacetaldehyde dimethyl acetal (ADMA) in ethanolic hydrochloric acid, acetone was evolved and **1j** (32%) or **2d** (54%), respectively, was isolated. The structures of these products were established by ir and nmr spectra. Assignments were reinforced by comparisons with the nmr spectra of the previously described 2-acetylthienopyridines **1i**, **1k**, and **2c** (structures known from the method of synthesis). A further check was also made by comparison of spectra of the isomeric ethylthienopyridines **1e**, **1f**, and **2e** derived in fair yields from Wolff-Kishner reduction of **1i** (admixed with **2c**), **1j**, and **2d**, respectively. Scheme I shows a possible pathway for the formation of **1j**. It is assumed that ADMA is first converted effectively into free acetoacetaldehyde, which condenses with the 2-amine salt to form the Schiff's base **9**. Condensation of **9** (which contains an active methylene group) with a second molecule of acetoacetaldehyde should give ketol **10**. Acid-catalyzed dehydration–cyclization to **11** followed by a reverse Michael reaction would then lead to **1j**.[27]

In one run the mother liquors from isolation of **1j** were examined carefully for the presence of by-products. Identified were small yields (2–5%) of the monomethylthienopyridines **1a** and **1b**. In reaction of the 2-amine

SCHEME I



salt with acetoacetaldehyde tetraethyl acetal (ADEA) Zhiryakov and Abramenko[14] reported the isolation of only **1b** (20% yield). The melting point (211°) of the picrate of their product,[28] however, is more nearly like

(27) In a separate experiment with ADMA and 2-naphthylamine the molar ratio of products was acetone–acetylbenzoquinoline 1:1.

(28) Zhiryakov and Abramenko[14] attempted to prove the structure of their product by an independent synthesis involving (as the first step) condensation of α-cyanothioacetamide with acetoacetaldehyde. Such process could, however, yield **1a** as well as **1b**.

that (218°) of our **1a** rather than that (171°) of our **1b**. Similarly, from the 3-amine salt the Russian workers report a 53% yield of **2a**, but again of unproved structure.[29]

In Table III are presented quantum chemical re-

TABLE III

QUANTUM CHEMICAL REACTIVITY INDICES[a] FOR THIENO[2,3-*b*]PYRIDINE (**1**)

Position r	q_r	S_r^{elec}	S_r^{nucl}
1 (S)	1.32	3.10	0.49
2	1.09	1.20	0.78
3	1.21	2.21	0.54
3a	1.08	1.02	0.60
4	0.94	0.96	1.19
5	1.06	1.13	0.71
6	0.93	0.92	1.15
7 (N)	1.32	1.59	0.94
7a	1.05	1.18	0.76

[a] S_r is given in units of β_C^{-1}: L. Salem, "Molecular Orbital Theory of Conjugated Systems," W. A. Benjamin, Inc., New York, N. Y., 1966, pp 326–332. Superscripts elec and nucl refer to electrophilic attack and nucleophilic attack, respectively. S_r^{rad} for free radical attack is readily calculated from the relationship $S_r^{rad} = {}^1/_2(S_r^{elec} + S_r^{nucl})$.

activity indices q_r (π-electron density) and S_r (exact superdelocalizabilities for electrophilic and nucleophilic attack) for direct substitution into **1**. Data were obtained by the use of simple Hückel molecular orbital theory and the parametric equations $\alpha_N = \alpha_C + 0.5\beta_{C-C}$, $\alpha_S = \alpha_C$, $\beta_{C-N} = 0.8\beta_{C-C}$, $\beta_{C-S} = 0.8\beta_{C-C}$. These equations neglect d-orbital interaction by the sulfur atom[30,31] and inductive effects of heteroatoms at distances beyond contiguous carbon atoms.[32] Observation of this table indicates that electrophilic substitution into **1** should occur predominantly in the thiophenoid ring with a strong preference for position C-3 over that of C-2 (analogous to observations for benzo[*b*]thiophene).[33] Nucleophilic substitution, on the other hand, should occur predominantly in the pyridinoid ring with preference shown for positions C-4 and C-6 (γ and α positions, respectively, with regard to N). Positional preference for nucleophilic substitution is thus predicted to be analogous to that which one finds in quinoline.[34,35]

Limited investigations of electrophilic and nucleophilic substitutions into **1** have qualitatively confirmed the preceding predictions. Treatment of **1** with bromine in carbon tetrachloride gave 2,3-dibromothieno-[2,3-*b*]pyridine in 17% yield. Reaction of **1** with deuteriosulfuric acid at 98.5° gave fastest deuteriodeprotonation at C-3 and slower exchange at C-2, as indicated by nmr studies (changes in the thiophenoid aromatic AB quartet) of samples withdrawn periodically.

Treatment of **1** with *n*-butyllithium at 25–35° gave, on addition of water, a yellow liquid (possibly containing 6-*n*-butyl-6,7-dihydrothieno[2,3-*b*]pyridine) which was converted into **1g** (47%, separated from recovered **1** by chromatography on alumina) on stirring with carbon disulfide. Assignment of the *n*-butyl group to the 6 position was made on the basis of the chromatographic elution order[20] (**1g** before **1**) and nmr analysis (absence of signal at $\delta > 8.0$). Repetition of this procedure with methyllithium (instead of *n*-butyllithium) gave a crude liquid containing *ca.* 25% of **1b** and 75% of **1**. With a reaction temperature of −25° and hydrolysis first with deuterium oxide and then with water, methyllithium gave a mixture of **1b** (11%) and deuterated **1** (containing *ca.* 50% of 2-deuteriothieno[2,3-*b*]pyridine, **1l**). Product **1l** apparently arises *via* metalation in a position *ortho* to the sulfur atom (*cf.* results for benzo[*b*]thiophene),[36] a process which competes with addition to the pyridinoid carbon–nitrogen double bond.[37]

Experimental Section[38]

2-Nitrothiophene.—Nitration of thiophene was conducted in acetic acid–acetic anhydride according to published directions.[16] Nmr analysis (CCl_4) of the product (mp 44–45°) showed that it consisted of an isomeric mixture containing 85% 2-nitrothiophene (δ 7.8–8.0, multiplet for H-3) and 15% 3-nitrothiophene (δ 8.1–8.3, multiplet for H-2).[39] Varying the reaction temperature over the range 10–30° did not alter the isomeric ratio. A reaction temperature of 25° is preferred since it gives the lightest colored product. Efforts to separate isomers by fractional crystallization and column chromatography were unsuccessful. The mixture was used directly in further reactions.

3-Nitrothiophene was prepared from thiophene in *ca.* 40% yield by the five-step procedure of previous workers.[17,18] Nmr analysis of the product (mp 74–75°) showed that it contained 5% of the isomeric 2-nitrothiophene. It was used without further purification.

Thieno[2,3-*b*]pyridine (1).—To a vigorously stirred mixture (maintained at 30°) of 13 g (0.1 mol) of the preceding 2-nitrothiophene and 195 ml of concentrated hydrochloric acid was added, in 5-g batches, a total quantity of 25 g of granular tin. After most of the tin had dissolved, 70 ml of EtOH and 6 g of anhydrous $ZnCl_2$ were added and the mixture was heated to 85°. A solution of 17.2 g (0.078 mol) of malondialdehyde tetraethyl acetal (Aldrich Chemical Co.) in 30 ml of EtOH was added all at once. The mixture was maintained at 85° for 1 hr and then poured onto 100 g of ice. The aqueous mixture was basified with concentrated aqueous NH_3 and extracted with three 75-ml portions of CCl_4. Distillation of combined extracts yielded 4.6 g (44%) of light yellow liquid, bp 61–62° (0.2 mm), found to contain about 6% of isomeric thieno[3,2-*b*]pyridine as determined by nmr analysis.

In a run conducted on five times the preceding scale the reaction mixture was basified with 40% aqueous NaOH and the resultant slurry was steam distilled. Continuous extraction for 16 hr with ether of the first 5 l. of distillate yielded 26.3 g (50%) of product.

For further purification 10.4 g (77 mmol) of mixed thienopyridine product was stirred for 1 hr with 15.3 ml of 1 *M* (15.3 mmol) hydrochloric acid and 300 ml of water. Extraction of

(29) Our picrates of **2a** and **2b** plus those reported by the Russian workers[13,14] have melting points in the range of 188–207°, but are otherwise inconsistent.

(30) R. Gerdil and E. A. C. Lucken, *J. Amer. Chem. Soc.*, **87**, 213 (1965).

(31) R. Gerdil and E. A. C. Lucken, *ibid.*, **88**, 733 (1966).

(32) The model used here is a combination of those suggested for thiophene by R. Zahradnik (*cf.* models B2 and B3) and for pyridine by R. Zahradnik and J. Koutecky, *Advan. Heterocycl. Chem.*, **5**, 2, 70 (1965).

(33) R. M. Acheson, "An Introduction to the Chemistry of Heterocyclic Compounds," 2nd ed, Interscience Publishers, New York, N. Y., 1967, pp 181–183.

(34) See ref 32, p 110.

(35) See ref 33, pp 249, 255.

(36) D. A. Shirley and M. D. Cameron, *J. Amer. Chem. Soc.*, **72**, 2788 (1950).

(37) H. Gilman and J. W. Morton, *Org. Reactions*, **8**, 272 (1954).

(38) Microanalyses were performed by Micro-Tech Laboratories, Skokie Ill. Infrared spectra were determined by means of a Beckman IR-5 instrument and nmr spectra by means of a Varian A-60 spectrometer and tetramethylsilane as an internal standard. Vapor phase chromatography was carried out with an F & M Model 202 gas chromatograph. Stationary phase A was 10% Apiezon L on Chromosorb P; B was 15% Carbowax 20M on firebrick. For many chromatograms relative retention volumes (r_V) of components are reported in terms of a selected internal standard (r_V = 1.0).

(39) R. A. Hoffman and S. Gronowitz, *Arkiv Kemi*, **16**, 515 (1960).

the acidic mixture with ether gave 9.4 g of pure (as adjudged by nmr) 1. Basification of the aqueous layer and extraction thereof with ether produced 0.58 g of mixed thienopyridines—enriched in 2.

Liquid–solid column chromatography of 3.6 g of 2-enriched thienopyridines was conducted with 108 g of Alcoa F-20 alumina. Elution with cyclohexane–benzene (3:2 by volume) gave 1.09 g of pure 1 in the first 400 ml of effluent and 0.51 g of mixed isomers in the next 300 ml of effluent. Changing the eluent to benzene alone then yielded 1.5 g of pure 2 in 1 l. of effluent.

The methiodide of 1 formed cream-colored prisms from absolute EtOH, mp 202–203° dec.

Anal. Calcd for C_8H_8INS: C, 34.67; H, 2.91; I, 45.79; N, 5.05; S, 11.57. Found: C, 34.72; H, 3.05; I, 46.08; N, 5.06; S, 11.82.

Nmr spectral data for 1 are given in Table I. In analogy to quinoline,[40,41] a doublet of doublets at lowest field (δ 8.46) in the spectrum is assigned to H-6 (α to the heterocyclic N-atom) and a doublet of doublets at next higher field (δ 7.85) is assigned to H-4 (γ to the nitrogen)—$J_{5,6}$ = 4.5, $J_{4,6}$ = 1.6, $J_{4,5}$ = 8.1 Hz (*cf.* corresponding values for the heteroring of quinoline—$J_{2,3}$ = 4.1, $J_{2,4}$ = 1.8, $J_{3,4}$ = 8.5 Hz, respectively). The high-field portion of the spectrum consists of two overlapping sets of doublets of doublets which correspond to H-5 (β to the nitrogen, centered at δ 7.10, coupling constants as noted above) and to the thiophenoid AB proton system H-2 and H-3 (centered at δ 7.24, $J_{2,3}$ = 5.9 Hz; *cf.* $J_{2,3}$ = 5.6 as measured for benzo[*b*]thiophene in CCl_4). The lower field doublet of the latter set is ascribed to H-2, in accordance with previous observations on the methylbenzo[*b*]thiophenes[42] and with the absence of this doublet in authentic 2-ethylthieno[2,3-*b*]pyridine (1e, *vide infra*).

Thieno[3,2-*b*]pyridine (2).—The synthetic procedure was essentially the same as that for 1, except that preceding 3-nitrothiophene (2.6 g) was used instead of its isomer and heating was conducted for 1.5 hr at 80°, yield 2.1 g (77%) of crude product from evaporation of combined CCl_4 extracts. The nmr spectrum of this crude product was identical with that of a sample of 2 prepared from 2-vinylpyridine and hydrogen sulfide by the vapor phase process of Klemm and Reed.[3] Also picrates of the two samples were identical, as based on melting points alone and after admixture.

An analytical sample of 2 was obtained as a faintly yellow-green liquid from vpc on A at 150°.

Anal. Calcd for C_7H_5NS: C, 62.19; H, 3.73; N, 10.36; S, 23.72. Found: C, 62.20; H, 4.08; N, 10.36; S, 23.34.

The nmr spectrum of 2 (Table II) shows more lines than that of 1 due to the presence of long-range coupling between H-2 and H-6 (J = 0.4 Hz) and between H-3 and H-7 (J = 0.8 Hz). The order of appearance in the spectrum of signals for the pyridinoid ring protons is the same as before, *i.e.*, α, γ, β (with respect to nitrogen) for increasing field strength, but signals for the thiophenoid ring protons are shifted downfield sufficiently that they fall cleanly between those for the γ and β protons (first-order spectrum). Only H-5 shows an unmodified doublet of doublets ($J_{5,6}$ = 4.8 Hz, $J_{5,7}$ = 1.6). All other spectral patterns ($J_{6,7}$ = 8.8, $J_{2,3}$ = 6.1) are again doubled by long-range spin–spin coupling constants which are consistent with observations on benzo[*b*]thiophene ($J_{2,6}$ not observed, $J_{3,7}$ = 0.7)[42] and on 5,7-dichloroquinoline and 5,7-dimethylquinoline ($J_{4,8}$ = 0.8, analogous to $J_{3,7}$ in 2).[43] Based on the consistency of these coupling constants one can again ascribe the lower half of the thiophenoid AB system in 2 to the proton at C-2. Although the geometry of thieno[3,2-*b*]pyrrole is considerably modified from that of 2, it is noteworthy that long-range couplings between two sets of aromatic protons have also been observed in this thienopyrrole system.[44]

Bis(2- and 3-thienylammonium) Hexachlorostannates(IV).—These mixed salts were isolated in crystalline form from reduction of the corresponding 2- and 3-nitrothiophenes according to the procedure of Steinkopf and Lützkendorf.[4] Partial separation of mixed isomers could be achieved by fractional precipitation. Thus the initially isolated (by filtration at room temperature) salt was enriched in the 2 isomer. Cooling the filtrate to −10° caused precipitation of salt enriched in the 3 isomer. In subsequent reactions the crude salts were used without isomeric enrichment.

Reaction of 2-Thienylammonium Salt with Methyl Vinyl Ketone.—Reaction of bis(2-thienylammonium) hexachlorostannate(IV) with methyl vinyl ketone (MVK) was conducted in a manner similar to that previously described.[13] To a warm (60°) mixture of 20 g of amine salt, 22.1 g of anhydrous $FeCl_3$ and 0.5 g of anhydrous $ZnCl_2$ in 50 ml of absolute EtOH in a nitrogen atmosphere were added dropwise (over a period of 1 hr) a solution of 2.9 g of MVK in 25 ml of absolute EtOH. The mixture was then heated at 80° for 2 hr, cooled, poured onto 500 g of ice, basified with 40% aqueous NaOH and continuously extracted with ether for 1 day. The dried ($MgSO_4$) ether extract was distilled to yield 1.5 g (25%) of light yellow liquid, bp 75–85° (2 mm). Vpc of this distillate on B at 200° gave two liquid products **6-methylthieno[2,3-*b*]pyridine** (1b, 40%, r_V = 1.0) and **4-methylthieno[2,3-*b*]pyridine** (1a, 60%, r_V = 1.4).

Anal. Calcd for C_8H_7NS: N, 9.39. Found for 1a: N, 9.80. Found for 1b: N, 9.55.

Picrates of the chromatographically separated fractions crystallized from absolute ethanol: mp 217–218° for 1a picrate, canary yellow needles (lit.[13] mp 213–215°), mp 169–171.5° for **1b picrate**, yellow prisms.

Anal. Calcd for $C_{14}H_{10}N_4SO_7$: C, 44.44; H, 2.66; N, 14.81; S, 8.48. Found for 1a picrate: C, 44.29; H, 2.60; N, 14.68; S, 8.56. Found for 1b picrate: C, 44.71; H, 2.75; N, 14.73; S, 8.42.

Reaction of 3-Thienylammonium Salt with Methyl Vinyl Ketone.—This reaction was conducted in the preceding manner to give 3 g (50%) of light yellow liquid. Vpc of this distillate gave two liquid products, **5-methylthieno[3,2-*b*]pyridine** (2a, 17%, r_V = 1.0) and **7-methylthieno[3,2-*b*]pyridine** (2b, 83%, r_V = 1.2).

The **picrate of 2b** formed yellow needles from EtOH, mp 206–207° (lit.[13] mp 193–195°).[29]

Anal. Calcd for $C_{14}H_{10}N_4SO_7$: C, 44.44; H, 2.66; N, 14.81; S, 8.48. Found: C, 44.78; H, 2.72; N, 14.61; S, 8.50.

Reaction of 6-Methyl-2-vinylpyridine with H_2S.—In an apparatus similar to that described previously,[3] 35 g of freshly distilled 6-methyl-2-vinylpyridine (K & K Laboratories) was added at a rate of 20 drops/min to a vertical Pyrex tube (2 cm i.d.) packed to a height of 24 cm with chromia–alumina (Harshaw Chem. Co., Cr-0101T, 1/8 in. pellets) at 630° in a stream of H_2S (molar ratio 4:1 H_2S:substrate). Liquid effluent was combined with the residue from evaporation of acetone extracts of the cooled tube packing. This crude mixture was analyzed by vpc on stationary phase A at 150°. Identified by comparison of retention times with those of authentic sampes were 2-picoline, 2,6-lutidine, starting material, 2-methyl-6-ethylpyridine (all with r_V < 0.2), 2 (0.4%, r_V = 1.0), and 2a (0.9%, r_V = 1.4).

For isolation of 2a, low-boiling components of the crude mixture were removed by distillation up to 150° (25 mm). A benzene solution of the residue was percolated through alumina (50 g) and evaporated. The residue was triturated with acetone (20 ml) to leave undissolved sulfur. The filtrate of this mixture was evaporated and chromatographed on stationary phase A at 125°. The 2a isolated was identical with that obtained from the 3-hexachlorostannate salt in the preceding section, as based on nmr. It formed a picrate, mp 195–196° (lit.[14] mp 188–189°).[29]

Reaction of 2-Methyl-5-vinylpyridine with H_2S.—In the preceding manner 50 g of freshly distilled 2-methyl-5-vinylpyridine (Phillips Petroleum Co.) was treated with H_2S (molar ratio 5:1 H_2S:substrate) at 630° in a flow apparatus. Identified, in the crude mixed product, by comparison of retention times (in vpc on A at 125°) with those of authentic samples (though not for 4a) were 2-methyl-5-ethylpyridine (18%, r_V = 0.2), 1 (0.5%, r_V = 1.0), 1b (2.2%, r_V = 1.5), and **6-methylthieno[3,2-*c*]pyridine** (4a, 0.3%, r_V = 1.9). Also identified in the mixture by comparative nmr analyses were 2,5-lutidine (8%) and **thieno[3,2-*c*]pyridine**[25] (4, 0.1%). A parallel run using 40 g of 2-methyl-5-ethylpyridine (Distillation Products) as substrate gave almost identical results except that there was more starting material (53% recovery) and some 2-methyl-5-vinylpyridine (6%) in the total product.

(40) J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. 2, Pergamon Press, New York, N. Y., 1966, pp 798–802.

(41) H. Suhr, "Anwendungen der Kernmagnetischen Resonanz in der Organischen Chemie," Springer-Verlag, Berlin, Germany, 1965, pp 232, 233.

(42) K. Takahashi, T. Kanda, and Y. Matsuki, *Bull. Chem. Soc. Jap.*, **37**, 768 (1964).

(43) F. A. L. Anet, *J. Chem. Phys.*, **32**, 1274 (1960).

(44) R. J. Tuite, H. R. Snyder, A. L. Porte, and H. S. Gutowsky, *J. Phys. Chem.*, **65**, 187 (1961).

For isolation of thienopyridine components the residue from distillation of the crude mixture up to 190° (0.5 mm) was chromatographed on a column of alumina (100 g). Elution with cyclohexane gave first **1b** (identified by the melting point of the picrate and its mixture melting point with product from the MVK reaction of the 2-thienylammonium salt) and then **1** (identified by comparison with preceding synthetic product). Further elution with $CHCl_3$–benzene 1:1 gave a mixture which was separated by sublimation at 60° (0.25 mm) to yield **4a**, mp 72.5–74°, picrate mp 224–226.5°, methiodide mp 241.5–242.5° (lit.[23] mp 71.5–72.5, 222–224, and 240–242°, respectively).

Reaction of 3-Ethyl-4-methylpyridine with H_2S.—In the preceding manner there was obtained from 35 g of 3-ethyl-4-methylpyridine (Aldrich) a crude product which showed two main components (identified by comparison of retention times with authentic samples) by vpc analysis on A at 125°, starting material (34% recovery, r_V = 1.0) and **1a** (1%, r_V = 3.3).

4,5,6-Trimethylthieno[2,3-*b*]pyridine (1d).—A mixture of 9 g (0.017 mol) of bis(2-thienylammonium) hexachlorostannate(IV), 3.3 g (0.029 mol) of 3-methylpentane-2,4-dione,[45] 2 g of anhydrous $ZnCl_2$, and 30 ml of dioxane was refluxed for 4 hr and then poured into absolute EtOH. To the black residue from evaporation *in vacuo* of nearly all of the solvent were added ice and 20 ml of concentrated aqueous NH_3. A CCl_4 extract of this mixture was chromatographed by means of 30 g of neutral Brinkman alumina with benzene–cyclohexane (1:3) and then $CHCl_3$ as eluents. The brown solid obtained from the $CHCl_3$ effluent was sublimed at 100° (2 mm) and combined with product from evaporation of the hydrocarbon effluent, total yield 1.65 g (32%) of white needles, mp 98–99°; uv max (95% EtOH) 234 mμ (ε 29,400), 272 (5590), 285 (4190), 291 (4190), 297 (3090), 302 (3710); uv max (95% EtOH + HCl) 242 mμ (ε 30,800), 306 (7430).

Anal. Calcd for $C_{10}H_{11}NS$: C, 67.76; H, 6.26; N, 7.90; S, 18.09. Found: C, 67.68; H, 6.42; N, 7.64; S, 17.86.

4,6-Dimethylthieno[2,3-*b*]pyridine (1c) was prepared from bis(2-thienylammonium) hexachlorostannate(IV) and acetylacetone in a manner similar to that used for **1d**, except that the product was extracted into benzene and purified by distillation (instead of chromatography) to give a light yellow liquid [45% yield, bp 100–105° (3 mm)] which slowly darkened in air [lit.[2] bp 103–108° (4 mm)].

5,6,7,8-Tetrahydrothieno[2,3-*b*]quinoline (1h).—A mixture of 0.5 g of anhydrous $ZnCl_2$, 15 ml of dioxane, 3 g (0.0057 mol) of bis(2-thienylammonium) hexachlorostannate(IV) and 1.3 g (0.01 mol) of 2-hydroxymethylenecyclohexanone[46] was stirred at 100° for 2 hr. The mixture was concentrated to a small volume and treated with 60 ml of 5% aqueous NH_3. The black product from the hydrolysate was extracted into $CHCl_3$, transferred to a benzene solution, passed through a column of Brinkman alumina, and evaporatively distilled *in vacuo* to yield 0.1 g (5%) of colorless liquid. This liquid formed a **picrate**, mp 188–189°, obtained as yellow plates from EtOH.

Anal. Calcd for $C_{17}H_{14}N_4O_7S$: C, 48.80; H, 3.37; N, 13.39; S, 7.66. Found: C, 48.95; H, 3.66; N, 13.70; S, 7.52.

Nitration of 2-Acetylthiophene.—2-Acetylthiophene (Winthrop Labs., New York, N. Y.) was nitrated in the same manner as used for thiophene itself[16] to give a mixture of solid products (37–62%), shown by nmr analysis to contain *ca.* equal parts of **4-nitro-2-acetylthiophene (7)** and **5-nitro-2-acetylthiophene (8)**. Repeated crystallization from EtOH[21] gave **7**, mp 123–125° (lit.[21] mp 125–126°), and then **8**, mp 100–110° (lit.[21] mp 106–107°); nmr ($CDCl_3$) for **7**, δ 2.62 (s, 3, CH_3CO), 8.55 (H_3), 8.61 (H_5, AB system, 2, J = 1.6 Hz); nmr ($CDCl_3$) for **8**, δ 2.62 (s, 3, CH_3CO), 7.61 (H_3), 7.91 (H_4, AB system, 2, J = 4.3 Hz). One of the authors developed a severe case of dermatitis (itching, swelling, and blistering) of the hands from handling these nitro compounds. Extreme care should be exercised in avoidance of contact with the skin.

The oxime of **8** was obtained as light yellow needles from EtOH: mp 187–188° (lit.[21] mp 189°); nmr (acetone) δ 7.25 (H_3), 7.96 (H_4, AB system, J = 4.5 Hz).

Bis[2-(5-acetylthienyl)ammonium] Hexachlorostannate(IV) (12).—To a vigorously stirred mixture of 10 g (0.058 mol) of **8**, 150 ml of concentrated hydrochloric acid, and 50 ml of EtOH was added 21 g (0.18 mol) of granular tin at such a rate as to maintain the reaction mixture at 30–34° while the reaction flask was cooled in a bath of tap water. After nearly all of the tin had dissolved the mixture was refrigerated at −10° for 10 hr and filtered to yield 6.6 g (37%) of **12**, dried *in vacuo*, used without further purification.

5-Acetylthieno[2,3-*b*]pyridine (1j).—To a stirred mixture of 9 g (0.017 mol) of bis(2-thienylammonium) hexachlorostannate(IV), 10 ml of concentrated hydrochloric acid, and 30 ml of EtOH in an atmosphere of purified nitrogen was added 12 g (0.09 mol) of acetoacetaldehyde dimethyl acetal (Aldrich Chemical Co.).[47] The mixture was heated at 75° for 8 hr (during which time acetone—detected by means of 2,4-dinitrophenylhydrazine reagent—was evolved) and then poured into sufficient excess 8% aqueous NaOH (175 ml) to basify the mixture and to dissolve most of the resultant precipitate. CCl_4 extracts of the hydrolysate were dried and evaporated to leave a residue which was sublimed at 120° (0.04 mm). Crystallization of the sublimate from cyclohexane gave needles: mp 116–117°; yield 1.9 g (32%); ir (CCl_4) 1690 cm^{-1} (C=O); uv max (95% EtOH) 247 mμ (ε 40,800), 275 (5910). The nmr spectrum showed a three-proton singlet at δ 2.69 for the acetyl group and coupling ascribed to protons at positions 2, 3, 4 and 6 but showed no evidence for coupling by a proton at C-5 (*cf.* Table I).

Anal. Calcd for C_9H_7NOS: C, 60.99; H, 3.98; N, 7.90; S, 18.09. Found: C, 61.33; H, 4.10; N, 7.89; S, 18.11.

In a larger run (0.5 mol of amine salt) evaporation of the mother liquor from crystallization of **1j** gave 11.8 g of black liquid. Chromatography of this liquid with 250 g of Alcoa F-20 alumina and successive eluents of cyclohexane–benzene (19:1), benzene, and $CHCl_3$ gave the following minor products (in order of elution):[20,48] **1b** (2.5% over-all yield), **1a** (4.6%), **2a** (?, <0.5%), additional **1j** (2%), and **2d** (1.2%, based on 3-amine salt in the starting material). No **2b** was detected.

6-Acetylthieno[3,2-*b*]pyridine (2d).—In the preceding manner 9 g of a mixture of bis(2- and -3-thienylammonium) hexachlorostannates(IV) (shown by nmr analysis to contain 40% of the 3 isomer) was allowed to react with acetoacetaldehyde dimethyl acetal (but at reflux conditions for 24 hr) and then processed further. The sublimate (3.4 g, 56%, analyzed by nmr by means of relative areas of the signals at δ 7.3 and 7.6, respectively) was found to contain equimolar amounts of **1j** and **2d**. Three recrystallizations of the sublimate from benzene–cyclohexane (1:1) gave 1.3 g (54%, based on 3 isomer only) of pure (by nmr analysis) **2d**: mp 134–135°; obtained as cream-colored crystals on sublimation at 90° (0.4 mm); ir ($CHCl_3$) 1690 cm^{-1} (C=O); uv max (95% EtOH) 246 mμ (ε 23,400), 292 (10,900); uv max (95% EtOH + HCl) 252 mμ (ε 24,900), 307 (6030), 325 (5150). The nmr spectrum showed a three-proton singlet at δ 2.69 for the acetyl group and coupling ascribed to protons at positions 2, 3, 5, and 7 but not at 6 (*cf.* Table II).

Anal. Calcd for C_9H_7NOS: C, 60.99; H, 3.98; N, 7.90; S, 18.09. Found: C, 60.76; H, 4.05; N, 8.04; S, 18.22.

2-Acetylthieno[2,3-*b*]pyridine (1i).—A mixture of 3 g (0.005 mol) of hexachlorostannate salt **12**, 2 g (0.09 mol) of MDTA, 2 g of anhydrous $ZnCl_2$, 15 ml of EtOH, and 5 ml of concentrated hydrochloric acid was refluxed for 3 hr and the mixture was processed further as for its isomer **1j**: yield 0.55 g (30%) of product from sublimation at 100° (10 mm); mp 124–126°. An additional sublimation gave light yellow needles: mp 122–123°; uv max (95% EtOH) 241 mμ (ε 14,000), 292 (17,300); uv max (95% EtOH + HCl) 248 mμ (ε 17,700), 294 (14,500).

Anal. Calcd for C_9H_7NOS: C, 60.99; H, 3.98; N, 7.90; S, 18.09. Found: C, 60.92; H, 3.86; N, 7.79; S, 18.30.

2-Acetyl-4,6-dimethylthieno[2,3-*b*]pyridine (1k).—In the manner used for preparation of **1d** (except that the reaction was

(45) Prepared by stirring 2.4 g of sodium acetylacetonate [R. G. Charles, "Organic Syntheses," Coll. Vol. IV, John Wiley & Sons, Inc., New York, N. Y., 1963, p 869] with 5.3 g of MeI in 10 ml of CH_3CN for 13 hr, and then filtration and distillation of the reaction mixture, yield 2 g (89%), bp 80–85°.

(46) C. Ainsworth, "Organic Syntheses," Coll. Vol. IV, John Wiley & Sons, Inc., New York, N. Y., 1963, p 536.

(47) For other syntheses with acetoacetaldehyde see W. Franke, R. Kraft, and K. Kosswig in "Newer Methods of Preparative Organic Chemistry," Vol. 2, W. Foerst, Ed., Academic Press, New York, N. Y., 1963, pp 1–30.

(48) The enhanced adsorbability of the acetyl derivatives over the methyl derivative is ascribed to strong anchoring by the carbonyl group (as well as by the pyridinoid nitrogen atom);[20] L. R. Snyder, "Chromatography," E. Heftmann, Ed., 2nd ed, Reinhold Publishing Corp., New York, N. Y., 1967, pp 63–66.

quenched with aqueous EtOH, and benzene was used as chromatographic eluent) there was obtained (from 1.9 g of amine salt 12 and 2 g of acetylacetone) 0.56 g (42%) of **1k**, mp 168–171° (after one crystallization from EtOH). Recrystallizations from EtOH and then sublimation at 120° (0.2 mm) gave light yellow needles: mp 168.5–169.5°; ir ($CHCl_3$) 1670 cm^{-1} (C=O).

Anal. Calcd for $C_{11}H_{11}NOS$: C, 64.36; H, 5.40; N, 6.82; S, 15.62. Found: C, 64.53; H, 5.45; N, 6.69; S, 15.71.

Conversion of Mixed Nitro-2-acetylthiophenes to 2-Acetylthienopyridines.—An isomeric mixture (mp 79–93°) of **7** (45% by nmr analysis) and **8** (55%) was reduced as in the preparation of **12**. The red-black solution was evaporated nearly to dryness and the crude mixture of amino-2-acetylthiophene hexachlorostannate salts (0.46 mol) was treated with 1.4 l. of EtOH, 0.45 l. of concentrated hydrochloric acid, 150 g of anhydrous $ZnCl_2$, and 150 g of MDTA. The mixture was refluxed in a nitrogen atmosphere for 5.5 hr, evaporated nearly to dryness, and extracted with 2 *N* HCl until the extract was no longer colored. Combined acid extracts were treated dropwise with 40% aqueous NaOH until a dense, dark precipitate coagulated (pH *ca.* 0.8). The filtrate of the mixture was brought to pH 1.5 and extracted with benzene. Evaporation of benzene extracts gave a dark tarry residue which was sublimed at 110–145° (1 mm) to give 27 g (17%) of yellow crystals of mixed 2-acetylthienopyridines—nearly equal parts of **1i** and of 2-acetylthieno[3,2-*b*]pyridine (**2c**) as determined by integration of the acetyl proton singlets observed in the nmr spectrum taken in CCl_4, *cf.* Table I and II.

On a 100-mg scale these isomers were separable by preparative tlc by means of a 20 × 40-cm plate coated to a thickness of 1 mm with Brinkman alumina G (activated at 110°) and elution with benzene–$CHCl_3$ (9:1 by volume) for 20 hr while the solvent overran the plate and the visually apparent yellow band approached the top closely. Spraying only the edges of the plate with Dragendorff's reagent[20] revealed the presence of an upper band (from which 32 mg of pure **1i** was obtained), an intermediate zone (mixed isomers), and a lower band (**2c**, free of **1i** but not of other impurities).

On a larger scale the isomers were separable by acid extraction. A solution of the crystalline mixed isomers in slightly more than the minimum quantity of benzene was stirred vigorously with four times the volume of 1 *N* HCl for 15–30 min. Layers were separated. Evaporation of the benzene layer gave **1i**, free of **2c** but not of other impurities.

The aqueous layer was basified with 40% aqueous NaOH and extracted with benzene until the extract remained colorless. Combined benzene extracts were evaporated nearly to saturation and the entire extraction process was repeated at least three more times, but with 0.1–0.2 *N* HCl instead of 1 *N* HCl. For the final time, combined benzene extracts were evaporated to dryness to give **2c**, free of **1i** but not of other impurities.

Extraneous impurities in preceding fractions were removed by sublimation at 80° (0.1 mm) for 3–4 hr. Two additional sublimations gave an analytically pure sample of **2c**, obtained as pale yellow prisms: mp 156–157°; ir ($CHCl_3$) 1675 cm^{-1} (C=O).

Anal. Calcd for C_9H_7NOS: C, 60.99; H, 3.98; N, 7.90; S, 18.09. Found: C, 61.30; H, 4.16; N, 7.75; S, 17.94.

2-Ethylthieno[2,3-*b*]pyridine (1e).—A mixture (1 g) of isomeric 2-acetylthienopyridines **1i** and **2c** (50% each), NaOH pellets (0.9 g), hydrazine hydrate (0.9 ml), and diethylene glycol (14 ml) was refluxed for 1.5 hr, distilled to bp 195°, and then refluxed for 3 hr longer. Addition of water to the cooled mixture, extraction with benzene, and evaporation of the extract gave 0.68 g (74%) of mixed 2-ethylthienopyridines (**1e** and its [3,2-*b*]isomer, 2:1 by vpc and nmr analysis). Vpc with 10% Bentone 34–silicone oil separated **1e** as a colorless liquid.

Anal. Calcd for C_9H_9NS: C, 66.22; H, 5.56. Found: C, 66.38; H, 5.80.

The picrate was obtained as canary yellow plates from absolute EtOH, mp 208–209°.

Anal. Calcd for $C_{15}H_{12}N_4O_7S$: C, 45.92; H, 3.08; N, 14.28; S, 8.17. Found: C, 45.77; H, 3.16; N, 14.07; S, 8.02.

5-Ethylthieno[2,3-*b*]pyridine (1f) and 6-Ethylthieno[3,2-*b*]pyridine (2e).—In the preceding manner **1j** was reduced to **1f**; and **2d** to **2e**. The respective ethyl derivatives were isolated as the picrates (65%, mp 188–190°; 83%, mp 238–239°) and recrystallized from EtOH to give bright yellow needles (mp 192–193 and 238.5–239.5°, respectively).

Anal. Calcd for $C_{15}H_{12}N_4O_7S$: C, 45.92; H, 3.08; N, 14.28; S, 8.17. Found for **1f** picrate: C, 45.94; H, 3.14; H, 14.07; S, 7.88. Found for **2e** picrate: C, 45.74; H, 3.07; N, 14.36; S, 8.13.

Dissociation of the picrates with chloroform and alumina gave the purified ethyl derivatives as light brown liquids, used for nmr characterization.

6-*n*-Butylthieno[2,3-*b*]pyridine (1g).—To a solution of 1.37 g (0.01 mol) of **1** in 20 ml of anhydrous ether in an atmosphere of nitrogen was added (over a period of 10 min) 13 ml (0.02 mol) of 1.5 *M* *n*-BuLi in ether. The mixture refluxed gently during the addition. Thereafter, it was stirred at room temperature for 30 min, while it acquired a deep red color. Water (10 ml) was added and the mixture was extracted with ether. Evaporation of the ether extract left 1.7 g of light yellow liquid (which turned dark slowly when neat, became black and gummy in CCl_4, but seemed fairly stable in ether). Addition of 20 ml of CS_2 gave a deep red solution and caused the evolution of H_2S—as evidenced by a test with lead acetate paper. The solution was stirred for 30 min and evaporated. The residual liquid was chromatographed by means of 40 g of Brinkman neutral alumina and eluents of cyclohexane (200 ml) and (then) benzene–cyclohexane (300 ml, 1:1 by volume). The first effluent yielded 0.9 g (47%) of liquid **1g**, while a later effluent gave 0.5 g of light yellow liquid—shown by nmr analysis to consist largely (*ca.* 90%) of recovered **1**. Vpc of the former liquid with a stationary phase of Apiezon L on firebrick gave an analytically pure sample.

Anal. Calcd for $C_{11}H_{13}NS$: C, 69.07; H, 6.85; N, 7.32; S, 16.76. Found: C, 69.23; H, 6.97; N, 7.14; S, 16.19.

A picrate was obtained as yellow needles from EtOH, mp 112–113°.

Anal. Calcd for $C_{17}H_{16}N_4O_7S$: C, 48.57; H, 3.84; N, 13.33; S, 7.63. Found: C, 48.87; H, 3.94; N, 13.47; S, 7.56.

Reaction of Thieno[2,3-*b*]pyridine with Methyllithium. A. At Room Temperature.—Following exactly the preceding directions, except that MeLi was used (in place of *n*-BuLi), the reaction mixture was stirred for 90 min at room temperature, and the CS_2 solution was stirred for 3 hr, there was obtained 1.2 g of crude, red liquid. Nmr analysis indicated that this liquid contained *ca.* 25% of **1b** and 75% of recovered **1**.

B. At −25°.—As before, **1** was treated with MeLi in ether solution but the reaction temperature was maintained at −25° and the time of stirring was 4 hr. To this cold ether solution was added 2 ml (excess) of D_2O (99.8 atom % D). The resultant slurry was allowed to warm (with stirring) to room temperature and treated with 10 ml of water. The ether layer, combined with ether extracts of the aqueous phase, was dried (Na_2SO_4), evaporated, and stirred with CS_2 for 2 hr. Evaporation gave 1.2 g of yellow liquid which was chromatographed as before. From the cyclohexane effluent (50 ml) was obtained 158 mg (11%) of liquid **1b**, identified by nmr. From the benzene–cyclohexane effluent (200 ml) was obtained 1.1 g (80%) of a light yellow liquid, identified as *ca.* a 1:1 mixture of **2-deuteriothieno[2,3-*b*]pyridine (1l)** and recovered **1**. The nmr parameters for **1l**, as determined on this mixture, are given in Table I.

Reaction of Thieno[2,3-*b*]pyridine with Deuteriosulfuric Acid.—A solution of **1** (0.5 g) in deuteriosulfuric acid (15 g, 85% solution in deuterium oxide) was heated at 98.5° while aliquots were removed periodically. Each aliquot portion was poured into water, basified with aqueous Na_2CO_3, extracted into CCl_4 (dried), and analyzed by nmr for deuterium incorporation. It was assumed that no deuterium exchange occurred in the pyridinoid ring. The signal at δ *ca.* 7.1 (assigned to H_3) disappeared much more rapidly than did that at δ *ca.* 7.4 (assigned to H_2). After 10 hr the former signal had decreased by >90% while the latter had decreased *ca.* 10%. The nmr parameters for **3-deuteriothieno[2,3-*b*]pyridine (1m)** and **2,3-dideuteriothieno[2,3-*b*]pyridine (1n)**, as determined on these solutions, are given in Table I.

2,3-Dibromothieno[2,3-*b*]pyridine (1o).—A mixture of 2.7 g (0.02 mol) of **1**, 9.6 g (0.06 mol) of bromine, 10 ml of CCl_4, and 50 ml of water was stirred at room temperature for 3 hr and then was evaporated. The residue was stirred with excess Na_2SO_3 and concentrated aqueous NH_3. A $CHCl_3$ extract of this mixture was evaporated and the residue therefrom was chromatographed by means of 20 g of neutral Brinkman alumina and petroleum ether. From the first liter of effluent was obtained 1 g (17%) of needles: mp 96–97°; uv max (95% EtOH) 236 mμ (ε 31,000), 282 (11,200), 288 (10,700), 299 (7860).

Anal. Calcd for $C_7H_3Br_2NS$: C, 28.70; H, 1.03; Br, 54.55; N, 4.78; S, 10.94. Found: C, 28.67; H, 1.17; Br, 54.54; N, 4.53; S, 10.83.

Registry No.—**1**, 272-23-1; 1 methiodide, 18366-61-5; **1a**, 13362-81-7; **1b**, 1759-30-4; **1b** picrate, 3395-13-9; **1c**, 18354-51-3; **1d**, 18354-52-4; **1e**, 18354-53-5; **1e** picrate, 18366-62-6; **1f**, 18354-54-6; **1f** picrate, 18366-63-7; **1g**, 18354-55-7; **1g** picrate, 18366-64-8; **1h**, 18425-96-2; **1h** picrate 18366-65-9; **1i**, 18354-56-8; **1j**, 18354-57-9; **1k**, 18354-58-0; **1l**, 18354-59-1; **1m**, 18366-53-5; **1n**, 18366-54-6; **1o**, 18366-55-7; **2**, 272-67-3; **2a**, 1759-29-1; **2b**, 13362-83-9; **2c**, 18366-58-0; **2d**, 18366-59-1; **2e**, 18366-60-4; **2e** picrate, 18425-97-3.

Determination of the Absolute Configuration of a Spiro Quaternary Ammonium Salt *via* Stevens Rearrangement[1,2]

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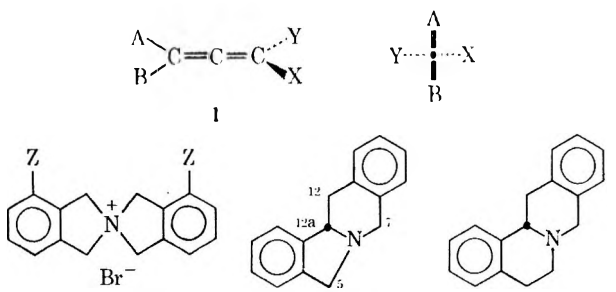
The levorotatory isomer of 4,4′-dimethoxy-1,1′,3,3′-tetrahydrospiro[isoindole-2,2′-isoindolium] bromide (2b) underwent Stevens rearrangement to give (−)-4,8-dimethoxy-5,7,12,12a-tetrahydroisoindolo[2,1-*b*]isoquinoline (5a). The absolute configuration of the latter substance was shown to be *S* by ozonolytic degradation to a derivative (6) of (*S*)-aspartic acid. The distribution of methoxy groups in 5a was determined by nmr spectroscopy. These results permit an assignment of the *R* configuration to the levorotatory spiro salt, in accord with Lowe's rule, the helix conductor model and the Eyring–Jones model of optical activity. It is pointed out that a seeming failure of these rules and models in another substance might be due to swamping by other long-range effects.

Lowe[3] has pointed out that allenes having the absolute configuration **1** are dextrorotatory at the sodium D line when A is more polarizable than B and X is more polarizable than Y. This rule, like the "conformational dissymmetry rule,"[4] can be arrived at by use of a helical conductor model of optical activity.[2a] Lowe[3] suggested further that this rule may be applicable to other axially dissymmetric series of compounds, as the spirans, but doubt on this latter point has been raised by the recent work of Krow and Hill.[5] We wish to report our assignment of the *R* configuration to the levorotatory isomer of the spiro quaternary salt **2b**, consistent with Lowe's rule[3] and with the Jones–Eyring model of optical activity[6] and to suggest a reason for the *seeming* failure of Lowe's rule for the compound of Krow and Hill.



Racemic **2b** was prepared from 3-methoxyphthalic anhydride[7] *via* reduction with lithium aluminum hydride,[8] treatment of the diol with phosphorus tribromide and reaction of the crude dibromide with ammonia. Its nmr spectrum was comparable with that of a sample of the unsubstituted spiro salt **2a** prepared by reaction of *o*-xylylene dibromide with ammonia.[9] The quaternary hydroxide, formed by reaction with silver oxide, gave a salt with *d*-camphor-ω-sulfonic acid that could be resolved by crystallization from acetone–methanol mixtures. The less soluble diastereomer gave the levorotatory spiro bromide, $[M]_D$ −41°, on treatment with hydrogen bromide in methanol. The rotation varied only slightly with concentration but could be more than doubled by the addition of several equivalents of lithium bromide, indicating that the counterion also plays a role in determining the rotatory properties of this substance. The ORD curve of a dilute solution in methanol showed a relatively small negative Cotton effect, amplitude[10] [*a* = −14 (270–250 mλ)] on a strong negative background, $[M]_{235}$ −10,600.

The unsubstituted spiro quaternary salt **2a** has been shown by Wittig[11] to undergo a Stevens rearrangement[12] with strong bases to form **3** (necessarily racemic). Optically active bases of the series **3** contain an asymmetric center that might, in analogy with the work of Corrodi and Hardegger[13] with alkaloids containing the tetrahydroprotoberberine nucleus, **4**, be related to that of a derivative (**6**)[14] of aspartic acid (**7**), the configuration of which is known.[15] It is to be expected, on the basis of earlier work,[12,16,17] that the bond-break-

(1) IX. A Useful Model of Optical Acitivity.

(2) (a) VIII: J. H. Brewster, "Topics in Stereochemistry," Vol. 2, N. L. Allinger and E. L. Eliel, Ed., Interscience Publishers, New York, N. Y., 1967, p 1. (b) VII: J. H. Brewster and J. G. Buta, *J. Amer. Chem. Soc.*, **88**, 2233 (1966).

(3) G. Lowe, *Chem. Commun.*, 411 (1965).

(4) J. H. Brewster, *J. Amer. Chem. Soc.*, **81**, 5475 (1959).

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(9) M. Scholz, *Ber.*, **24**, 2402 (1891).

(10) C. Djerassi and W. Klyne, *J. Chem. Soc.*, 4929 (1962).

(11) G. Wittig, H. Tenhaeff, W. Schock, and G. Koenig, *Ann.*, **572**, 1 (1951).

(12) T. S. Stevens, *Progr. Org. Chem.*, Vol. 7, J. W. Cook and W. Carruthers, Ed., Plenum Press, New York, N. Y., 1968, p 48.

(13) H. Corrodi and E. Hardegger, *Helv. Chim. Acta*, **39**, 889 (1956).

(14) S. Korman and H. T. Clarke, *J. Biol. Chem.*, **221**, 113 (1956).

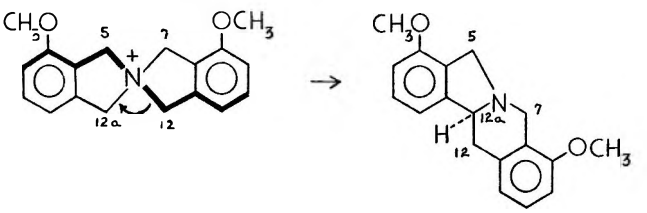
(15) J. P. Greenstein, *Advan. Protein Chem.*, **9**, 184 (1954).

(16) J. H. Brewster and M. W. Kline, *J. Amer. Chem. Soc.*, **74**, 5179 (1952).

(17) R. K. Hill and T. H. Chan, *ibid.*, **88**, 866 (1966).

ing and bond-making phases of the Stevens rearrangement will occur on the same side of the intact ring. Rearrangement of optically active **2b**, then, should occur with retention of dissymmetry and there should be a simple relation between the configuration of the spiro salt and the rearranged amine (*cf. e.g.*, Chart I).

CHART I



(−)-*R*-2b 5a

It is readily seen, however, that establishment of this configurational relationship requires a determination of the pattern of distribution of methoxy groups. Four amines with an *S* configuration at position 12a are possible; two (**5a** and **5b**) could arise from the *R* spiro salt and two (**5c** and **5d**) from the *S* isomer (Chart II). Mechanistic considerations are not of much help here since the effects of *o*- or *m*-methoxy groups on migration rates in Stevens rearrangements of N-benzylphenacylammonium salts are not very different[12] and may not be relevant in this more rigid system.

The dimethoxy spiro compound **2b** proved to be much more resistant to Stevens' rearrangement than was the parent compound **2a**, which gave up to 41% of ±**3** under a variety of conditions. In a number of instances more than 70% of starting material (**2b**) was recovered. Best results were obtained when the quaternary hydroxide was treated with sodium hydride in diglyme; isolation of the water insoluble, acid soluble fraction and crystallization from methanol gave 7–11% of a substance with nmr spectra, as base and as methiodide, clearly analogous to those of the unsubstituted compound **3**. The levorotatory spiro salt gave a levorotatory base $[M]_D$ −511° ($CHCl_3$), −672° (CH_3OH), showing a plain negative ORD curve as free base in methanol and, as hydrochloride, a small negative Cotton effect, $a = 7$ (279–270 mμ), on a strong negative background.

The absolute configuration of the asymmetric center of the rearrangement product was shown to be *S* by ozonolysis[13] to the aspartic acid derivative **6**. The mercuric salt of **6** was dextrorotatory in 0.05 *N* NaCl and levorotatory in 0.5 *N* HCl, as was a sample prepared[14] from L-aspartic acid (**7**). It is of interest that the analogous tetrahydroprotoberberine nucleus, **4**, is also levorotatory (D line) in the *S* configuration.[13] No conclusions about optical purity can be drawn from this work because sizeable losses were incurred in the purification of intermediates by crystallization and optical fractionation may have occurred.

The data given above indicate that the product of the Stevens rearrangement is one of the four positional isomers **5a–d** and has the absolute configuration shown in the drawings. Nmr evidence indicates that this substance has the structure **5a** and, thus, that the spiro compound had the *R* configuration. As seen in Table I the protons of the benzylammonium methylene

CHART II

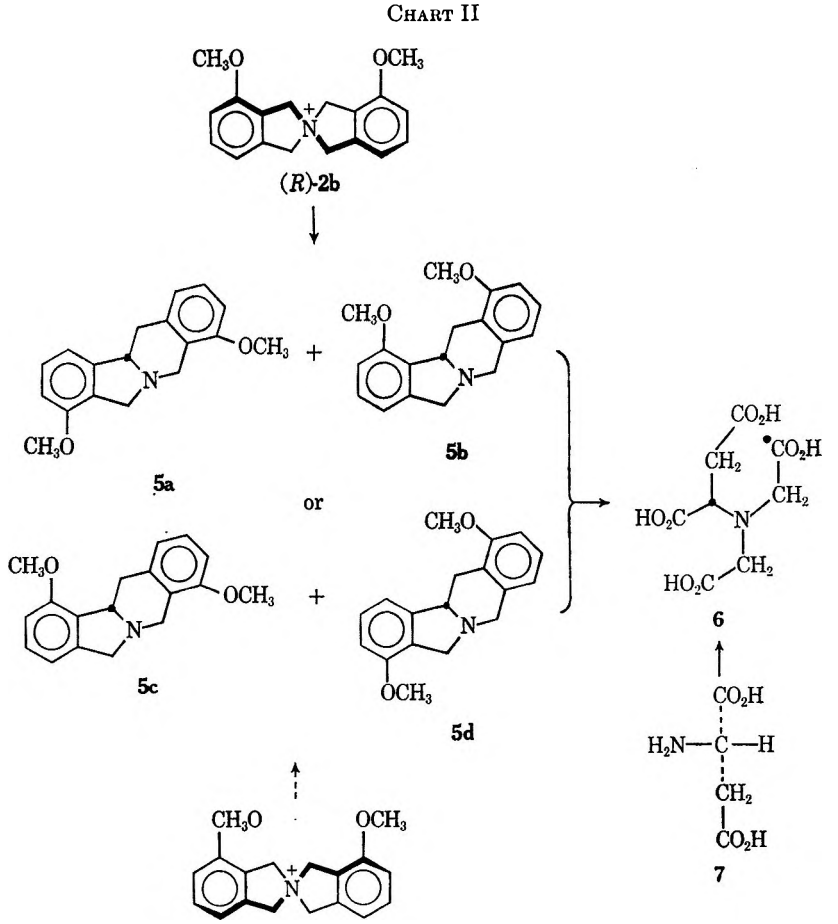


TABLE I

NMR CHEMICAL SHIFTS FOR QUATERNARY SALTS IN TRIFLUOROACETIC ACID

Salt	Cps from TMS at 60 Mc $ArCH_2N^+$	CH_3N^+
Dimethylisoindolinium iodide	297	210
Dimethyltetrahydroisoquinolinium iodide	279	202
2a	305	
2b	303, 300	
3·CH_3I	287, 303	212 (180)
5a·CH_3I	282, 298	211 (180)

TABLE II

NMR CHEMICAL SHIFTS FOR AROMATIC METHYL GROUPS, $ArCH_3$, IN TRIFLUOROACETIC ACID

Compound	Cps from TMS at 60 Mc
Toluene	136
2-Methylanisole	133
3-Methylanisole	137
2,3-Dimethylanisole	134, 130

groups ($ArCH_2N^+$) give sharp singlets at different positions in tetrahydroisoquinolinium and isoindolinium salts (δ 4.65 and 4.95, respectively). Thus positions 7 and 5 should be distinguishable in the methiodide of any of the four positional isomers. The presence of an *o*-methoxy group has an appreciable shielding effect in the spiro salt **2b** (Table I) and in the methylanisoles (Table II). The separation of the two peaks should, then, be the same as in the methiodide of **3** (15–16 cps at 60 mc in trifluoroacetic acid) if the product has either structure **5a** or **5b** (both derived from (*R*)-**2b**). The separation should be larger (19–21 cps) if the structure is **5c** and smaller (11–13 cps) if it is **5d** (both derived from (*S*)-**2b**). The observed separation (16 cps) and the observed upfield shift (5 cps) of the peaks in the methiodide indicate that the amine is isomer **5a** (compare **2a** and **2b** in Table I). The remaining benzylic protons appear, in the methiodide of **3**, to form an ABX system (δ_A 3.43, δ_B 3.80, δ_X 5.38; J_{AB} = 16 Hz; $J_{AX} = J_{BX}$ = 6 Hz). In the dimethoxy derivative the pattern appears to be similar, though the AB portion is obscured; the signal for the methine proton at 12a is shifted upfield by about 2 cps, consistent with the presence of a *m*-methoxy group (compare **2a** and **2b** in Table I).

Amines of series **3** and **5** would be expected to give two methiodides, one with a *cis* and one with a *trans* ring fusion. The quaternary methyl protons would be expected to give distinctly different signals, since the *cis* compound is more flexible and its methyl group can receive some shielding from the tetrahydroisoquinoline aromatic nucleus. Thus the methyl signal for the more flexible dimethyltetrahydroisoquinolinium salts is a singlet at δ 3.37 while that for the isoindolinium salts is a singlet at δ 3.50. In all the methiodides of series **3** and **5** sharp singlets were observed at about δ 3.52 and 3.00, in varying ratios but integrating *together* to three protons. The comparisons above were made with samples in which the peak at δ 3.52 predominated. It seems likely that this corresponds to the rigid *trans* isomer, for here the methyl group would have an environment most like that found in the isoindolinium salt. In this isomer the benzylammonium methylene (5 and 7) groups should not show significant geminal splitting because each proton of a given pair has almost exactly the same environment as its twin (see Figure 1). The protons of benzylmethylene group 12, however, would be held rigidly in quite different environments and the observed ABX splitting would thus be expected.

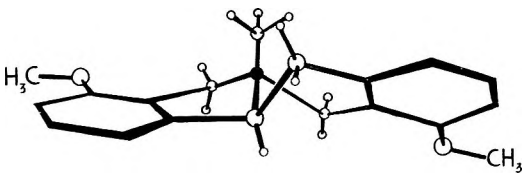


Figure 1.—**trans**-Methiodide of (*S*)-**5a**. The quaternary nitrogen is shown in black; the iodide ion is not shown.

The nmr spectra of the tertiary amines point to this same conclusion. Here the benzylamine methylene groups (5 and 7) give rise to a double quartet,[18] indicating that the anisotropy of the nitrogen atom makes the protons of each benzyl group nonequivalent.[19] In the parent amine **3**, one pair appears to show δ 3.73, 4.30 (J = 11 Hz), while the other shows δ 3.89, 4.17 (J = 15 Hz). The dimethoxy compound gives evidence for two pairs with similar coupling constants but larger chemical shift separations: δ 3.63, 4.43 (J = 11 Hz), 3.75, 4.32 (J = 16 Hz). These changes indicate that the methoxy groups influence both methylene groups in the same way and to about the same extent. The effect seems simply to be an amplification of the effect of the nitrogen atom. The signal for the other methylene group is seen as the AB part of an ABX pattern (δ 2.84, 3.32 (J_{AB} = 15 Hz, $J_{AX} + J_{BX}$ = 8 Hz) in **3** and [δ 2.82, 3.27 (J_{AB} = 16.5 Hz, $J_{AX} + J_{BX}$ = 8 Hz)] in the dimethoxy compound. Here the effect of the methoxy groups is almost negligible. It seems reasonable to assume that the methoxy effect depends on proximity; if so, then methoxy groups must be near both 5 and 7 as in structure **5a**.

All of the nmr data thus support structure **5a** for the Stevens rearrangement product, on which grounds we assign the *R* configuration to the levorotatory isomer of the spiro salt **2b**. We recognize the desirability of obtaining additional evidence for structure **5a** by unambiguous synthesis and for the configuration of **2b** by the X-ray method and hope to undertake work on both matters.

Experimental Section[20]

2,3-Bis(hydroxymethyl)anisole was prepared by methylation of 2,3-dimethylphenol,[6] oxidation with basic potassium permanganate to give the anhydride[6,7] and reduction with lithium aluminum hydride,[7] mp 92–93° (lit.[7] mp 95–96°).

4,4′-Dimethoxy-1,1′,3,3′-tetrahydrospiro[isoindole-2,2′-isoindolium] Bromide (2b).—A solution of 60 g of 2,3-bis(hydroxymethyl)anisole in 1 l. of anhydrous ether was cooled in ice while

(18) See S. Naruto, S. Arakawa, and H. Kaneko, *Tetrahedron Lett.*, 1705 (1968), for a similar case.

(19) H. P. Hamlow, S. Okuda, and N. Nakagawa, *ibid.*, 2553 (1964); F. Bohlmann, *ibid.*, 176 (1965).

(20) All melting points were determined on a Fisher-Johns melting point block and are uncorrected. Elemental analyses were performed at Purdue by Dr. C. S. Yeh and her staff. Optical rotations were determined on a Zeiss polarimeter, using a 2-dm cell and ORD curves were obtained on a Bendix Polarmatic, Model 62, using a 250-W xenon arc lamp. Nmr spectra were recorded on Varian A-60 and A-60-A instruments using tetramethylsilane as internal standard.

81 g of phosphorus tribromide was added dropwise, with stirring. The mixture was allowed to warm to room temperature, with stirring, and let stand overnight. It was then cooled again in ice and 230 ml of concentrated aqueous ammonia (a fivefold excess) was added to the stirred mixture, dropwise and with caution during the initial vigorous stages of the reaction. Stirring was continued for 36 hr and the mixture was then allowed to stand several days. The solid was collected and stirred with warm ethanol; undissolved inorganic salts were removed by filtration and the solution was cooled to give 30 g (46%) of **2b**, mp 157–159°. The microanalytical sample, purified by recrystallization from deionized water, had mp 159–160°: nmr ($CDCl_3$–DMSO-d_6 3:1) δ 3.95 (s, 6, Ar**OCH**$_3$), 5.27, 5.47 (s, 4, s, 4, Ar**CH**$_2$N^{-+}), 5.58 (s, 2, H_2O), 7.05–7.73 (m, 6, Ar**H**).

Anal. Calcd for $C_{18}H_{20}ON_2Br \cdot H_2O$: C, 56.84; H, 5.79; Br, 21.05; H, 3.68. Found: C, 56.90; H, 5.99; Br, 20.37; N, 3.96.

4,4′-Dinitro-1,1′,3,3′-tetrahydrospiro[isoindole-2,2′-isoindolium] Bromide (2c).—A mixture of 15 g of 2,3-dimethylnitrobenzene in 150 ml of carbon tetrachloride, 36 g of N-bromosuccinimide and 0.3 g of benzoyl peroxide was heated at reflux for 18 hr. The hot solution was transferred to another flask by inverted filtration and the solvent was removed. The dark oil was dissolved in chloroform and boiled with excess ammonia. The resulting solid was filtered, washed with ether and recrystallized (charcoal) from water to give 2.2 g (11%) of product: mp 305° dec; nmr (DMSO-d_6) δ 5.33, 5.55 (s, 4, s, 4, Ar**CH**$_2$N$^+$), 7.6–8.3 (m, 6, Ar**H**).

Anal. Calcd for $C_{16}H_{14}BrN_3O_4$: C, 48.98; H, 3.57; Br, 20.41; N, 10.71. Found: C, 49.06; H, 3.81; Br, 20.05; N, 10.58.

Resolution of 4,4′-Dimethoxy-1,1′,3,3′-tetrahydrospiro[isoindole-2,2′-isoindolium] Bromide (2b).—In a typical run 17.0 g of the quaternary salt was dissolved in methanol and 6.5 g of silver oxide was added. The solution was stirred for 15 min, filtered, let stand 6 hr and filtered again; the filter cake was washed with methanol. The solution was neutralized with 10.9 g of *d*-camphor-ω-sulfonic acid. Methanol was removed at the aspirator and ethyl acetate was added to the resulting oil. Crystals separated on refrigeration and a second crop on concentration: yield 14 g; mp 145–180°.

Systematic recrystallization of 42 g of such material, $[\alpha]_D$ +18.7° (methanol), from mixtures of acetone–methanol 2–5:1, decreasing the acetone content as the less soluble isomer accumulated, gave, finally, 8.3 g of less soluble isomer, $[\alpha]_D$ +9.55° (*c* 2.3, methanol), rotation unchanged on further crystallization. This was dissolved in anhydrous methanol and treated with an excess of hydrogen bromide. Anhydrous ether was added to precipitate 5.3 g of the bromide: mp 194–195° $[M]^{26}_D$ −38.2° (*c* 0.425, methanol), −64.1° (*c* 0.425, with LiBr *c* 0.66 in methanol), −76.3° (*c* 0.425, with LiBr *c* 2.18, methanol), −58.0° (*c* 0.46, water); λ_{max}^{MeOH} 270 mμ; ORD (methanol) $[M]_{585}$ −26° (*c* 0.382); $[M]_{270}$ −2816°, $[M]_{263}$ −2304°, $[M]_{235}$ −10,560° (*c* 7.64 × 10^{-3}).

The mother liquors from each stage of the resolution were evaporated and the most dextrorotatory of the residues combined to give 9.8 g, $[\alpha]_D$ +22.79° (methanol). A methanol solution of this material was passed through a column of Dowex 1-X8 ion exchange resin, previously washed with sodium hydroxide until the effluent was chloride free and then with methanol. There was recovered 4.7 g of the dextro quaternary hydroxide, $[M]^{26}_D$ +17.4° (*c* 2.15, methanol).

Stevens Rearrangements.—The unsubstituted spiro compound **2a**, mp 297° (lit.[10] mp 295°), gave 41% of **3**, mp 105–106° (lit.[10] mp 109–110°), when phenyllithium was used as the base[10] and 35% when the quaternary hydroxide was treated with sodium hydride in diglyme (below). Dimethoxy compound **2b** gave little or no rearrangement with a variety of methods, large amounts of starting material being recovered. In no instance could rearrangement product be obtained from attempted rearrangement of dinitro compound **2c**.

A solution of 2.8 g of dimethoxy quaternary bromide **2b** in 25 ml of methanol was stirred with 1.0 g of silver oxide. The solid was removed by filtration and washed with methanol. Removal of the solvent from the filtrates gave 2.9 g of a basic oil. This was dissolved in 20 ml of freshly distilled diglyme and the solution was added dropwise to a suspension of 0.7 g of sodium hydride in diglyme under nitrogen. The mixture was stirred at room temperature for 18 hr and then hydrolyzed with 150 ml of water. An oil separated. This was extracted into ether and the ether solution was twice extracted with water to remove diglyme. The ether was extracted with 2 *N* sulfuric acid; the aqueous layer was made basic with concentrated sodium hydroxide. The oil which separated was extracted into ether and the ether solution was dried and evaporated to give an oil which could be crystallized from methanol to give 0.25 g (11%) of amine, mp 153–156°.

Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.87; H, 6.76; N, 4.98. Found: C, 77.09; H, 6.92; N, 4.81.

A portion of the amine was dissolved in benzene and treated with excess methyl iodide to give a salt, mp 215–217° after two crystallizations from absolute methanol.

Anal. Calcd for $C_{19}H_{22}INO_2$: C, 53.90; H, 5.20; N, 3.31; I, 30.02. Found: C, 54.05; H, 5.48; N, 3.26; I, 30.00.

When this procedure was applied to 5.3 g of levorotatory spiro bromide there was obtained, after recrystallization from methanol, 0.27 g of product: mp 135–137°; $[M]^{26}_D$ −511° (*c* 0.54, chloroform), −672° (*c* 0.11, methanol); ORD plain negative in methanol (*c* 5.5 × 10^{-3}) $[M]_{238}$ −28, 100°; hydrochloride, in methanol (*c* 5.5 × 10^{-3}); $[M]_{303}$ −12,210°, $[M]_{279}$ −22,230°, $[M]_{270}$ −21,510°, $[M]_{235}$ −50,130°.

Mercuric N,N-bis(carboxymethyl)-(*S*)-aspartate was prepared from L-aspartic acid by alkylation with bromoacetate as described by Korman and Clarke[13]: mp 177–178° dec (lit.[13] mp 180–188°); $[\alpha]^{25}_D$ +10.4° (*c* 0.448, 0.05 *N* NaCl), −8.6° (*c* 0.70, 0.5 *N* HCl).

Anal. Calcd for $C_8H_7NO_6Hg_2 \cdot 0.135HgCl_2$ (based on Cl content): C, 13.09; H, 0.95; N, 1.91; Hg, 63.55; Cl, 3.10. Found: C, 13.00; H, 1.04; N, 1.91; Hg, 63.53; Cl, 3.10.

Ozonolysis of 250 mg of the optically active dimethoxyamine (**5a**) in chloroform and methanol was carried out by the procedure of Corrodi and Hardegger.[12] After destruction of the ozonide with 30% hydrogen peroxide and formic acid the aqueous solution was continously extracted with ethyl acetate for 36 hr. The ethyl acetate solution was extracted with two 25-ml portions of water and the mercuric salt precipitated therefrom by adding mercuric nitrate solution and 1 drop of concentrated hydrochloric acid, following the procedure of Korman and Clarke,[13] $[\alpha]^{28}_D$ +8.3° (*c* 0.12, 0.05 *N* NaCl), −5.6° (*c* 0.72, 0.5 *N* HCl).

Discussion

Spiro salt **2b** has a twofold rotation axis passing through the nitrogen atom (broken line in Figure 2);

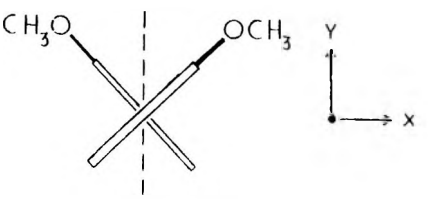
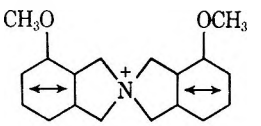


Figure 2.—(*R*)-**2b** in projection along the *Z* axis.

this is, then, one of the principal axes of polarizability along which electronic displacements, in effect, occur.[21] It seems likely that a second axis coincides with the line that would be formed by intersection of the two planes which each contain one aromatic ring. The third axis is then perpendicular to both at the point of intersection, the nitrogen atom. We establish a right-handed coordinate system, labeling these axes *X*, *Y* and *Z* as shown in Figure 2, in order of increasing polarizability, following the Eyring-Jones model.[6] It is seen at once that all parts of the *R* isomer that do not lie on the *Z* axis lie in octants in which the product of coordinates is positive; in the Eyring–Jones model this means that they will make negative contributions to long wavelength rotatory power, in accord with our present findings.

(21) See C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p 131.

Since the ^1L_b transition[22] moments for both rings should lie along the Z axis,[23] it is to be expected that that transition will not be optically active (see **8**); indeed, we find only a trivial Cotton effect in this region of the spectrum. Aromatic transitions perpendicular to the ^1L_b, but in the plane of the ring, would, on the other hand produce strong Cotton effects at lower wavelengths. The unsymmetrical pairing of transitions shown in **9** would be



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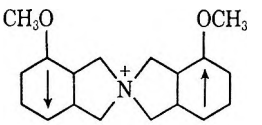

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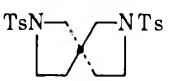
favored over the symmetrical pairing by inductive coupling along the Z axis; this coupling of these transitions would be expected[2a,24] to produce a negative Cotton effect in the R isomer. Although we could not penetrate deeply enough into the ultraviolet region to show such a Cotton effect, the last rotation observable ($[M]_{235} - 10{,}560°$) suggests that it had been approached. It is clear that this system is also consistent with Lowe's[3] empirical rule and, thus, with the simple helical conductor model.[2a]

Exceptions to rules and models are, of course, more significant than examples, not so much because they *disprove* rules but because they indicate how they may be *improved.* Thus Krow and Hill, in the first determination of configuration of a carbon spiro compound,[5] showed that (*S*)-**10** is levorotatory. This constitutes a



(−)-(S)-**10**

clear *formal* exception to Lowe's rule[3] and could, conceivably, turn out to be the first piece of evidence requiring the abandonment of that rule. Before that can happen, however, it is necessary to establish that the phenomena covered by Lowe's rule should, indeed, be expected to *control* the optical rotation of (*S*)-**10**. This point has not been established. The toluenesulfonamide groups are the most polarizable components of the structure and, being certainly bent at the sulfur atom[25-27] and probably bent at the nitrogen atom as well,[27] can be oriented in dissymmetric patterns which might be strongly optically active without relation to Lowe's rule. The pattern in Figure 3, for example, would be expected to be strongly levorotatory by the helix model[2a] and might easily swamp out contributions from forms with other configurations at nitrogen and conformations about N–S and C–S bonds. These complications would vanish were the tosyl groups replaced by nonflexible groups of moderate polarizability, as in the dihydrochloride of the amine or the tetramethyl diquaternary salt, where Lowe's rule should be controlling and where it would lead to an unequivocal prediction that the *S* isomer would be dextrorotatory. We believe that a test of this nature should be made before otherwise widely applicable rules and principles are discarded. Meanwhile, we would point out that when one is using simple rules and models to predict long wavelength rotations it can be dangerous to neglect the possible rotatory effects of highly polarizable groups in highly dissymmetric orientations. If, as in the case of (*S*)-**10**, the magnitude of these effects cannot adequately be estimated, then no firm prediction of sign or magnitude of rotation can be made.

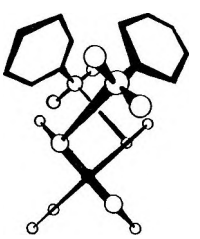


Figure 3.—One conformation of the isomer of (*S*)-**10** having *R* configurations at the nitrogen atoms. Completely analogous conformations would be possible even if the nitrogen atoms were planar. Note the highly developed left-handed helicity around the *Y* axis.

Registry No.—**2b**, 18366-87-5; **2c**, 18426-01-2; **5a**, 18366-88-6; **5a** methiodide, 18366-89-7.

Acknowledgment.—We wish to thank the Eli Lilly Co. for a grant which supported part of the work on this subject.

(22) J. R. Platt, *J. Chem. Phys.*, **17**, 484 (1949).

(23) See P. E. Stevenson, *J. Chem. Educ.*, **41**, 254 (1964), for a brief but clear review of a method for making this prediction.

(24) See, especially, the work of S. F. Mason, cited in ref 2a.

(25) See H. P. Koch and W. E. Moffitt, *Trans. Faraday Soc.*, **47**, 7 (1951), for a theoretical discussion of resonance and structure in sulfones, and J. G. Sime and S. C. Abrahams, *Acta Cryst.*, **13**, 1 (1960), for confirmatory X-ray data on a sulfone.

(26) See A. M. O'Connell and E. M. Maslen, *Acta Cryst.*, **22**, 134 (1967), for an X-ray study of sulfanilamide.

(27) See C. Tamura and G. A. Sim, *J. Chem. Soc.*, 8 (1968), for an X-ray study of a benzenesulfonylhydrazide.

Thermolysis of Substituted 1-Acetoxybenzotriazoles. Carbon-to-Oxygen Migration of an Alkyl Group

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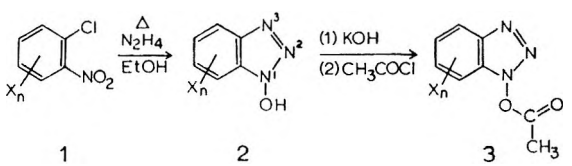
In examining the pyrolysis of 1-acetoxybenzotriazoles (**3**), it was found that tetrachloro substitution moderated the reaction favorably. At 350–400° under vacuum, 1-acetoxy-4,5,6,7-tetrachlorobenzotriazole (**4a**) gave a primary product with spectral properties suggestive of 2-methoxy-3,4,5,6-tetrachlorophenylisocyanate (5a), which was identified chemically by conversion with methanol into the carbamate (6a) and by ammonia to the correspondingly substituted urea (**7a**). The unique translocation of the R group of the original ester to alkoxy in the product was checked by variation in R and by variation in the alcohol (R'OH) used to convert the primary product into carbamate. The possible mechanism of the new rearrangement has been investigated using carbonyl-^{18}O-labeled 1-acetoxy-4,5,6,7-tetrachlorobenzotriazole (**10**), whereby it was established that the carbonyl oxygen appears in the methoxy group (**12**), suggesting a pathway such as **4** → **8** → **9** → **5**. Suitable controls were applied to show that the oxygens in **10** did not become equivalent. The position of the oxygen-18 was determined by the mass spectral fragmentation of labeled product **7a**.

In connection with the study of azirines,[1-3] the irradiation of substituted benzotriazoles[4] suggests a route to benzazirines, which have not yet been isolated but have been postulated as intermediates.[5,6] In the related formation of benzocyclopropenes from substituted 3H-indazoles and in the thermal rearrangement of the latter, diradical intermediates have been detected.[7] We were guided by these precedents and also by the reported oxidation of 1-aminobenzotriazoles with lead tetraacetate, which results in nitrogen evolution and benzyne-derived products.[8]

As generators of diradical (or possibly carbene) intermediates the 1-hydroxybenzotriazoles appeared to offer an advantage since they are already at an oxidation level which should facilitate the liberation of gas (N_2, N_2O, H_2O) on heating. Descriptions of 1-hydroxybenzotriazoles as explosive[9-11] support this judgment. The synthesis of substituted 1-hydroxybenzotriazoles (2) was accomplished by the general method[12-15] of heating the appropriately substituted *o*-nitrohalobenzene (1) with hydrazine hydrate in ethanol under reflux. In this manner, the following compounds were made: 1-hydroxybenzotriazole,[12,15] 4,5-dichloro-1-hydroxybenzotriazole, 5,6-dichloro-1-hydroxybenzotriazole,[14] 1-hydroxy-4,5,6-trichlorobenzotriazole, 1-hydroxy-4,6,7-trichlorobenzotriazole, 1-hydroxy-4,5,6,7-tetrachlorobenzotriazole, and 6-bromo-1-hydroxybenzotriazole. The increasing degree of chlorine substitution in this series was intended to moderate the thermal decomposition and to stabilize



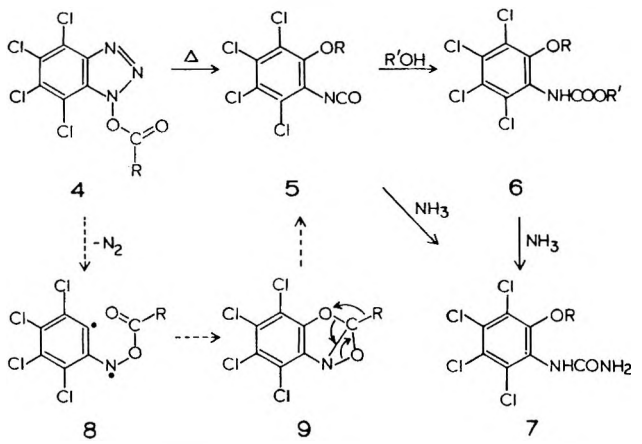
1 2 3

the benzene ring toward rearrangement, especially since such substitution had been employed favorably in thermal cyclization reactions involving loss of nitrogen from 3,4,5,6-tetrachlorobenzo-2-diazo 1-oxide.[16] However, attempts to control the thermal decomposition process of these compounds were not successful. All of the substituted 1-hydroxybenzotriazoles decomposed violently at 200–210° to carbonaceous material.

Further modification was therefore sought by means of the acetylation of the 1-hydroxybenzotriazoles. The general procedure,[14] which involved the formation and isolation of the potassium salt and then reaction of the salt with acetyl chloride in acetone, produced the seven 1-acetoxybenzotriazoles (3) corresponding to the 1-hydroxybenzotriazoles listed above. Two features regarding spectroscopic properties in this series are of special interest. The infrared maximum corresponding to the C=O stretch was found at relatively high frequency, within the range 1795–1825 cm^{-1} in Nujol. The absorption frequencies for the model compounds acetone oxime O-acetate and benzophenone oxime O-acetate, 1773 and 1782 cm^{-1},[17] respectively, are confirmatory for the structure of the 1-acetoxybenzotriazoles (3) and indicative of the electron-withdrawing power of the heterocyclic ring system. The proton magnetic resonance corresponding to the acetate methyl group was relatively invariant, τ 7.43–7.48 ($CDCl_3$), for all of the 1-acetoxybenzotriazoles unsubstituted on the 7 position, whereas the τ value for the methyl protons of 1-acetoxy-4,5,6,7-tetrachlorobenzotriazole (**4a**) was 7.86 ppm. In this compound, because of the bulky 7 substituent, conformations in which the acetoxy group lies above (or below) the plane of the aromatic ring system are probably favored on a time average and hence the protons

(1) N. J. Leonard and B. Zwanenburg, *J. Amer. Chem. Soc.*, **89**, 4456 (1967).
(2) N. J. Leonard, E. F. Muth, and V. Nair, *J. Org. Chem.*, **33**, 827 (1968).
(3) V. Nair, *ibid.*, **33**, 2121 (1968).
(4) E. M. Burgess, R. Carithers, and L. McCullagh, *J. Amer. Chem. Soc.*, **90**, 1923 (1968).
(5) M. Appl and R. Huisgen, *Ber.*, **92**, 2961 (1959).
(6) R. Huisgen and M. Appl, *ibid.*, **91**, 12 (1958).
(7) G. L. Closs, L. R. Kaplan, and V. I. Bendall, *J. Amer. Chem. Soc.*, **89**, 3376 (1967), and references therein.
(8) (a) C. D. Campbell and C. W. Rees, *Proc. Chem. Soc.*, 296 (1964); (b) *Chem. Commun.*, 192 (1965); (c) C. W. Rees and R. C. Storr, *ibid.*, 193 (1965).
(9) H. Goldstein and R. Voegeli, *Helv. Chim. Acta*, **26**, 475 (1943).
(10) B. Vis, *Rec. Trav. Chim. Pays-Bas*, **58**, 847 (1939).
(11) A. Mangini, *Gazz. Chim. Ital.*, **66**, 675 (1936).
(12) T. Zincke and P. Schwarz, *Ann.*, **311**, 329 (1900).
(13) R. Nietzki and E. Braunschweig, *Ber.*, **27**, 3381 (1894).
(14) E. Müller and W. Hoffmann, *J. Prakt. Chem.*, **111**, 293 (1925).
(15) E. Müller and G. Zimmermann, *ibid.*, **111**, 277 (1925).
(16) (a) R. Huisgen, G. Binsch, and H. König, *Chem. Ber.*, **97**, 2868 (1964); (b) *ibid.*, **97**, 2884, 2893 (1964).
(17) O. Exner and M. Horák, *Chem. Listy*, **52**, 1613 (1958).

SCHEME I



a, R = CH_3, R' = CH_3; b, R = CH_3, R' = C_2H_5; c, R = C_2H_5, R' = CH_3

experience a shielding effect compared with the methyl protons in the other compounds. 1-Acetoxy-4,5,6,7-tetrachlorobenzotriazole, which was selected as the prototype for the thermal decomposition study, was also prepared unequivocally by the action of ketene on 1-hydroxy-4,5,6,7-tetrachlorobenzotriazole in acetone at 0°.

The pyrolysis of 1-acetoxy-4,5,6,7-tetrachlorobenzotriazole, $C_8H_3Cl_4N_3O_2$ (**4a**), was carried out *in vacuo* by subliming the compound into an area heated at about 400° (Scheme I). The crude pyrolysis product was obtained as an oil, the most characteristic spectral feature of which was a very strong infrared absorption band at 2220 cm^{-1} suggestive of an isocyanate grouping. The band was retained after partial purification of the oil by vacuum distillation.

Reaction with methanol furnished a crystalline product, $C_9H_7Cl_4NO_3$, corresponding to loss of nitrogen and addition of the elements of methanol to the original **4a**. The infrared maximum at 1725 cm^{-1} ($CHCl_3$) was indicative of a carbamate grouping, and the seven hydrogens per molecule were fully accounted for in the nmr spectrum, which showed two singlets at τ 6.10 and 6.19 ($CDCl_3$) of three hydrogens each, characteristic of CH_3O, and one exchangeable proton at 3.57, characteristic of NH. The feature at first surprising was the indication of *two* methoxyl groups; however, one methoxyl group was already indicated in the suspected isocyanate precursor by the strong nmr signal at τ 6.02. The second methoxyl was obviously introduced in the conversion of isocyanate to methyl carbamate. The mass spectrum of the product resulting from pyrolysis followed by methanol treatment was confirmatory of the $C_9H_7Cl_4NO_3$ formula, showing peaks at *m/e* 317 (M^+), 319 $(M + 2)^+$, and 321 $(M + 4)^+$ in relative abundances 1.00:1.25:0.65, which are close to the expected ratios (1:00:1.31:0.64) for a Cl_4-containing molecule.[18] The mass spectral fragmentation pattern included the loss of Cl· [*m/e* 282 $(M - 35)^+$, 284 $[(M + 2) - 35]^+$, and 286 $[(M + 4) - 35]^+$, in relative abundance 1.00:1.00:0.40 (close to theoretical for a Cl_3-containing fragment, 1.00:1.00:-32)];[18] the loss of CH_3O·[286 $(M - 31)^+$, 288 $[(M + 2) - 31]^+$, and 290 $[(M + 4) - 31]^+$; the loss of CH_3OH: 285 $(M - 32)^+$, 287 $[(M + 2) - 32]^+$, and 289 $[(M + 4) - 32]^+$; and the loss of ·$COOCH_3$ [258 $(M - 59)^+$, 260 $[(M + 2) - 59]^+$, and 262 $[(M + 4) - 59]^+$, *inter alia*. These analytical and spectroscopic features limited the structure to that of methyl *N* - (2 - methoxy - 3,4,5,6 - tetrachlorophenyl)-carbamate (**6a**), which in turn required that the initial pyrolysis product, which posessed tetrachlorophenyl, methoxyl, and isocyanate groupings, be 2-methoxy-3,4,5,6-tetrachlorophenylisocyanate (**5a**).

Treatment of the pyrolysis product in methylene chloride with ammonia yielded a urea derivative identical with the compound $C_8H_6Cl_4N_2O_2$ obtained from the carbamate **6a** and methanolic ammonia under pressure, hence N-(2-methoxy-3,4,5,6-tetrachlorophenyl)-urea (**7a**). The elemental analysis and the infrared spectrum were in accord with this assignment. The mass spectrum, which provided further confirmation of the structure, was also useful in delineating the mechanism of the pyrolytic rearrangement, as will be described in detail subsequently. When the pyrolysis product from **4a** was treated with ethanol in place of methanol the corresponding ethyl carbamate derivative was obtained, as indicated by the infrared spectrum and by conversion to the substituted urea **7a** with ammonia in ethanol under pressure.

In order to provide independent confirmation that the R group initially attached to carbonyl in **4** ends up on the ether oxygen in **5**, the pyrolysis of 1-propionoxy-4,5,6,7-tetrachlorobenzotriazole (**4c**) was investigated under the same conditions. The crude pyrolysis product showed infrared absorption at 2220 cm^{-1} typical for isocyanate. Treatment with methanol converted it into a carbamate ($\nu_{max}^{CHCl_3}$ 1740 cm^{-1}) of molecular formula $C_{10}H_9Cl_4NO_3$. The nmr spectrum exhibited a singlet at τ 6.20 ($CDCl_3$) characteristic of CH_3O and a triplet–quartet combination at 8.60, 5.90 indicative of CH_3CH_2O, with a broad signal at 3.47 for NH. The structural assignment as methyl N-(2-ethoxy-3,4,5,6-tetrachlorophenyl)carbamate (**6c**) was confirmed chemically by conversion with ammonia to a urea derivative, $C_9H_8Cl_4N_2O_2$, which still possessed the ethoxyl group, hence N-(2-ethoxy-3,4,5,6-tetrachlorophenyl)urea (**7c**). The formula and structure of **6c** were also confirmed by the mass spectrum, which showed peaks at *m/e* 331 (M^+), 333 $(M + 2)^+$, and 335 $(M + 4)^+$ in relative abundances 1.00:1.27:0.62,[18] respectively. The mass spectral fragmentation pattern included the loss of C_2H_5 [*m/e* 303 $(M - 28)^+$, 305 $[(M + 2) - 28]^+$, and 307 $[(M + 4) - 28]^+$ in relative abundances 1.00:1.27:0.61]; the loss of Cl· [296 $(M - 35)^+$, 298 $[(M + 2) - 35]^+$, 300 $[(M + 4) - 35]^+$ in relative abundances 1.00:0.91:0.32]; and the loss of ·$COOCH_3$ $(M - 59)^+$, of $CO_2 + CH_2$ $(M - 58)^+$, and of C_2H_4 + ·$COOCH_3$ $(M - 87)^+$, although departure from the theoretical abundance ratios[18] for the +2 and +4 peaks in the last three cases indicates the presence of some double peaks, *i.e.*, alternate fragmentation processes.

Tetrachloro-*o*-anisidine, mp 90–91°, prepared by chlorination of *o*-methoxyacetanilide,[19] was treated with phosgene and triethylamine in benzene solution.

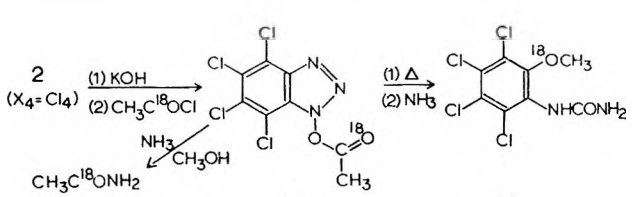
(18) R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," John Wiley & Sons, Inc., New York, N. Y., 1963, p 17.

(19) E. Bureš and B. Havlinová, *Časopis Československ. Lékárnictva*, **9**, 101 129, 153 (1929); *Chem. Zentr.*, II, 1402 (1929).

Reaction of the resulting 2-methoxy-3,4,5,6-tetrachlorophenyl isocyanate (**5a**), ν_{max} 2220 cm^{-1}, with methanol gave authentic methyl N-(2-methoxy-3,4,5,6-tetrachlorophenyl) carbamate (**6a**) (70% yield), mp 181–182°, identical in all respects with the product obtained *via* the pyrolysis of **4a** (→ **5a** → **6a**). By this independent synthesis the structures of all of the compounds under consideration have been fully secured.

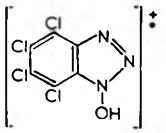
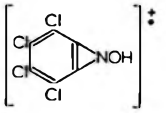
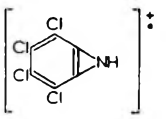
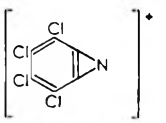
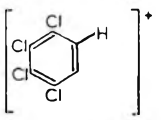
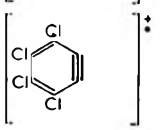
The mechanism of the thermal rearrangement, **4** → **5**, is of interest especially since it involves the unique translocation of the R group in the original ester to alkoxy in the product. A logical initiation of the process would be by loss of nitrogen to give the diradical **8**.[4-7,20] Rehybridization and electron pairing could lead to the strained intermediate **9**, which is a bicyclic oxaziridine. Rearrangements of oxaziridines are well documented,[21-23] and the N–O bond is usually expected to cleave first under conditions of high temperature, although C–O bond cleavage has also been observed. Formation of product **5** can be envisaged as resulting from migration of the alkyl group from carbon to oxygen and sequential or concerted bond cleavage and bond formation shown in **9**. The representations in **8** and **9** are not to be considered restrictive, especially since the homolytic *vs.* heterolytic details of the process are not available. If the thermal rearrangement followed the pathway indicated, it can be seen that the carbonyl oxygen of 1-acetoxy-4,5,6,7-tetrachlorobenzotriazole (**4a**) would appear in the methoxyl group of the isocyanate **5a**. This is subject to test by ^{18}O labeling.

First we examined the mass spectra of the rearranged products **6** and **7** to decide which compound would offer the better fragmentation pattern to enable us to locate ^{18}O. After careful study of all the spectra obtained we decided to follow the rearrangement from carbonyl-^{18}O-labeled 1-acetoxy-4,5,6,7-tetrachlorobenzotriazole (**10**) to the corresponding ^{18}O-labeled N-(2-methoxy-3,4,5,6-tetrachlorophenyl)urea. Treatment of the potassium salt of 1-hydroxy-4,5,6,7-tetrachlorobenzotriazole **2** (X_n = Cl_4) with acetyl-^{18}O chloride, 90% enrichment, yielded **10**. The mass spectrum was first compared with that (see Figure 1) of unlabeled material (**4a**), which showed peaks at *m/e* 313 (M^+), 315 $(M + 2)^+$, and 317 $(M + 4)^+$, in relative abundances 1.00:1.24:0.67, corresponding to the molecular ion(s) of a Cl_4-containing molecule.[18] The major fragment ions may be rationalized as shown in Table I. The mass spectrum of carbonyl-^{18}O-labeled 1-acetoxy-4,5,6,7-tetrachlorobenzotriazole (**10**) exhibited similar major fragments (see Figure 2), but calculations based on relative abundances for a Cl_4-containing molecule suggested the presence of $C^{18}OCH_3$, $C^{18}OCH_2D$, $C^{18}OCHD_2$, and $C^{18}OD_3$ moieties and of minor oxygen-16 components, mainly $C^{16}OCHD_2$ and $C^{16}OCD_3$.



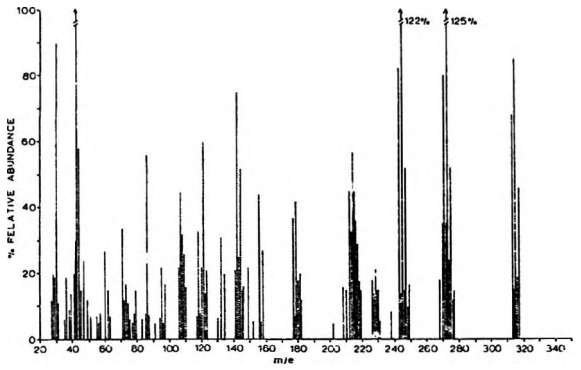
(20) W. Kirmse and L. Horner, *Ann.*, **614**, 1 (1958).
(21) L. S. Kaminsky and M. Lamchen, *J. Chem. Soc.*, 2128 (1967).
(22) W. D. Emmons, *J. Amer. Chem. Soc.*, **79**, 5739 (1957).
(23) J. S. Splitter and M. Calvin, *J. Org. Chem.*, **30**, 3427 (1965).

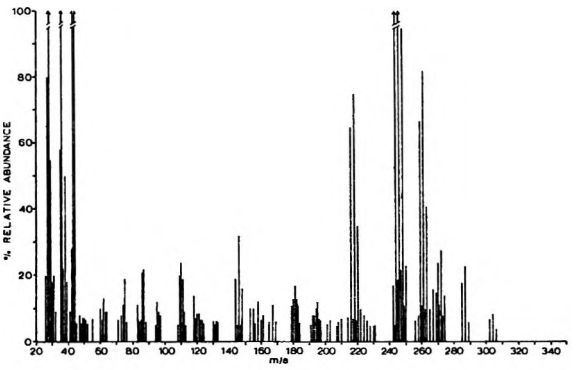
TABLE I
FRAGMENTATION OF
1-ACETOXY-4,5,6,7-TETRACHLOROBENZOTRIAZOLE (4a) AT 70 eV

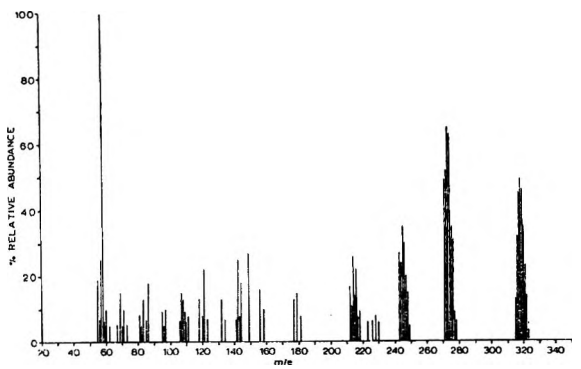
	m/e	Relative abundance	
	271	$(M - 42)^+$	1.00
	273	$[(M + 2) - 42]^+$	1.25
	275	$[(M + 4) - 42]^+$	0.65
	CH_2CO = 42		
	243	$(M - 70)^+$	1.00
	245	$[(M + 2) - 70]^+$	1.22
	247	$[(M + 4) - 70]^+$	0.63
	$CH_2CO + N_2$ = 70		
	227	$(M - 86)^+$	1.00
	229	$[(M + 2) - 86]^+$	1.07
	231	$[(M + 4) - 86]^+$	0.39
	$CH_2CO + N_2 + O$ = 86		
	226	$(M - 87)^+$	1.00
	228	$[(M + 2) - 87]^+$	1.16
	230	$[(M + 4) - 87]^+$	0.83
	$CH_2CO + N_2 + OH$ = 87		
	213	$(M - 100)^+$	1.00
	215	$[(M + 2) - 100]^+$	1.34
	217	$[(M + 4) - 100]^+$	0.86
	$CH_2CO + N_2 + NO$ = 100		
	212	$(M - 101)^+$	1.00
	214	$[(M + 2) - 101]^+$	1.27
	216	$[(M + 4) - 101]^+$	0.80
	$CH_2CO + N_2 + NOH$ = 101		

At this stage a check was made to ascertain whether the oxygen-18 enrichment was contained only in the carbonyl function of the 1-acetoxy-4,5,6,7-tetrachlorobenzotriazole and that no mechanism was readily available for translocation of the label in the ether oxygen. The oxygen-18-labeled compound was ammonolyzed using ammonia in methanol, giving 1-hydroxy-4,5,6,7-tetrachlorobenzotriazole and acetamide. The mass spectrum of the former at 13.5 eV showed M (271), M + 2, M + 4, and M + 6 positive ions in the ratio of 1.00:1.30:0.65:0.27 relative abundance. For comparison, the mass spectrum at 14 eV of unlabeled 1-hydroxy-4,5,6,7-tetrachlorobenzotriazole showed M (271), M + 2, M + 4, and M + 6 positive ions in the ratio of 1.00:1.30:0.66:0.30 relative abundance, indicating that the 1-hydroxy-4,5,6,7-tetrachlorobenzotriazole portion of the oxygen-18-labeled acetate did not contain the heavy isotope. That the label was still at the site of the carbonyl oxygen in the acetate was confirmed by the mass spectrum of the acetamide ammonolysis product (**11**), which gave prominent peaks at *m/e* 44 (15%), 46 (>100), 61 (17), 62 (47), 63 (49), 64 (20), compared with unlabeled acetamide similarly formed: *m/e* 44 (100%), 59 (75), 60 (25).

The mass spectrum of N-(2-methoxy-3,4,5,6-tetrachlorophenyl)urea (**7a**) showed peaks at *m/e* 302 (M^+), 304 $(M + 2)^+$ and 306 $(M + 4)^+$, in relative abundances 1.00:1.21:0.57 (see Figure 3). The major fragment ions containing oxygen are at $(M - 32)^+$, $(M - 43)^+$, $(M - 44)^+$, and $(M - 58)^+$. The last three have retained only one oxygen, which is the one attached to the aromatic ring, barring unprecedented rearrangements. It will be seen from Table II that the +2 and +4 fragments in each case provide an internal check, by means of the abundance ratios compared with the







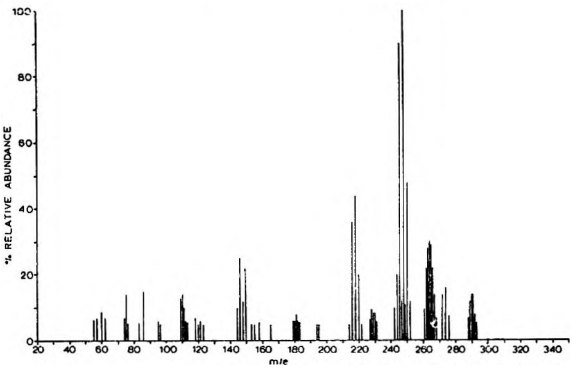
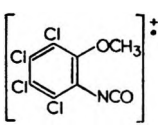
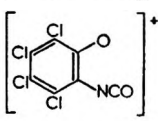
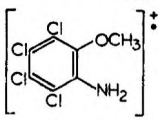
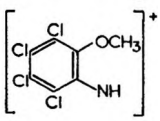
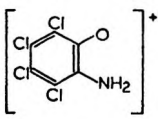
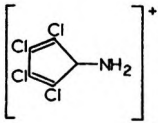


Figure 1 (upper left).—Mass spectrum of 1-acetoxy-4,5,6,7-tetrachlorobenzotriazole (4a) at 70 eV.
Figure 2 (lower left).—Mass spectrum of carbonyl-^{18}O-labeled 1-acetoxy-4,5,6,7-tetrachlorobenzotriazole (10) at 70 eV.
Figure 3 (upper right).—Mass spectrum of N-(2-methoxy-3,4,5,6-tetrachlorophenyl)urea (7a) at 70 eV.
Figure 4 (lower right).—Mass spectrum of ^{18}O-labeled N-(2-methoxy-3,4,5,6-tetrachlorophenyl)urea (12) at 70 eV.

TABLE II

FRAGMENTATION OF N-(2-METHOXY-3,4,5,6-TETRACHLOROPHENYL)UREA (7a) AT 70 eV

	m/e		Relative abundance
	285	$(M - 17)^+$	1.00
	287	$[(M + 2) - 17]^+$	1.28
	289	$[(M + 4) - 17]^+$	0.30
	$NH_3 = 17$		
	270	$(M - 32)^+$	1.00
	272	$[(M + 2) - 32]^+$	1.16
	274	$[(M + 4) - 32]^+$	0.58
	$NH_3 + CH_3 = 32$		
	259	$(M - 43)^+$	1.00
	261	$[(M + 2) - 43]^+$	1.22
	263	$[(M + 4) - 43]^+$	0.61
	HNCO = 43		
	258	$(M - 44)^+$	1.00
	260	$[(M + 2) - 44]^+$	1.37
	262	$[(M + 4) - 44]^+$	1.25
	$H_2NCO = 44$		
	244	$(M - 58)^+$	1.00
	246	$[(M + 2) - 58]^+$	1.00
	248	$[(M + 4) - 58]^+$	0.90
	$HNCO + CH_3 = 58$		
	216	$(M - 86)^+$	1.00
	218	$[(M + 2) - 86]^+$	1.15
	220	$[(M + 4) - 86]^+$	0.54
	$HNCO + CH_3 + CO = 86$		

theoretical ratios (1.00:1.31:0.64) for Cl_4-containing units, as to whether the fragment pictured is solely or partly responsible for the *m/e* values observed. The molecular ion peak for the ^{18}O-labeled N-(2-methoxy-3,4,5,6-tetrachlorophenyl)urea, which was obtained from carbonyl-^{18}O-labeled 1-acetoxy-4,5,6,7-tetrachlorobenzotriazole (**10**), was diffuse (304–309) because of the presence of deuterated species as in the starting material **10**. Moreover, the $(M - 17)^+$ peaks suffered from the same difficulty in attempted analysis. In the case where the fragment ion contained no hydrogen (or deuterium), as in $(M - 32)^+$, corresponding to the loss of NH_3 and $CH_3\cdot$ (see Table II), the relative abundance ratios for *m/e* 272, 274, and 276 of 1.00:1.14:0.53 provided a reasonably accurate indication that one of the two oxygens present in the fragment ion was ^{18}O. The $(M - 43)^+$ peak corresponding to loss of HNCO from the parent ion was diffuse (261–268) due to the presence of deuterium in this fragment, but if $HNC^{18}O$ had been lost there should have been a strong peak at $(M - 45)^+$ (Figure 4), or *m/e* 259. Since the peak at *m/e* 259 was only 3.5% in relative abundance (100% for base peak), this provides strong indication that the ^{18}O label was not lost from the major fragment but was retained on the aromatic ring. The main proof for the ^{18}O atom being attached to the aromatic ring came from the fact that the $(M - 58)^+$ fragment ion (see Table II) contained ^{18}O (*ca.* 10:1 over ^{16}O) and showed satisfactory relative abundance ratios for *m/e* 246, 248, and 250 of 1.00:1.11:0.54. Additionally, in the mass spectrum of the unlabeled urea product **7a** (Table II) there were peaks corresponding to $[(M - 58) - 28]^+$. It was unknown initially whether the 28 loss was due to CO or CNH_2. In the mass spectrum of the oxygen-18-labeled urea product the main peaks appeared at $[(M - 58) - 30]^+$. Thus the 30 loss can only be due to $C^{18}O$, giving *m/e* 216, 218, and 220 in the relative abundance ratios of 1.00:1.24:0.66.

TABLE III

SUBSTITUTED 1-HYDROXYBENZOTRIAZOLES (2)

Compound[a]	Registry no.	Mp, °C[b]	Yield, %	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
1-Hydroxybenzotriazole[e]		158	90	$C_6H_5N_3O$						
4,5-Dichloro-1-hydroxybenzotriazole	18355-00-5	213	85	$C_6H_3Cl_2N_3O$	35.32	1.48		35.35	1.47	
5,6-Dichloro-1-hydroxybenzotriazole		210[c]	66	$C_6H_3Cl_2N_3O$						
1-Hydroxy-4,5,6-trichlorobenzotriazole	18355-01-6	210	67	$C_6H_2Cl_3N_3O$	30.22	0.84		30.34	1.03	
1-Hydroxy-4,6,7-trichlorobenzotriazole	18355-02-7	210	6[d]	$C_6H_2Cl_3N_3O$	30.22	0.84	17.62	30.24	0.84	17.53
1-Hydroxy-4,5,6,7-tetrachlorobenzotriazole	18226-02-3	213	40	$C_6HCl_4N_3O$	26.40	0.37	15.39	26.35	0.58	15.64
6-Bromo-1-hydroxybenzotriazole	18355-04-9	208–209	66	$C_6H_4BrN_3O$	33.68	1.88	19.63	33.60	2.06	19.31

[a] All colorless needles. [b] All melt with violent decomposition. [c] Lit.[14] mp 194–196°. [d] The main product was 2,3,5,6-tetrachlorophenylhydrazine. [e] See ref 12 and 15.

TABLE IV

SUBSTITUTED 1-ACETOXYBENZOTRIAZOLES (3)

Compound[a]	Registry no.	Mp, °C	Yield, %	Formula	Calcd, % C	Calcd, % H	Found, % C	Found, % H	Ir[b] $\nu_{C=O}$, cm^{-1}	Nmr[c] CH_3, τ
1-Acetoxybenzotriazole	18355-05-0	104–105	62	$C_8H_7N_3O_2$	54.22	3.98	54.57	4.06	1805	7.48
1-Acetoxy-4,5-dichlorobenzotriazole	18355-06-1	116.5–117.5	74	$C_8H_5Cl_2N_3O_2$	39.06	2.09	39.10	2.12	1795	7.45
1-Acetoxy-5,6-dichlorobenzotriazole		150.5–151.5[d]	70	$C_8H_5Cl_2N_3O_2$					1800	7.47
1-Acetoxy-4,5,6-trichlorobenzotriazole	18355-07-2	174	50	$C_8H_4Cl_3N_3O_2$	34.25	1.44	34.30	1.71	1805	7.43
1-Acetoxy-4,6,7-trichlorobenzotriazole	18355-08-3	119.5–120.5	48	$C_8H_4Cl_3N_3O_2$	34.25	1.44	34.29	1.58	1825	
1-Acetoxy-4,5,6,7-tetrachlorobenzotriazole		197.5–199.5	71	$C_8H_3Cl_4N_3O_2$	30.51	0.96	30.36	0.79	1825	7.86
1-Acetoxy-6-bromobenzotriazole	18355-10-7	135	60	$C_8H_6BrN_3O_2$	37.52	2.36	37.52	2.34[e]	1815	7.45

[a] All colorless needles. [b] Nujol mull. [c] $CDCl_3$ containing TMS. [d] Lit.[14] mp 150°. [e] Calcd for N, 16.41. Found: N, 16.69.

With the oxygen-18-labeled N-(2-methoxy-3,4,5,6-tetrachlorophenyl)urea definitely established as possessing structure **12**, any mechanism to be satisfactory must account for the facts that the oxygens in the original 1-acetoxy-4,5,6,7-tetrachlorobenzotriazole retain their nonequivalence during the thermolysis process and that the carbonyl oxygen ends up attached to the aromatic ring in the ether function. The product structures also require alkyl migration from the original carbonyl carbon to the final ether oxygen. The formal sequence which we have proposed, *i.e.*, **4** → **8** → **9** → **5**, fully satisfies these requirements, but it cannot be regarded as exclusive since other sequences may be devised which are satisfactory to varying extents. It should be emphasized that we have accounted for the structure and have offered a possible route of formation of the compound, 2-methoxy-3,4,5,6-tetrachlorophenyl isocyanate, which makes up about 50% of the crude thermolysis product of 1-acetoxy-4,5,6,7-tetrachlorobenzotriazole. The spectral characteristics of the crude product indicate the presence of additional materials which suggest the operation of alternative pathways following the initial triazole ring opening[4] and rearrangements of the kind encountered with oxaziridines.[21]

Experimental Section[21]

General Synthesis of Substituted 1-Hydroxybenzotriazoles (2).—The appropriate chloronitrobenzene (5 g) was dissolved in 15–20 ml of hot ethanol, and 5 g of 85% hydrazine hydrate was added. The mixture was heated under reflux for 3 hr and cooled. The precipitate was filtered, dissolved in hot water, and the 1-hydroxybenzotriazole derivative was precipitated with hydrochloric acid. The crude product was decolorized with charcoal and recrystallized from 50% ethanol or methanol. In the reaction of hydrazine hydrate with 2,5-dibromonitrobenzene, the reflux period was 5 hr. With pentachloronitrobenzene, benzene was added to the reaction mixture to retain solubility. Following the reflux period, the solvents were evaporated *in vacuo*, 50 ml of 5% aqueous potassium hydroxide was added, the undissolved pentachlorophenylhydrazine was removed by filtration, and 1-hydroxy-4,5,6,7-tetrachlorobenzotriazole was precipitated with concentrated hydrochloric acid. The properties of the substituted 1-hydroxybenzotriazoles are shown in Table III.

In the reaction of 5 g of 2,3,5,6-tetrachloronitrobenzene with 5 g of hydrazine hydrate in 15 ml of ethanol, after a reflux period of 1 hr, the mixture solidified. The precipitate, which was filtered and washed with ethanol and ether, was a mixture of 2,3,5,6-tetrachlorophenylhydrazine and the hydrazine salt of 1-hydroxy-4,6,7-trichlorobenzotriazole, yield 3.16 g. When the crude mixture (250 mg) was heated at 0.5 mm and 130–135°, the **2,3,5,6-tetrachlorophenylhydrazine** sublimed, mp 173–173.5°, yield 180 mg.

Anal. Calcd for $C_6H_4Cl_4N_2$: C, 29.27; H, 1.62; N, 11.38. Found: C, 29.31; H, 1.73; N, 11.52.

The residue remaining after sublimation (30 mg) was recrystallized from ethanol, yielding the **hydrazine salt of 1-hydroxy-4,6,7-trichlorobenzotriazole**, mp 206–207°.

Anal. Calcd for $C_6H_6Cl_3N_5O$: C, 26.64; H, 2.23; N, 25.89. Found: C, 26.98; H, 2.34; N, 25.98.

General Procedure for Acetylation of the Substituted 1-Hydroxybenzotriazoles.—The substituted 1-hydroxybenzotriazole (5 g) was dissolved in 50 ml of ethanol and treated with 20 ml of an ethanol solution containing an equimolar amount of potassium hydroxide. The crystallized potassium salt of 1-hydroxybenzotriazole was filtered, dried, and used without further purification. In several cases the ethanolic solution had to be concentrated to cause precipitation of the potassium salt. To a suspension of 0.01 mol of the potassium salt in 30 ml of anhydrous acetone was then added 0.012 mol of acetyl chloride. The mixture was heated under reflux for 30 min and poured into 1.5 l. of ice water. The acetyl derivative was collected by filtration, dried, and recrystallized from benzene. It could be reconverted into the 1-hydroxy compound by treatment with aqueous ammonia in methanol. The properties of the acetoxy derivatives are shown in Table IV.

1-Propionoxy-4,5,6,7-tetrachlorobenzotriazole (4c).—The propionate ester of 1-hydroxy-4,5,6,7-tetrachlorobenzotriazole was

(24) All melting points are corrected; boiling points are uncorrected. Infrared spectra were obtained with a Perkin-Elmer grating spectrophotometer, Model 337. Nmr spectra were obtained on a Varian Associates Model A-60 spectrometer using tetramethylsilane (TMS) as an internal standard. We are indebted to Mr. R. Thrift for these determinations, to Mr. J. Nemeth and his associates for the microanalyses, and to Mr. Joseph Wrona for the mass spectra determinations using an Atlas Model CH4 low resolution spectrometer.

obtained similarly to the acetate ester. The crude product was purified by recrystallization from petroleum ether (bp 40–60°), colorless needles: mp 122–123°, yield 50%; ν_{max}^{Nujol} 1820 cm^{-1} (C=O); nmr ($CDCl_3$) τ 8.58 (t, CH_3), 7.09 (q, CH_2).

Anal. Calcd for $C_9H_5Cl_4N_3O_2$: C, 32.86; H, 1.53; N, 12.77. Found: C, 32.94; H, 1.66; N, 13.06.

1-Ethoxycarbonyloxy-4,5,6,7-tetrachlorobenzotriazole was made in a similar manner from the potassium salt of 1-hydroxy-4,5,6,7-tetrachlorobenzotriazole and ethyl chloroformate and was recrystallized from benzene–hexane, colorless needles: mp 100°, yield 86%; ν_{max}^{Nujol} 1810 cm^{-1} (C=O); nmr ($CDCl_3$) τ 8.50 (t, CH_3), 5.42 (q, CH_2).

Anal. Calcd for $C_9H_5Cl_4N_3O_3$: C, 31.33; H, 1.46; N, 12.18. Found: C, 31.39; H, 1.43; N, 12.17.

1-Methoxy-4,5,6,7-tetrachlorobenzotriazole.—1-Hydroxy-4,5,6,7-tetrachlorobenzotriazole (2.0 g, 7.3 mmol) was dissolved in 20 ml of hot ethanol. A solution of 0.44 g of potassium hydroxide in 10 ml of ethanol was added, followed by 2.0 g of methyl iodide. As the suspension was heated under reflux for 2 hr the solid gradually went into solution. When the solution was cooled the precipitate which formed was collected by filtration, washed with water, and recrystallized from ethanol, colorless needles: mp 139–140°, yield 1.42 g (67%); nmr ($CDCl_3$) τ 5.50.

Anal. Calcd for $C_7H_3Cl_4N_3O$: C, 29.30; H, 1.05; N, 14.64. Found: C, 29.16; H, 1.06; N, 14.73.

1-Ethoxy-4,5,6,7-tetrachlorobenzotriazole.—A similar procedure using excess ethyl iodide and a reflux time of 3 hr produced the ethyl ether, colorless needles: mp 105–106°; yield 66%; nmr ($CDCl_3$) τ 8.43 (t, CH_3), 5.27 (q, CH_2).

Anal. Calcd for $C_8H_5Cl_4N_3O$: C, 31.93; H, 1.67; N, 13.96. Found: C, 31.91; H, 1.82; N, 14.13.

Pyrolysis of 1-Acetoxy-4,5,6,7-tetrachlorobenzotriazole (4a).—The pyrolysis *in vacuo* was effected in a vertical tube, the lower part of which was a sublimation area heated at 200–210° and the upper part, a decomposition area filled with Pyrex wool and heated at 400°. The top of the tube was bent horizontally and through it the products were vented into a cooled flask for collection. The side arm of the flask was evacuated at 0.025 mm. From 600 mg (1.9 mmol) of 1-acetoxy-4,5,6,7-tetrachlorobenzotriazole was obtained 120–130 mg of crude pyrolysis product as an oil, ν_{max}^{film} 2220 cm^{-1}. While an attempt to purify the oil by freezing at −70° was unsuccessful, distillation *in vacuo* was partially successful. The distillate retained the infrared band at 2220 cm^{-1} and the analysis was indicative of, but not fully satisfactory for, the elemental composition $C_8H_3Cl_4NO_2$, corresponding to **2-methoxy-3,4,5,6-tetrachlorophenylisocyanate (5a)**.

Anal. Calcd for $C_8H_3Cl_4NO_2$: C, 33.49; H, 1.05; N, 4.88. Found: C, 34.93; H, 1.20; N, 5.10.

On the basis of nmr the isocyanate corresponded to at least 50% of the crude. The nmr spectrum showed a strong signal for OCH_3 at τ 6.02 (in $CDCl_3$), but an additional signal at 8.48 and a weak, complex pattern at 7.13–8.82. The results of various forms of chromatography suggested that chemical conversions were probably taking place during such a process and indicated the presence of at least two components. The reactivity of the crude product was consistent with the presence of an isocyanate group, and this observation was utilized in the preparation of characterizable derivatives from the pyrolysis product.

Methyl N-(2-Methoxy-3,4,5,6-tetrachlorophenyl)carbamate (6a).—The crude pyrolysis product (500 mg) from 1-acetoxy-4,5,6,7-tetrachlorobenzotriazole was dissolved in 10 ml of methanol, and the solvent was removed *in vacuo*. Methanol (4 ml) was added to the brown semisolid residue, and the mixture was filtered immediately. After purification of the precipitate with charcoal in hot methanol 40 mg of colorless needles were obtained: mp 183.5–184°; $\nu_{max}^{CHCl_3}$ 3400, 2925, 2825, 1725, 1550, 1480, 1450, 1400, 1370, 1330, 1240, 1070, and 1020 cm^{-1}; nmr ($CDCl_3$) τ 6.10 (3 H, CH_3O), 6.19 (3 H, CH_3O), and 3.57 (1 H, NH).

Anal. Calcd for $C_9H_7Cl_4NO_3$: C, 33.89; H, 2.21; N, 4.39; Cl, 44.46. Found: C, 34.16; H, 2.25; N, 4.48; Cl, 44.01.

N-(2-Methoxy-3,4,5,6-tetrachlorophenyl)urea (7a).—A sample of the compound described above (50 mg), mp 183°, which resulted from treatment of the acetate pyrolysis product with methanol, was dissolved in 25 ml of anhydrous methanol. The solution was placed in a glass pressure tube and saturated with ammonia while cooling in an ice bath. While the solution was cooled further in Dry Ice–acetone the tube was sealed. After the sealed tube had been heated at 100° for 10 hr it was allowed to stand overnight. The solvent was evaporated *in vacuo* to dryness, and the residue was recrystallized from methanol, yielding 36 mg (75%) of N-(2-methoxy-3,4,5,6-tetrachlorophenyl)urea, colorless needles: subl pt >250°; ν_{max}^{Nujol} 3490, 3330, 3250, 3160, 1660, and 1019 cm^{-1}.

Anal. Calcd for $C_8H_6Cl_4N_2O_2$: C, 31.61; H, 1.99; N, 9.22. Found: C, 31.83; H, 2.25; N, 9.16.

N-(2-Methoxy-3,4,5,6-tetrachlorophenyl)urea was also obtained directly by dissolving the acetate pyrolysis product (200 mg) in 30 ml of methylene chloride and passing in gaseous ammonia. The gray precipitate was filtered, decolorized with charcoal in hot methanol, and recrystallized from methanol as colorless needles: subl pt >250°; yield 18 mg; infrared spectrum identical with that described above.

When the acetate pyrolysis product was treated with ethanol in place of methanol the infrared spectrum showed the disappearance of the 2220-cm^{-1} maximum and the appearance of new maxima at 3400–3200 (br) and 1715 cm^{-1}. When the ethanol solution was saturated with ammonia and then heated in a sealed tube for 10 hr at 100°, the urea derivative isolated was identical in all respects with the product obtained by treatment of the pyrolysis product directly with ammonia or by following the methanol treatment with ammonia.

Pyrolysis of 1-Propionoxy-4,5,6,7-tetrachlorobenzotriazole (4c).—The pyrolysis of 600 mg was carried out under conditions identical with those employed with the 1-acetoxy derivative. The crude oily product (45 mg) showed ν_{max}^{film} 2220 cm^{-1}.

Methyl N-(2-Ethoxy-3,4,5,6-tetrachlorophenyl)carbamate (6c).—The crude propionate pyrolysis product (500 mg) was dissolved in 5 ml of methanol and the solvent was then removed *in vacuo*. The residue was recrystallized from hexane–methylene chloride as colorless needles: mp 162–163°; yield 100 mg; $\nu_{max}^{CHCl_3}$ 3400, 2975, 2948, 1740, 1549, 1495, 1450, 1440, 1420, 1380, 1355, 1240, 1074, 1024, 950, and 860 cm^{-1}; nmr ($CDCl_3$) τ 8.60 (t, CH_3), 6.20 (s, OCH_3), 5.90 (q, CH_2), 3.47 (br, NH).

Anal. Calcd for $C_{10}H_9Cl_4NO_3$: C, 36.07; H, 2.72; N, 4.21. Found: C, 36.16; H, 2.64; N, 4.48.

N-(2-Ethoxy-3,4,5,6-tetrachlorophenyl)urea (7c).—The crude propionate pyrolysis product (100 mg) was dissolved in 20 ml of methylene chloride and gaseous ammonia was passed in. The resulting suspension was evaporated *in vacuo* and the residue was recrystallized from methanol: mp 252.5°; yield 20 mg; ν_{max}^{Nujol} 3425, 3325, 3250, 1670, 1610, 1570, 1530, 1460, 1440, 1390, 1370, 1350, 1225, 1026.

Anal. Calcd for $C_9H_8Cl_4N_2O_2$: C, 33.98; H, 2.53; N, 8.81. Found: C, 34.43; H, 2.55; N, 8.70.

Pyrolysis of Carbonyl-^{18}O-labeled 1-Acetoxy-4,5,6,7-tetrachlorobenzotriazole (10).—In three practice runs the sequence 1-hydroxy-4,5,6,7-tetrachlorobenzotriazole → 1-acetoxy-4,5,6,7-tetrachlorobenzotriazole → 2-methoxy-3,4,5,6-tetrachlorophenylisocyanate → N-(2-methoxy-3,4,5,6-tetrachlorophenyl)urea was carried out starting with 250 mg of acetyl chloride and following the directions described above.

When the method was sufficiently standardized, 1-acetoxy-4,5,6,7-tetrachlorobenzotriazole-carbonyl-^{18}O was prepared from 250 mg of acetyl-^{18}O chloride, 90% enrichment (Research Products Department of Miles Laboratories, Inc.). The yield of crude material was 96%. After recrystallization from benzene, pure material was obtained in 55% yield: mp 196°; ν_{max}^{Nujol} 1825 (C=^{18}O) and 1795 cm^{-1} (C=^{18}O), ratio ~1.10; nmr (CCl_4) τ 7.90 (s). In the mass spectrum the following peaks were observed in the region of the molecular ion: *m/e* 315 (13% relative abundance), 316 (32), 317 (45), 318 (50), 319 (46), 320 (35), 321 (23), 322 (14), 323 (5.5), indicating some replacement of hydrogen by deuterium. A portion of 500 mg of 1-acetoxy-4,5,6,7-tetrachlorobenzotriazole-carbonyl-^{18}O was pyrolyzed under conditions identical with those described for the unlabeled compound, yielding 79 mg of pyrolysis product, ν_{max}^{film} 2220 cm^{-1}. The crude pyrolysis product was subjected immediately to reaction with gaseous ammonia in methylene chloride. Yield was sacrificed for purity of the oxygen-18-labeled N-(2-methoxy-3,4,5,6-tetrachlorophenyl)urea (12) isolated (*ca.* 3 mg), and this product was subjected to mass spectrometric analysis, as described in the discussion, to prove the location of the oxygen-18.

Reaction of 1-Hydroxy-4,5,6,7-tetrachlorobenzotriazole (2, X_n = Cl_4) with Ketene.—As an alternative synthesis of the substituted 1-acetoxybenzotriazoles and as a check on their structural assignments, the 1-hydroxybenzotriazoles could be acetylated with ketene. For example, through a solution of 100 mg of 1-hydroxy-4,5,6,7-tetrachlorobenzotriazole in 50 ml of acetone

cooled at 0° was passed excess ketene in a stream of dry nitrogen. The solution was then poured into ice water, and the precipitate was collected by filtration and dried, yield 98 mg (85%) of 1-acetoxy-4,5,6,7-tetrachlorobenzotriazole. Following recrystallization from benzene, the compound had mp 197.5–199.5° and was identical in all respects (ir, etc.) with the sample obtained by acetylation using the potassium salt and acetyl chloride, as described above.

Chlorination of o-Methoxyacetanilide (o-Acetanisidide).—Dry chlorine was passed through a solution of *o*-acetanisidide in glacial acetic acid, and upon completion of the reaction the solution was poured into ice water. The precipitated material was recrystallized from ethanol as colorless needles of 2-methoxy-3,4,5,6-tetrachloroaniline, mp 224–225° (lit.[19] mp 227.5°), with the correct elemental analysis for $C_9H_7Cl_4NO_2$, nmr ($CDCl_3$ τ 7.78 (s, CH_3CO), 6.13 (s, CH_3O).

Reaction of 2-Methoxy-3,4,5,6-tetrachloroaniline with Phosgene Followed by Methanol.—To a solution of 200 mg of 2-methoxy-3,4,5,6-tetrachloroaniline in 20 ml of anhydrous benzene and 0.5 ml of anhydrous triethylamine was added 4 ml of a 12.5% solution of phosgene in benzene, and the reaction mixture was maintained at ambient temperature for 1 hr. The solvent was evaporated *in vacuo*, the residue was treated with anhydrous ether, and triethylamine hydrochloride was removed by filtration. Ether was evaporated from the filtrate under reduced pressure, leaving a half-solid residue which showed very strong infrared absorption at 2220 cm^{-1}. The residue was treated with 10 ml of methanol, and from this solution pure methyl N-(2-methoxy-3,4,5,6-tetrachlorophenyl)carbamate crystallized, yield 170 mg (70%), mp 181–182°, undepressed on admixture with a sample of methyl N-(2-methoxy-3,4,5,6-tetrachlorophenyl)carbamate (**6a**). The infrared spectra of the samples from the two sources were identical.

Registry No.—**4a**, 18355-09-4; **4c**, 18425-98-4; **5a**, 18355-11-8; **6a**, 18355-12-9; **6c**, 18355-13-0; **7a**, 18355-14-1; **7c**, 18355-15-2; **10**, 18346-74-2; **12**, 18346-75-3; 2,3,5,6-tetrachlorophenylhydrazine, 18355-16-3; hydrazine salt of 1-hydroxy-4,6,7-trichlorobenzotriazole, 18355-17-4; 1-ethoxycarbonyloxy-4,5-6,7-tetrachlorobenzotriazole, 18355-18-5; 1-methoxy-4,5,-6,7-tetrachlorobenzotriazole, 18355-19-6; 1-ethoxy-4,5,6,7-tetrachlorobenzotriazole, 18355-20-9.

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The Structures of Two Diastereoisomeric Sulfoxides. 3,5-Dihydro-3-methyl-4,1-benzothiazepin-2(1H)-one 4-Oxides

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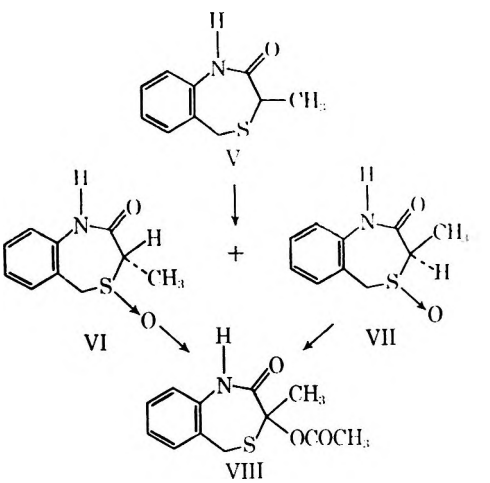
The sodium metaperiodate oxidation of 3,5-dihydro-3-methyl-4,1-benzothiazepin-2(1H)-one gave two diastereoisomeric sulfoxides with mp 220–223 and 246–248°, respectively. The crystal structure of the major product (mp 220–223°) has been determined and the 3-methyl group has been shown to be *trans* to the sulfoxide oxygen atom. The crystals are monoclinic, with $a = 13.20 \pm 0.02$ Å, $b = 4.71 \pm 0.01$ Å, $c = 17.16 \pm 0.03$ Å and $\beta = 113°15' \pm 15'$. There are four molecules of $C_{10}H_{11}NO_2S$ in the space group $P2_1/c$. The structure has been refined to an R factor of 0.09 on 1427 reflections, obtained photographically. The detailed geometry of the molecule in the crystal is described. In boiling acetic anhydride solution both sulfoxides interconvert and rearrange to 3-acetoxy-3,5-dihydro-3-methyl-4,1-benzothiazepin-2(1H)-one.

In the course of the study of 4,1-benzothiazepines, a new class of heterocyclic compounds[2] with interesting pharmacological properties, the Pummerer rearrangement[3] of sulfoxides was investigated as a method for the introduction of an acetoxy group on the carbon next to sulfur. In the 3-methyl series, we encountered the problem of separation and structure determination of two diastereoisomeric sulfoxides. This was resolved as follows.

The sodium metaperiodate oxidation[4] of racemic 3,5-dihydro-3-methyl-4,1-benzothiazepin-2(1H)-one (V), the synthesis[2] of which is fully described in the Experimental Section, gave two diastereoisomeric sulfoxides in a ratio of 3:1. They were separated by chromatography on a silica gel column. The major product was eluted first with 15% ethyl acetate–85% benzene mixture. The minor product was eluted subsequently with 75% ethyl acetate–25% benzene mixture and pure ethyl acetate. The structure of the major product was elucidated by X-ray analysis and determined as that of the *trans*-sulfoxide VI.



The X-Ray Analysis of the *trans*-Sulfoxide VI.—The crystals of VI are transparent needles belonging to the monoclinic system with $a = 13.20 \pm 0.02$ Å,

(1) (a) University of Illinois. (b) Alfred P. Sloan Research Fellow. (c) Hoffmann-La Roche.

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(4) N. J. Leonard and C. R. Johnson, *J. Org. Chem.*, **27**, 282 (1962).

TABLE I

FRACTIONAL COORDINATES WITH ESTIMATED STANDARD DEVIATIONS IN PARENTHESES. ORIGIN AS IN "INTERNATIONAL TABLES FOR X-RAY CRYSTALLOGRAPHY." BEYOND C_{9a}, THE NUMBERING CONVENTION IS ARBITRARY

	x	*y*	*z*
N_1	0.3665 (4)	0.272 (1)	0.4621 (3)
C_2	0.3931 (5)	0.289 (1)	0.3932 (4)
C_3	0.3285 (4)	0.101 (1)	0.3195 (4)
S_4	0.1940 (1)	0.258 (1)	0.2511 (1)
C_5	0.1526 (5)	0.385 (1)	0.3352 (4)
C_{5a}	0.1692 (5)	0.175 (1)	0.4037 (4)
C_6	0.0803 (5)	0.027 (1)	0.4080 (4)
C_7	0.0945 (6)	−0.163 (1)	0.4728 (4)
C_8	0.1966 (6)	−0.202 (2)	0.5349 (4)
C_9	0.2875 (5)	−0.061 (2)	0.5326 (4)
C_{9a}	0.2747 (5)	0.126 (1)	0.4659 (4)
O_{10}	0.4681 (4)	0.442 (1)	0.3922 (3)
C_{11}	0.3906 (5)	0.029 (2)	0.2636 (5)
O_{12}	0.1233 (4)	0.006 (1)	0.2111 (3)
H_1	0.417	0.33	0.502
H_3	0.315	−0.11	0.343
$H_{5,1}$	0.075	0.42	0.306
$H_{5,2}$	0.190	0.56	0.353
H_6	0.016	0.02	0.357
H_7	0.033	−0.27	0.474
H_8	0.206	−0.33	0.581
H_9	0.360	−0.12	0.568
$H_{11,1}$	0.400	0.20	0.237
$H_{11,2}$	0.462	−0.04	0.297
$H_{11,3}$	0.347	−0.09	0.218

TABLE II

BOND DISTANCES (Å) WITH ESTIMATED STANDARD DEVIATIONS[a]

N_1–C_2	1.361 (8)
N_1–C_{9a}	1.419 (8)
C_2–C_3	1.505 (9)
C_2–O_{10}	1.229 (8)
C_3–S_4	1.853 (7)
C_3–C_{11}	1.525 (10)
S_4–C_5	1.833 (6)
S_4–O_{12}	1.498 (6)
C_5–C_{5a}	1.482 (9)
C_{5a}–C_6	1.393 (9)
C_{5a}–C_{9a}	1.400 (9)
C_6–C_7	1.382 (10)
C_7–C_8	1.361 (11)
C_8–C_9	1.387 (11)
C_9–C_{9a}	1.399 (10)

[a] The N–H and C–H distances all lie in the range 0.8–1.1 Å.

TABLE III

BOND ANGLES (DEGREES) WITH ESTIMATED STANDARD DEVIATIONS[a]

C_{9a}–N_1–C_2	125.9 (4)	C_5–C_{5a}–C_6	120.8 (5)
N_1–C_2–C_3	116.1 (6)	C_5–C_{5a}–C_{9a}	120.4 (4)
N_1–C_2–O_{10}	122.1 (7)	C_6–C_{5a}–C_{9a}	118.7 (4)
C_3–C_2–O_{10}	121.7 (6)	C_{5a}–C_6–C_7	121.3 (6)
C_2–C_3–S_4	112.3 (3)	C_6–C_7–C_8	119.6 (4)
C_2–C_3–C_{11}	113.0 (4)	C_7–C_8–C_9	121.0 (6)
S_4–C_3–C_{11}	107.9 (4)	C_8–C_9–C_{9a}	119.8 (4)
C_3–S_4–C_5	98.0 (3)	C_9–C_{9a}–N_1	120.9 (5)
C_3–S_4–O_{12}	104.0 (3)	C_9–C_{9a}–C_{5a}	119.5 (4)
C_5–S_4–O_{12}	107.1 (3)	C_{5a}–C_{9a}–N_1	119.6 (3)
S_4–C_5–C_{5a}	114.3 (3)		

[a] The bond angles involving hydrogen atoms bonded to atoms with sp^3 hybridization lie in the range 104–116°, and those involving hydrogen atoms bonded to sp^2-hybridized atoms lie in the range 108–124°.

b = 4.71 ± 0.01 Å, c = 17.16 ± 0.03 Å, and β = 113° 15′ ± 15′. There are four molecules of $C_{10}H_{11}NO_2S$ (mol wt 209.27) in the unit cell and the space group is $P2_1/c$. Least-squares refinement incorporating anisotropic temperature factors has given a final R factor of 0.09 on the 1427 independent structure amplitudes obtained by visual estimates of equiinclination Weissenberg photographs. The final values of the positional parameters are given in Table I. The bond distances and angles found in the molecule are listed in Tables II and III. Views of the molecule looking along the b and a axes are shown in Figures 1 and 2.

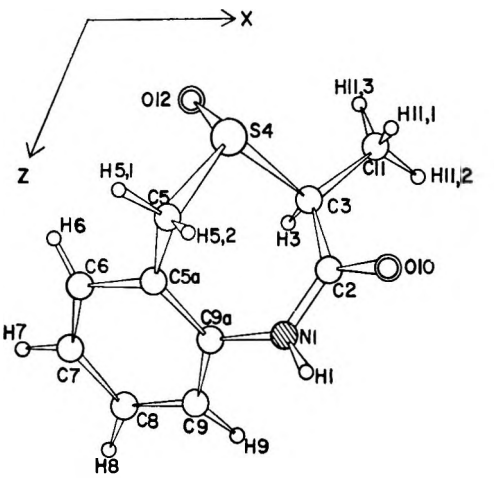

Figure 1.—View of the molecule along the b axis showing the atom numbering used in the analysis. The numbering after C-9a does not correspond to any established chemical convention.

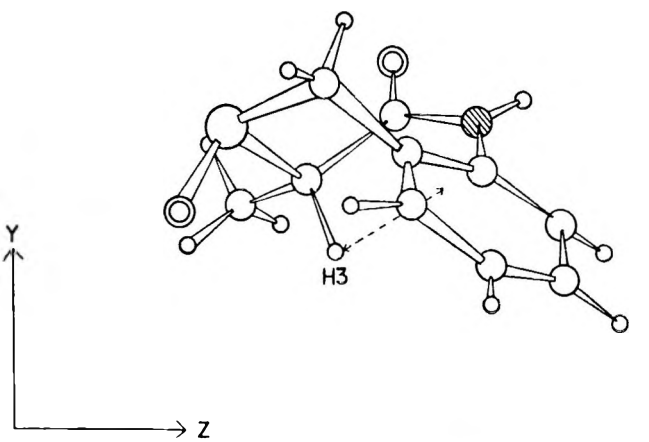

Figure 2.—View of the molecule along the a axis.

The relative configuration of the C—CH_3 and S→O groups is seen to be *trans*, with the methyl group adopting an equatorial position, while the sulfoxide oxygen is pseudoequatorial. The conformation of the seven-membered ring can be described as a distorted "boat" [5] relative to either the approximate plane through atoms C_3, S_4, C_{5a}, and C_{9a} with C_5, N_1, and C_2 lying 0.63, 1.15, and 1.08 Å, respectively, from this plane, or the very approximate plane through atoms N_1, C_2, S_4, and C_5 with C_3, C_{9a} and C_{5a} lying 0.18, 1.56 and 1.45 Å out of the plane. In the saturated carbocyclic series, seven-

(5) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965, pp 206–209.

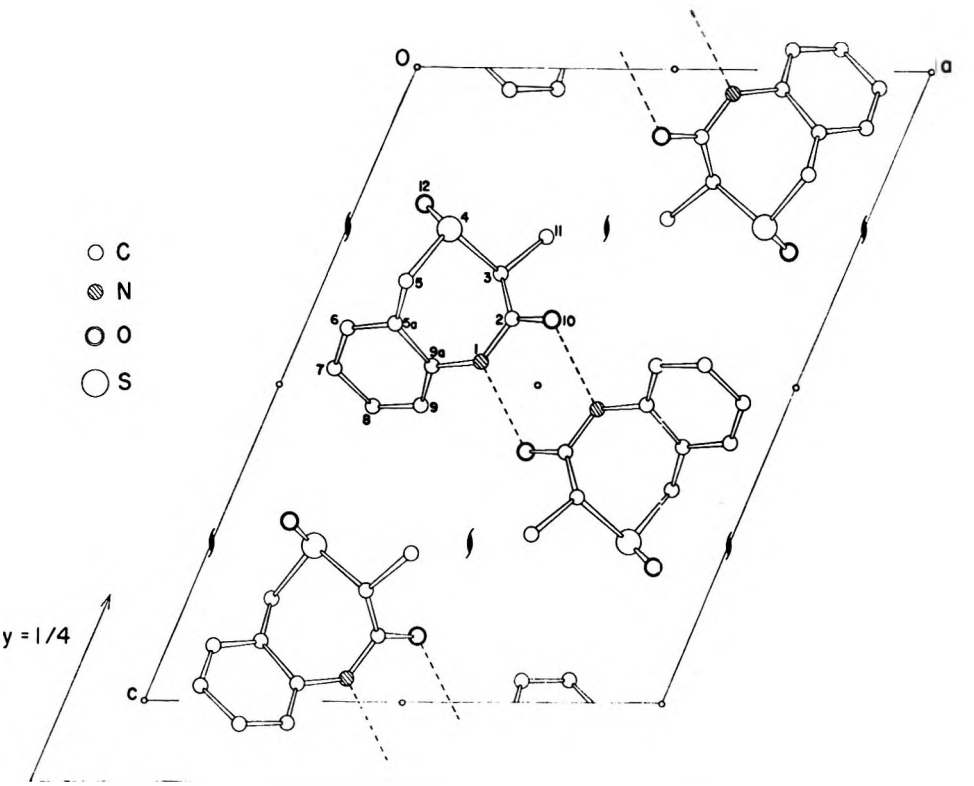

Figure 3.—Packing diagram viewed down *b*. The hydrogen bonds are marked by discontinuous lines.

membered rings can exist in a number of flexible conformations with the twist chair being considered the most stable.[6] The six atoms of the benzene ring, N_1, and C_5 are approximately planar (mean deviation 0.02 Å), as is the group of atoms C_{9a}, N_1, C_2, O_{10}, and C_3 (mean deviation 0.037 Å). These two rigid groups of atoms will impose considerable constraints on the conformation of the ring. These adjacent groups of four planar atoms (each containing C_{9a}) and the presence of the sulfur atom which forms much longer bonds to carbon make it unlikely that results valid in the flexible carbocyclic system will necessarily pertain in the thiazepine ring of VI. Furthermore, a survey[7] of carbocyclic seven-membered rings in sesquiterpenes indicates that the ring conformation is greatly dependent on the molecular environment.

The conformation of the seven-membered ring can also be described in terms of the dihedral angles involving the atoms in the ring (Table IV). The principal difference in detailed geometry of the ring from that implied by a Dreiding model can be described as an "unfolding" about the N_1–C_5 axis. This effect increases the C_2–N_1–C_{9a} and C_{5a}–C_5–S_4 angles to values of 125.9 and 114.3°, respectively, and is probably responsible for the unexpectedly large deviation from planarity in the group of atoms C_{9a}, N_1, C_2, O_{10}, and C_3. The groups of four atoms, C_{9a}, C_2, C_3, and O_{10} and N_1, C_2, C_3, and O_{10} are accurately planar with N_1 lying −0.11 Å from the plane through the first group, and C_{9a} lying 0.15 Å from that through the second group. This deviation is also shown by the dihedral angle of −9.4° made by atoms C_{9a} and C_3 when viewed along the N_1–C_2 bond. The most probable cause of this unfolding when compared with a wire model would be a repulsion between the C_3 proton and the π cloud of the aromatic ring. This hydrogen atom is reasonably well defined (although positioned to relatively low accuracy) and the small value of 104° for the H_3–C_3–H_{11} angle may be significant.

TABLE IV

DIHEDRAL ANGLES (DEGREES) IN THE SEVEN-MEMBERED-RING PORTION OF THE MOLECULE. THE DIHEDRAL ANGLE A–B–C–D IS CONSIDERED POSITIVE IF ATOM A HAS TO BE ROTATED CLOCKWISE TO ECLIPSE ATOM D

A	B	C	D	τ	A	B	C	D	τ
C_{9a}	N_1	C_2	C_3	−9.4	C_3	S_4	C_5	C_{5a}	−45.7
C_{9a}	N_1	C_2	O_{10}	173.0	O_{12}	S_4	C_5	C_{5a}	−81.3
N_1	C_2	C_3	S_4	82.7	S_4	C_5	C_{5a}	C_6	−103.7
N_1	C_2	C_3	C_{11}	−154.8	S_4	C_5	C_{5a}	C_{9a}	76.9
O_{10}	C_2	C_3	S_4	−99.7	C_5	C_{5a}	C_{9a}	N_1	−1.4
O_{10}	C_2	C_3	C_{11}	22.8	C_5	C_{5a}	C_{9a}	C_9	−145.5
C_2	C_3	S_4	C_5	−43.8	C_6	C_{5a}	C_{9a}	N_1	179.2
C_2	C_3	S_4	O_{12}	28.2	C_6	C_{5a}	C_{9a}	C_9	−3.0
C_{11}	C_3	S_4	C_5	−169.1	C_{5a}	C_{9a}	N_1	C_2	−51.2
C_{11}	C_3	S_4	O_{12}	−97.1	C_9	C_{9a}	N_1	C_2	131.1

A packing diagram of the structure viewed down the *b* axis is shown in Figure 3. Intermolecular hydrogen bonding involving the amide groups in adjacent molecules to form centrosymmetric dimers in the crystal is an important facet of the molecular packing. The N···O distance is 2.92 Å and the C_2–O_{10}···N_1, C_{9a}–N_1···O_{10}, and C_2–N_1···O_{10} angles are 126, 123, and 111°, respectively. These dimensions are fully consistent with N–H···O hydrogen bonding.[8] All other

(6) J. B. Hendrickson, *J. Amer. Chem. Soc.*, **83**, 4537 (1961); **89**, 7036 (1967).

(7) A. M. Mathieson in "Perspectives in Structural Chemistry," Vol. I, John Wiley & Sons, Inc., New York, N. Y., 1967, p 70.

(8) G. C. Pimentel and A. L. McClellan, "The Hydrogen Bond," W. H. Freeman and Co., San Francisco, Calif., 1960, p 287.

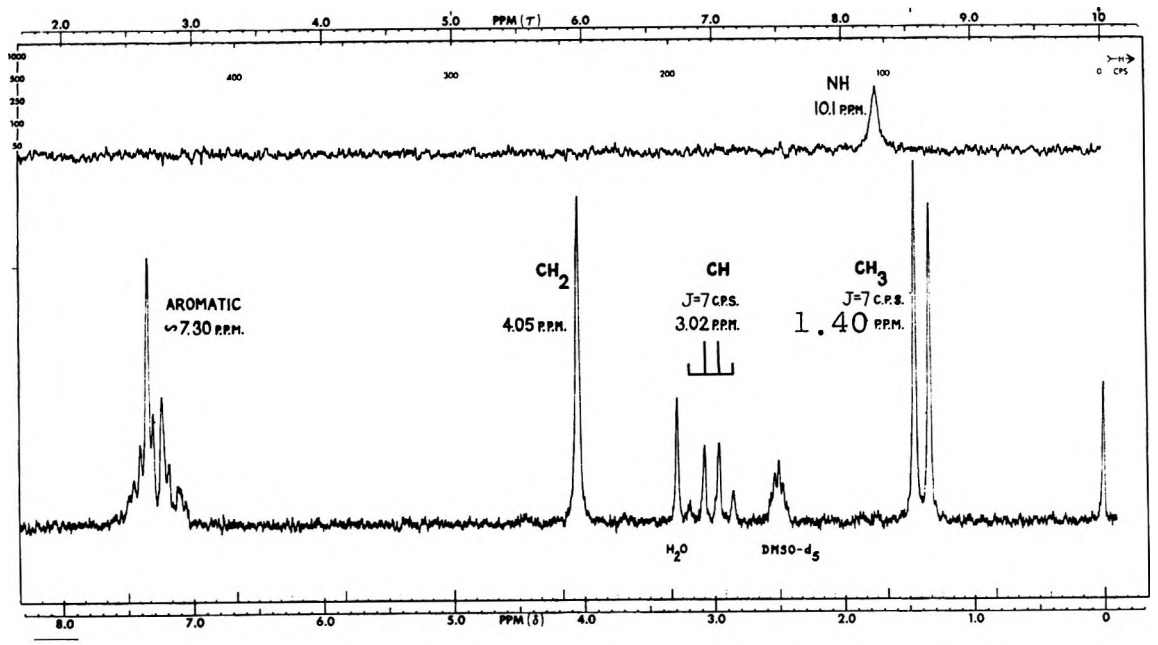

Figure 4.—Nmr spectrum of *trans*-sulfoxide VI.

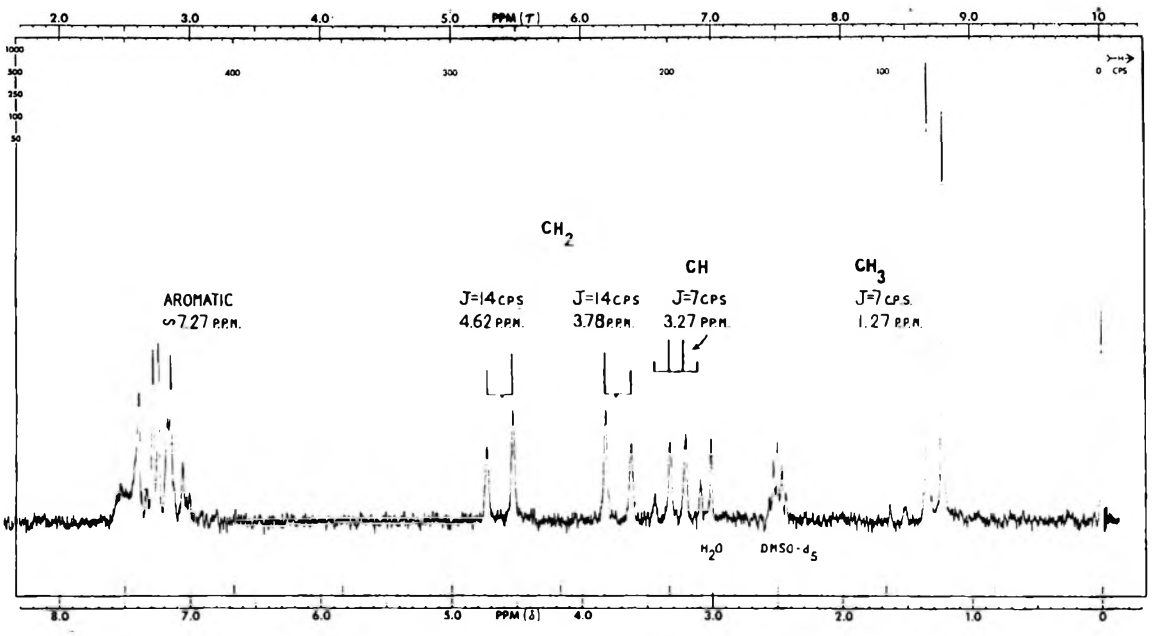

Figure 5.—Nmr spectrum of *cis*-sulfoxide VII.

intermolecular contacts are greater than the sums of the corresponding van der Waals radii (Table V).

The Nmr Data of the *trans*-Sulfoxide VI and *cis*-Sulfoxide VII.—The two diastereoisomeric sulfoxides VI and VII exhibit significant differences in the nmr spectra taken in dimethyl sulfoxide-d_6. The methyl protons appear as a doublet in the *trans* compound VI at δ 1.40 (J = 7 cps) (Figure 4) and in the *cis* compound VII at 1.27 (J = 7 cps) (Figure 5). The C_3-methine proton is shown as a quartet at δ 3.02 (J = 7 cps) in VI and at 3.27 (J = 7 cps) in VII. In the *trans*-sulfoxide VI the C_5-methylene protons appear as a singlet at δ 4.05 and in the *cis*-sulfoxide VII as an AB pattern at 3.78 (J = 14 cps) and 4.62 (J = 14 cps). When the nmr spectra were taken in dimethylformamide-d_7 at −30 and +150°, no significant changes were found. The last observation indicates that both sulfoxides exist in fairly rigid conformations.

Two sulfoxides, VI and VII, differ significantly in the rate of exchange of the C_3-methine proton with deuterium.[9,10] Both compounds were separately treated with 0.5 N NaOD in D_2O–dimethyl sulfoxide solution for 10 min and then acidified with CD_3COOD. In the recovered *cis*-sulfoxide VII, more than 75% of the C_3 proton was replaced with deuterium, as shown (Figure 6) by the disappearance of the signal for this proton (a quartet at δ 3.27, Figure 5) and by the collapse of the C_3-methyl doublet [δ 1.27 (J = 7 cps), Figure 5] to a singlet (Figure 6). In the same time, little or none of the C_3 proton in *trans*-sulfoxide VI was exchanged for deuterium (compare Figures 4 and 7). The inspection of Dreiding molecular models suggests that one should consider rigid distorted "boat" conformations for both

(9) S. Wolfe and A. Rauk, *Chem. Commun.*, 778 (1966).
(10) A. Rauk, E. Buncel, R. Y. Moir, and S. Wolfe, *J. Amer. Chem. Soc.*, **87**, 5498 (1965).

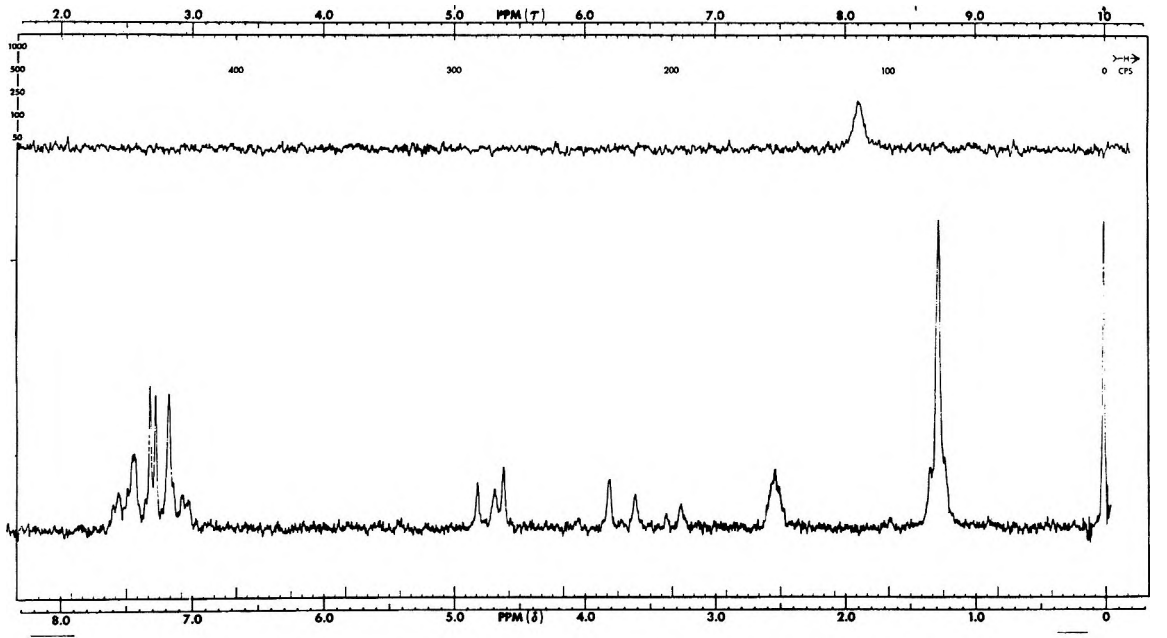

Figure 6.—Nmr spectrum of *cis*-sulfoxide VII after treatment with 0.5 *N* NaOD in D_2O–DMSO for 10 min.

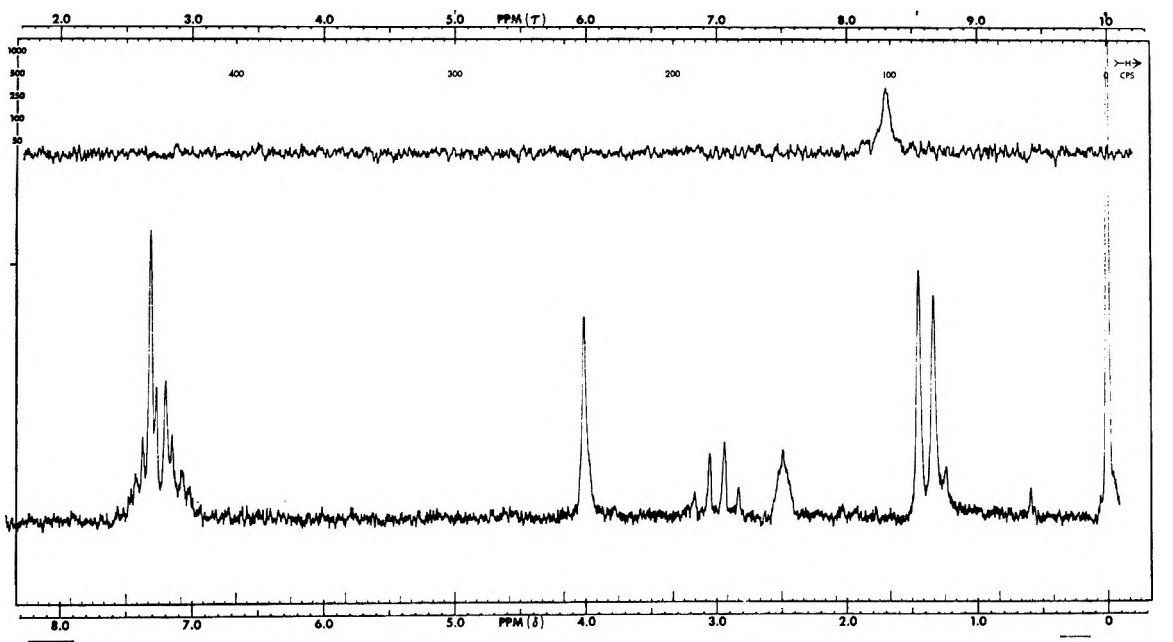

Figure 7.—Nmr spectrum of *trans*-sulfoxide VI after treatment with 0.5 *N* NaOD in D_2O–DMSO for 10 min.

TABLE V
INTERMOLECULAR DISTANCES (Å) LESS THAN 3.70 Å

$N_1 \cdots O_{10}$ (I)[a]	2.92
$C_2 \cdots O_{10}$ (I)	3.63
$C_9 \cdots O_{10}$ (II)[b]	3.47
$C_7 \cdots O_{12}$ (III)[c]	3.67
$C_6 \cdots O_{12}$ (III)	3.62
$O_{12} \cdots C_5$ (III)	3.46
$O_{12} \cdots C_6$ (III)	3.49
$C_7 \cdots C_7$ (IV)[d]	3.36
$C_7 \cdots C_6$ (IV)	3.69

[a] I refers to atom related to that in Table I by $1 - x$, $1 - y$, $1 - z$. [b] II refers to atom related to that in Table I by $1 - x$, $-y$, $1 - z$. [c] III refers to atom related to that in Table I by $-x$, $-1/2 + y$, $1/2 - z$. [d] IV refers to atom related to that in Table I by $-x$, $-y$, $1 - z$.

sulfoxides VI and VII. The X-ray analysis demonstrates such a conformation for the *trans* compound VI in the crystalline state. For the *cis* compound VII two distorted "boat" conformations may be considered, one with the oxygen of the sulfoxide group in pseudoequatorial position, the other with a pseudoaxial arrangement. The analysis of the nmr, ir, and uv data did not allow us to make any definite choice regarding one of these conformations. However, on the basis of the findings by Wolfe and Rauk,[9] the C_3-methine proton of VII, which exchanges rapidly with deuterium, should be positioned on a bisector of the angle between oxygen and lone electron pair of sulfur. From this viewpoint the conformation with the oxygen of the sulfoxide group in pseudoequatorial position would be favored.

At room temperature, the *trans*-sulfoxide VI is the thermodynamically more stable isomer. Individual treatment of both sulfoxides VI and VII for 3 days with 0.5 *N* sodium hydroxide in aqueous dimethyl sulfoxide solution gave the same equilibrium mixture which consisted of the *trans*-sulfoxide VI and *cis*-sulfoxide VII in a ratio of approximately 2:1, as indicated

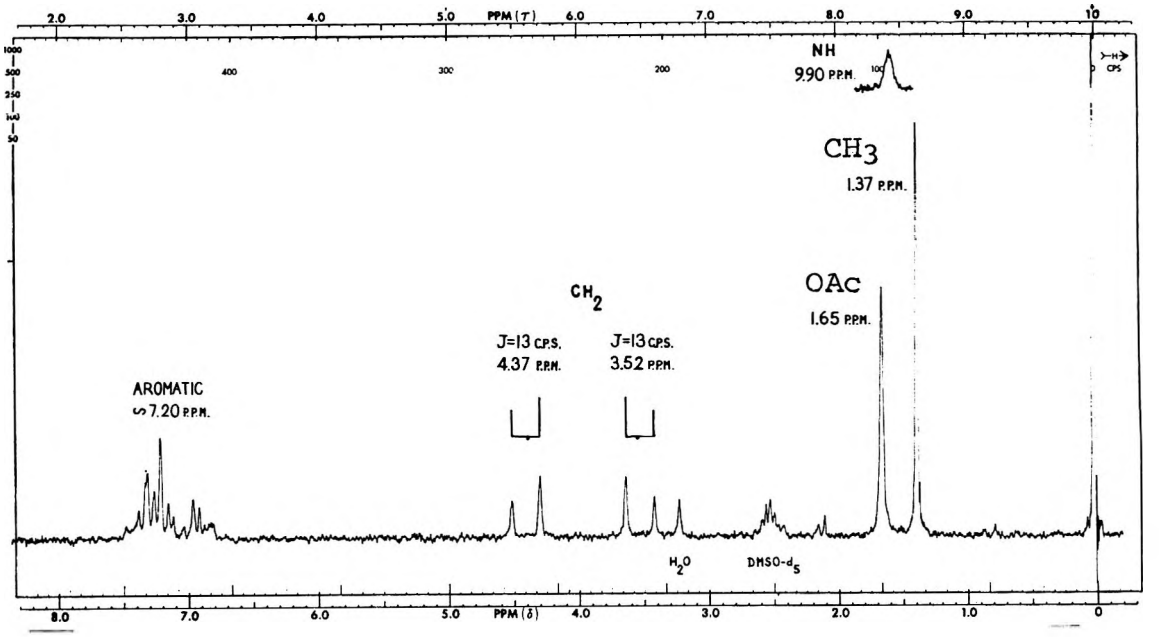

Figure 8.—Nmr spectrum of the rearranged product VIII.

by nmr. The isomerization occurred also under the conditions of Pummerer rearrangement, which was carried out with both sulfoxides VI and VII in boiling acetic anhydride for 5 hr. In each case, a 25:30:42 mixture of VI, VII, and rearranged product, 3-acetoxy-3,5-dihydro-3-methyl-4,1-benzothiazepin-2(1H)-one (VIII), was produced. The structure of VIII is supported by elemental analysis and by ir (the acetoxy group at 1730 and 1230 cm^{-1}) and nmr spectra [Figure 8, C_3-methyl singlet at δ 1.37, the acetoxymethyl singlet at 1.65, C_5-methylene protons' AB pattern at 3.58 and 4.48 (J = 13 cps), and aromatic protons' multiplet centered at 7.20].

Experimental Section[11]

(2-Nitrobenzylmercapto)lactic Acid (III).—To a solution of 69 g of *o*-nitrotoluene in 300 ml of carbon tetrachloride were added 90 g of bromosuccinimide and 2 g of benzoyl peroxide and the suspension was refluxed for 3 hr. After cooling, the succinimide was filtered, and the solution was evaporated to dryness. The crude *o*-nitrobenzylbromide (I) was dissolved in 200 ml of acetone and the solution was added dropwise to an ice-cold stirred solution of 53 g of thiolactic acid (II) and 40 g of sodium hydroxide in 300 ml water. The reaction mixture was stirred for 24 hr at room temperature, made strongly alkaline, extracted with methylene chloride, then acidified with acetic acid, and extracted again with methylene chloride. The last extract was washed with water, dried over anhydrous sodium sulfate, and evaporated. The crystalline residue was recrystallized from acetone. It gave 82 g of III: on heating, the crystals transformed at 127–128 and melted at 130–132°; ir ($CHCl_3$) 1712 (-COOH) and 1530 and 1336 cm^{-1} (-NO_2); uv (isopropyl alcohol), λ_{max} 250 mμ (ϵ 5200).

Anal. Calcd for $C_{10}H_{11}NO_4S$ (241.27): C, 49.78; H, 4.60; N, 5.81; S, 13.26. Found: C, 49.76; H, 4.43; N, 5.57; S, 13.21.

***dl*-3,5-Dihydro-3-methyl-4,1-benzothiazepin-2(1H)-one (V) from III.**—To a solution of 48.2 g of III in 1200 ml of methanol was added 5 g of 10% palladium-on-carbon catalyst, and the suspension was hydrogenated at room temperature at a pressure of 200–270 psi until the theoretical amount of hydrogen was absorbed. The catalyst was filtered and the solution was evaporated. The noncrystalline residue was dissolved in 2000 ml of xylene and the solution was refluxed for 2 hr with slow distillation of xylene, so that at the end the volume was reduced to 1000 ml. After cooling, the crystalline precipitate was filtered and recrystallized from acetone. It gave 28 g of V: mp 188–189°, after transformation at 183–187°; ir ($CHCl_3$) 3400 (>N—H) and 1680 cm^{-1} (>C=O); uv (isopropyl alcohol) λ_{max} 236 mμ (ϵ 6440).

Anal. Calcd for $C_{10}H_{11}NOS$ (193.27): C, 62.15; H, 5.74; N, 7.25; S, 16.59. Found: C, 61.97; H, 5.62; N, 7.26; S, 16.68.

***trans*- (VI) and *cis*-*dl*-3,5-Dihydro-3-methyl-4,1-benzothiazepin-2(1H)-one 4-oxide (VII) from V.**—To a suspension of 3.86 g of V in 250 ml of methanol at 0° was added 42 ml of 0.5 *N* sodium metaperiodate solution. The mixture was stirred for 1 hr in an ice bath, then for 3 hr at room temperature. The precipitated sodium iodate was filtered, and the solution was evaporated to dryness. To the residue was added 500 ml of acetone, the mixture was refluxed 30 min and filtered, and the filtrate was evaporated. The crystalline residue was recrystallized from acetone to give 3.4 g of a mixture of sulfoxides, mp 199–205°. Three grams of this mixture was chromatographed on a 100-g silica gel column. The fractions eluted with 15% ethyl acetate–85% benzene mixture were combined and recrystallized from acetone to give 2.25 g of VI: mp 220–223°; ir (Nujol) 1665, 1046, and 1065 cm^{-1}; uv (isopropyl alcohol) λ_{max} 264–266 mμ (ϵ 3050).

Anal. Calcd for $C_{10}H_{11}NO_2S$ (209.27): C, 57.40; H, 5.30; N, 6.69; S, 15.32. Found: C, 57.63; H, 5.52; N, 6.63; S, 15.12.

The fractions eluted with 75% ethyl acetate–25% benzene mixture and pure ethyl acetate were combined, and after recrystallization from acetone gave 0.75 g of VII: mp 246–248°; ir (Nujol) 1665 and 1045 cm^{-1}; uv (isopropyl alcohol) λ_{max} 225–226 mμ (ϵ 21,300) and 268–269 (2700).

Anal. Calcd for $C_{10}H_{11}NO_2S$ (209.27): C, 57.40; H, 5.30; N, 6.69; S, 15.32. Found: C, 57.14; H, 5.53; N, 6.67; S, 15.58.

***dl*-3-Acetoxy-3,5-dihydro-3-methyl-4,1-benzothiazepin-2(1H)-one (VIII) from VI or VII.**—A mixture of 2 g of VI and 40 ml of acetic anhydride was heated for 5 hr at 100°. After evaporation the residue was chromatographed on a 60-g silica gel column. The fractions eluted with a 2% ethyl acetate–98% benzene mixture were combined, and after recrystallization from acetone gave 1 g of VIII: mp 186–187°; ir (KBr) 3250 (>N—H), 1730, 1685, and 1250 cm^{-1}; uv (isopropyl alcohol) λ_{max} 207 mμ (ϵ 29,000) and 243 (5800).

Anal. Calcd for $C_{12}H_{13}NO_3S$ (251.31): C, 57.35; H, 5.19;

(11) Melting points are corrected. The nmr spectra were recorded on a Varian A-60 spectrometer using tetramethylsilane as internal reference.

N, 5.57; S, 12.76. Found: C, 57.53; H, 5.18; N, 5.45; S, 12.48.

The fractions eluted with a 15% ethyl acetate–85% benzene mixture were combined, and after crystallization from acetone gave 0.5 g of VI, mp 213°. This product was identified by comparison of the spectra with those of the sample prepared in the preceeding experiment. The fractions eluted with a 75% ethyl acetate–25% benzene mixture were combined and crystallized from acetone to give 0.6 g of VII, mp 242.5–245°. This material was also identified by comparison with the sample prepared in the preceding experiment.

The same result was obtained when the reaction was carried out with VII instead of VI.

X-Ray Analysis of *trans-dl*-3,5-Dihydro-3-methyl-4,1-benzothiazepin-2(1H)-one 4-oxide VI. Crystal Data and Data Collection.—Transparent needlelike crystals of VI were obtained by recrystallization from acetone. Cell parameters, as determined on a 60-mm precession camera using Mo K_α radiation (λ = 0.7107 Å), are a = 13.20 ± 0.02 Å, b = 4.71 ± 0.01 Å, c = 17.16 ± 0.03 Å, and β = 113° 15′ ± 15′. The volume of the unit cell is 980.2 × 10^{-24} cm³, and, assuming four molecules of $C_{10}H_{11}NO_2S$ (mol wt 209.27) in the unit cell, the calculated density is 1.417 g cm^{-3}; the value measured by flotation in a mixture of methylene dichloride and methyl iodide is 1.40 g cm^{-3}. Systematic absences, $h0l$, when $l = 2n + 1$, and $0k0$, when $k = 2n + 1$, determine the space group as $P2_1/c$ (C^5_{2h}, no. 14). $F(000)$ is 440, and the absorption coefficient for Cu K_α is 22.9 cm^{-1}.

A needle with an approximate equidimensional cross-sectional area was mounted about the needle axis (*i.e.*, b axis) and the levels of data $h0l$ to $h4l$ were collected on multiple-film packs with an equiinclination Weissenberg camera (Cu K_α radiation). The intensities were measured visually by comparison with a calibrated strip. Corrections were applied for Lorentz, polarization, spot shape,[12] and the K_{α_1}-K_{α_2} splitting effects. The intensities from the various hnl levels were initially placed on the same relative scale by consideration of the X-ray exposure times. A total of 1427 independent, nonzero structure amplitudes was obtained.

Structure Determination.—A three-dimensional Patterson synthesis indicated two possible positions for the sulfur atom (the y coordinate was 0.25 in each case and the z coordinate of one of the positions differed by 0.25 from that of the other position). A Fourier synthesis, with calculated signs based on the sulfur atom occupying one of these positions, gave a relatively clear picture of the molecule, but also contained a pseudoimage reflected through a false mirror plane at y = 1/4. Only in the case of the sulfoxide oxygen atom, however, did a pseudoimage appear as a possible genuine position. A further round of structure factor and Fourier calculations clearly indicated the *trans* configuration for the sulfoxide oxygen atom relative to the C-CH_3 group.

Least-squares refinement[13] on positional and isotropic thermal parameters for all atoms other than hydrogen reduced the crystallographic R factor, $R = \Sigma||F_o| - |F_c||/\Sigma F_o|$, to 0.14. The weighting scheme used has $\sqrt{w} = |F_o|/12.8$, when $|F_o| \leq 12.8$, and $\sqrt{w} = 12.8/|F_o|$, when $|F_o| > 12.8$; the quantity minimized was $\Sigma w||F_o| - |F_c||^2$. At the conclusion of the isotropic refinement, the interlevel scale factors were adjusted to give the best fit to the $\Sigma|F_c|$. Three cycles of least-squares refinement on positional and anisotropic parameters for all atoms other than hydrogen further reduced R to 0.11.

A difference map was calculated and the largest positive peaks corresponded to reasonable positions for most of the hydrogen atoms in the molecule. In the few instances, where doubt existed regarding the location of the hydrogen atoms, these atoms were positioned using standard criteria. Two cycles of least-squares refinement, varying positional and anisotropic thermal parameters on all atoms other than hydrogen, and including all hydrogen atoms in the structure factor calculations (B_θ = 3.0 Å²) gave a final R factor of 0.094 on all observed reflections.[14] The principal change in molecular dimensions involved the C-CH_3 distance which decreased from 1.55 to 1.525 Å.

While unobserved reflections were not included in the refinement, structure factors for these reflections were calculated from the final parameters. In no case were any significant discrepancies found.[14]

Registry No.—III, 1141-22-6; V, 18520-97-3; VI, 18520-98-4; VII, 18520-99-5; VIII, 18521-00-1.

Acknowledgment.—We thank Mr. James McKechnie[1a] and Miss Linda Kubina[1a] for considerable technical assistance, Mr. S. Traiman[1c] and Dr. V. Toome[1c] for the ir and uv spectra, and Dr. Al Steyermark[1c] for the elemental analysis. All crystallographic computations were made on the IBM 7094 at the University of Illinois. Fourier calculation were made with ERFR-3, written by J. H. van den Hende.

(12) D. C. Phillips, *Acta Cryst.*, **7**, 746 (1954).

(13) Using a modified version of the program written by P. K. Gantzel, R. A. Sparks, and K. N. Trueblood, "I. U. C. World List of Crystallographic Computer Programs," International Union of Crystallography, 1962, no. 384.

(14) The final values of h, k, l, F_o, and F_c and the anisotropic thermal parameters are available (order document no. NAPS-00094) from ASIS National Auxiliary Publications Service, c/o CCM Information Sciences, Inc., 22 West 34th Street, New York, N. Y. 10001; remit $1.00 for microfilm or $3.00 for photocopies.

Studies on the Formation and Transformation of Esters. LXXX.[1] On the Reaction of Isothiocyanates and Phenyl Isocyanate with Hydrazinoethanol and Hydrazinoethyl Hydrogen Sulfate

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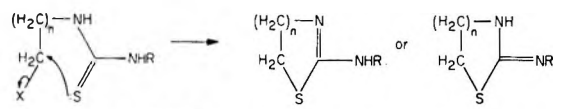
Reactions of hydrazinoethanol (**3a**) and hydrazinoethyl hydrogen sulfate (**3b**) with phenyl isothiocyanate take place at the substituted nitrogen atom. The corresponding monophenylthiocarbamoyl derivatives undergo ring closure to **6** in hydrochloric acid and 1 *N* sodium hydroxide, respectively. The N,N′-bis(phenylthiocarbamoyl) derivative of **3b** is converted into **7** in alkaline medium, whereas that of **3a** is transformed into **6** and **9** (**a** or **b**) in acid medium. Monothiocarbamoylation of **3b** with *o*-methoxycarbonylphenyl isothiocyanate occurs at the unsubstituted nitrogen atom, yielding **11a** upon cyclization in HCl. Monophenylcarbamoylation of **3a** or **3b** takes place at the substituted nitrogen atom. The reaction of **3a** with a molar excess of phenyl isocyanate affords the N,N′-bis(phenylcarbamoyl) derivative. The reaction of **3b**, however, appears to afford mixtures of mono- and N,N′-bis(phenylcarbamoyl) derivatives; cyclization in 1 *N* NaOH yields **14** and **15**, respectively.

Previous papers in this series have reported that the N-thiocarbamoyl derivatives of 2-aminoethyl and 3-aminopropyl alcohols[3] or their orthophosphate[3,4] and sulfate monoesters[4-6] undergo ring closure to yield heterocyclic bases containing either endo- (**1a**) or exocyclic (**1b**) C=N double bonds.



X=OH, OPO_3H_2 or OSO_3H, n=1 or 2 **1a** **1b**

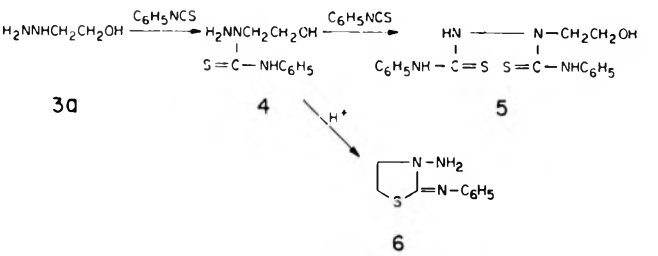
N-Arylcarbamoyl aminoethyl or aminopropyl sulfate monoesters also undergo ring closure to yield five- or six-membered cyclic ureas **2**.[7]

2

Therefore, it was of further interest to extend these reactions to hydrazinoethanol (**3a**) and its sulfate monoester (**3b**).[8]

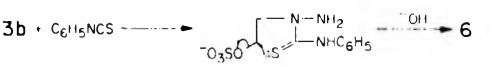
Results and Discussion

Thiocarbamoylation of Hydrazinoethanol (3a) and Hydrazinoethyl Hydrogen Sulfate (3b).—The reaction of **3a** with an equimolar amount of phenyl isothiocyanate in dioxane occurs at the substituted nitrogen atom producing **4** in 86% yield. In the presence of a molar excess of reagent **3a** is converted into the N,N′-bis(thiocarbamoyl) derivative **5** in 80% yield.



3a **4** **5** **6**

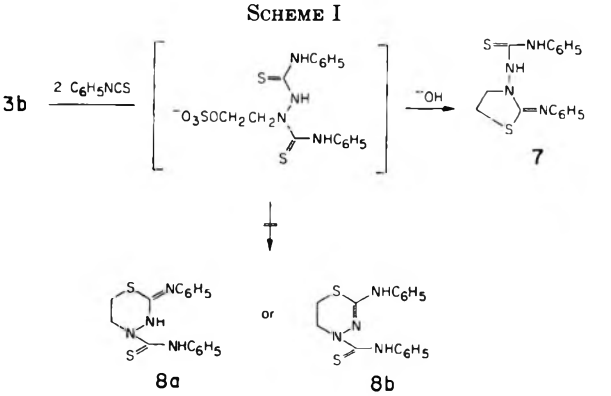
Equimolar amounts of hydrazinoethyl hydrogen sulfate (**3b**) and phenyl isothiocyanate are allowed to react in aqueous dioxane in the presence of an equivalent quantity of sodium hydroxide. When the crude derivative is isolated and treated with 1 *N* sodium hydroxide, 3-amino-2-(phenylimino) thiazolidine (**6**) is



obtained in 30% yield as the only cyclic product. In its high resolution mass spectrum, major fragments, $C_9H_{10}N_2S^+$ and $C_9H_9N_2S^+$, corresponding to loss of NH and NH_2 from the molecular ion, are consistent with the five-membered heterocyclic structure. Compound **6** is also obtained in 26% yield by warming **4** overnight in concentrated hydrochloric acid.

Treatment of **3b** with a molar or greater excess of phenyl isothiocyanate in alkaline aqueous dioxane (pH 8.5–9.0), followed by warming overnight at 40°, produces 3-(N-phenylthiocarbamoylamino)-2-(phenylimino)thiazolidine (**7**) in 38% yield. Mass spectral and nmr data make it possible to distinguish between **7** and alternative structures **8a** and **8b** (Scheme I).

SCHEME I



3b **7** **8a** **8b**

(1) For the previous paper in this series, see E. Cherbuliez, O. Espejo, B. Willhalm, and J. Rabinowitz, *Helv. Chim. Acta*, **51**, 241 (1968).

(2) National Academy of Sciences–National Aeronautics and Space Administration-Senior Research Associate.

(3) E. Cherbuliez, Br. Baehler, H. Jindra, G. Weber, G. Wyss, and J. Rabinowitz, *ibid.*, **48**, 1069 (1965).

(4) E. Cherbuliez, Br. Baehler, S. Jaccard, H. Jindra, G. Weber, G. Wyss, and J. Rabinowitz, *ibid.*, **49**, 807 (1966).

(5) E. Cherbuliez, Br. Baehler, O. Espejo, S. Jaccard, H. Jindra, and J. Rabinowitz, *ibid.*, **49**, 2408 (1966).

(6) E. Cherbuliez, Br. Baehler, O. Espejo, H. Jindra, B. Willhalm, and J. Rabinowitz, *ibid.*, **50**, 334 (1966).

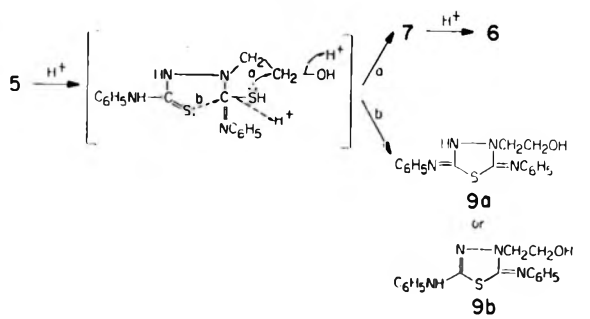
(7) E. Cherbuliez, S. Jaccard, H. Jindra, F. Tissot, and J. Rabinowitz, *ibid.*, **49**, 2400 (1966).

(8) E. Cherbuliez, O. Espejo, H. Jindra, and J. Rabinowitz, *ibid.*, **50**, 2019 (1967).

The nmr spectrum of **7** contains a two-proton, D_2O-exchangeable singlet at δ 9.86. The assignment of this singlet to the protons of the thiourea group is supported by the analogous assignment of a signal at δ 9.50 in the nmr spectrum of **5**. Protons bound to nitrogen in **8a** and **8b** would be expected to give rise to two singlets.[9] Furthermore, the high resolution mass spectrum of **7** contains major fragments, $C_9H_{10}N_2S^+$ and $C_9H_9N_2S^+$, which are difficult to reconcile with **8a** or **8b**, but are consistent with the proposed structure. These two fragments appear as major ions in the mass spectrum of **6**.

Two products are isolated after **5** (or the crude mixture resulting from reaction of **3a** with a molar excess of phenyl isothiocyanate) is heated overnight in concentrated hydrochloric acid. In addition to **6** obtained in 18% yield, a second compound obtained in 13% yield is assigned structure **9** (a or **b**, Scheme II).

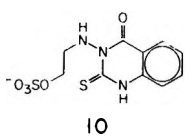
SCHEME II



A clearcut choice between the tautomeric structures cannot be made with available data.

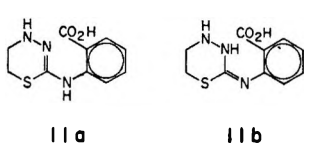
Acid-catalyzed cyclization of **5** apparently proceeds by two paths involving either one or the other sulfur atom (Scheme II). Either path a (displacement of water gives rise to **7** and ultimately **6** by hydrolysis of the thiocarbamoyl group) or path b (the displacement of hydrogen sulfide furnishes **9a** or **b**).

Treatment of **3b** with an equimolar amount of *o*-methoxycarbonylphenyl isothiocyanate yields a crude product whose infrared (ir) spectrum contains a broad band at 1675 cm^{-1}, which is suggestive of a 2-thiono-4-tetrahydroquinazolinone structure **10**.[10]



10

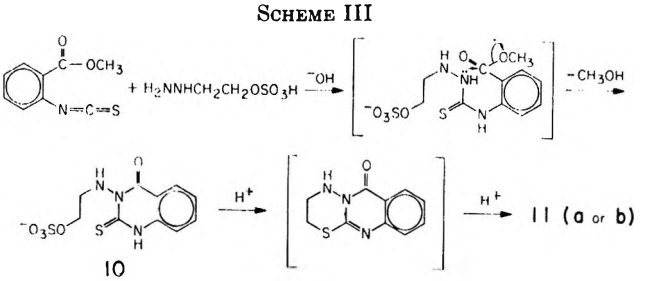
Refluxing the crude product overnight in hydrochloric acid converts it in 26% over-all yield into what appears to be either **11a** or **11b**. The absence of major fragments in the mass spectrum corresponding to loss of NH and NH_2 from the molecular ion, which was observed in the spectra of **6** and **7**, supports the six-membered heterocyclic structure. Of particular significance in the nmr spectrum is a triplet at δ 6.03 (J = 5.0 Hz) assigned to an amino proton adjacent to a methylene group. With the available data it is not possible to make a definite choice between structures **11a** and **11b**. However, the ultraviolet (uv) spectrum with maxima at 222 and 310 mμ is identical with that of 2-(*o*-carboxyphenylamino)-5,6-dihydro-4H-1,3-thiazine[10] and suggests the structure **11a** containing an endocyclic CN double bond.



11a **11b**

A probable pathway for formation of **11a** or **b** is presented in Scheme III. Thiocarbamoylation of **3b** at the unsubstituted nitrogen followed by intramolecular acylation produces **10**. Treatment of **10** with refluxing hydrochloric acid yields **11a** or **b** through ring closure and hydrolysis of the lactam function.

SCHEME III



Monothiocarbamoylation of hydrazinoethyl derivatives with phenyl isothiocyanate apparently takes place at the substituted nitrogen atom. Similar results have been reported for methyl- and isopropylhydrazine.[11] In direct contrast, the reaction of hydrazinoethyl sulfate (**3b**) with *o*-methoxycarbonylphenyl isothiocyanate involves the *un*substituted nitrogen atom. The probable and simplest explanation is that the proximity of the *o*-methoxycarbonyl to the isothiocyanate group may well cause sufficient steric crowding in the transition state for thiocarbamoylation that reaction at the unsubstituted nitrogen atom is preferred.[12]

Mono- and di-N,N alkylations of monosubstituted hydrazines (H_2NNHR) with organic halides and sulfates are known to take place at the substituted nitrogen atom. Only in the case of severe steric crowding (*e.g.*, triphenylmethylation of triphenylmethylhydrazine) is alkylation at the unsubstituted nitrogen atom preferred.[11] Acylation, however, is much more sensitive to steric effects. Reactions with anhydrides occur primarily at the substituted nitrogen atom, whereas reactions with esters and acid chlorides take place at either or both nitrogen atoms.[11] These observations, coupled with our results, suggest that the sensitivity to steric crowding in the transition state for thiocarbamoylation lies between those for alkylation and acylation.

Phenylcarbamoylation of Hydrazinoethanol (3a) and Hydrazinoethyl Hydrogen Sulfate (3b).—The reaction of **3a** with an equimolar amount of phenyl isocyanate

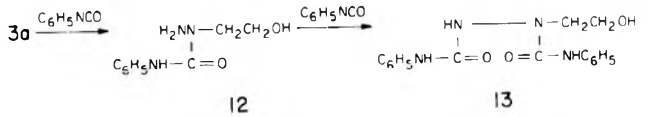
(9) The proton on the amino nitrogen of **8a** and **8b** would be expected to appear at higher field (δ < 9.0) since a similar proton in **9** appears at δ 8.25.

(10) E. Cherbuliez, B. Willhalm, O. Espejo, S. Jaccard, and J. Rabinowitz, *Helv. Chim. Acta*, **50**, 1440 (1967).

(11) P. A. S. Smith, "Nitrogen Compounds," Vol. II, W. A. Benjamin, Inc., New York-Amsterdam, 1966, Chapter 9, pp 119–201.

(12) Acylation of hydrazinoethanol (**3a**) with methyl benzoate required elevated temperatures, thus excluding the possibility of an initial acylation of **3b** with *o*-methoxycarbonylphenyl isothiocyanate.

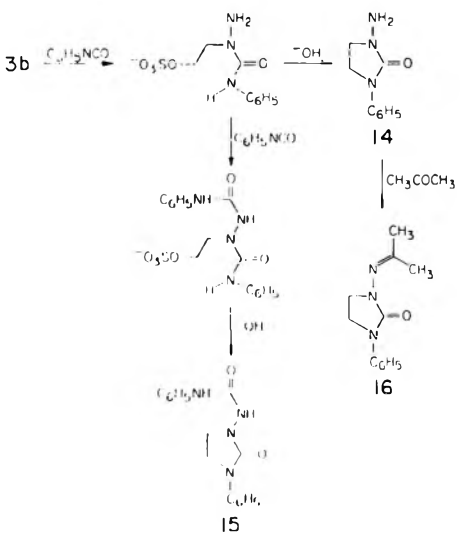
in dioxane produces **12** in 79% yield. Reaction with a molar excess of reagent furnishes **13** in 90% yield.



12 **13**

Reactions of **3b** with varying amounts of phenyl isocyanate are carried out in aqueous dioxane containing an amount of sodium hydroxide equivalent to that of **3b**. The crude carbamoyl sulfates, after treatment with 1 *N* sodium hydroxide, furnish mixtures of 3-amino-1-phenyl-2-imidazolidinone (**14**) and 3-(N-phenyl-carbamoylamino)-1-phenyl-2-imidazolidinone (**15**) as the major products in total yields ranging from 25 to 50% (Scheme IV).

SCHEME IV



14 **16** **15**

The ir spectrum with carbonyl absorption at 1715 cm^{-1} and the high resolution mass spectrum with major fragments $C_9H_{10}N_2O^+$ and $C_9H_9N_2O^+$, corresponding to loss of NH and NH_2 from the molecular ion, are clearly characteristic of **14**. When acetone is used as a solvent in the isolation of **14**, the Schiff base 3-isopropylidenamino-1-phenyl-2-imidazolidinone (**16**) is obtained (Scheme IV).

Structure **15** is consistent with strong bands in its ir spectrum at 1720 and 1642 cm^{-1} which are characteristic of a carbonyl group in five-membered cyclic and open ureas, respectively.[13] Major fragments in the high resolution mass spectrum, $C_9H_{10}N_2O^+$ and $C_9H_9N_2O^+$, correspond to loss of C_6H_5NHCON and $C_6H_5NHCONH$ from the molecular ion or NH and NH_2 from the most abundant ion $C_9H_{11}N_3O^+$.

The reaction between equimolar quantities of **3b** and phenyl isocyanate followed by cyclization of the crude product furnishes a 50% combined yield of **14** and **15**, in which **15** comprises 15% of the total mixture. Apparently, the reaction of the monophenylcarbamoyl derivative of **3b** with a second molecule of reagent at the unsubstituted nitrogen atom can compete with monophenylcarbamoylation of unreacted **3b** at the substituted nitrogen atom. Phenylcarbamoylation of **3b** somehow enhances the reactivity of the unsubstituted nitrogen atom to phenyl isocyanate.

Exclusive N,N′ diderivatization using large excesses of phenyl isocyanate cannot be achieved owing to facile reaction of the reagent with water. Mixtures of **14** and **15** are produced with **15** predominating.

Like monophenylthiocarbamoylation, monophenylcarbamoylation of hydrazinoethyl derivatives takes place at the substituted nitrogen atom. These observations are similar to those made in reactions of methyl and isopropyl hydrazine with phenyl isocyanate and cyanic acid.[11]

Experimental Section

Materials.—Hydrazinoethanol, phenyl isothiocyanate, and phenyl isocyanate were used as obtained commercially. Hydrazinoethyl hydrogen sulfate was prepared from equimolecular amounts of hydrazinoethanol and concentrated sulfuric acid.[8] *o*-Methoxycarbonylphenyl isothiocyanate was prepared from methyl anthranilate and thiophosgene.[14]

Spectroscopic Data.—Melting points are uncorrected. Ir spectra were measured on a Perkin-Elmer 521 grating ir spectrometer. Uv spectra were obtained on a Cary 14 recording spectrophotometer. Unless otherwise specified, nmr spectra were recorded with an HR-100 Varian spectrometer with dimethyl sulfoxide-d_6 as solvent and capillary tetramethylsilane as internal standard. All mass spectra were obtained on a Consolidated Electrodynamics Corp. Model 21-110B high resolution mass spectrograph.[15]

Thiocarbamoylation of Hydrazinoethanol (3a) and Hydrazinoethyl Hydrogen Sulfate (3b). N-Phenyl-N′-hydroxyethyl-N′-aminothiourea (4).—A solution of 13.5 g (0.1 mol) of phenyl isothiocyanate in 30 ml of dioxane was added to 7.6 g (0.1 mol) of hydrazinoethanol in 50 ml of dioxane and stirred overnight at 30°. The dioxane was evaporated and the residue was stirred with 75 ml of anhydrous ether to bring about crystallization. The solid was filtered and dried under vacuum. The filtrate was evaporated to dryness and treated again with ether, affording a second crop of material for a total of 18.2 g (86%) of the thiourea **4**: mp 84–85°; ir (KBr) 3220 (NH) and 3340 cm^{-1} (OH); nmr δ 10.00 (s, 1, **NH**), 7.27 (m, 5, C_6H_5), 5.04 (s, 2, NH_2), 4.78 (t, 1, J = 5.0 Hz, CH_2OH), 4.06 (t, 2, J = 5.7 Hz, CH_2N), 3.70 ppm (t, 2, J = 5.9 Hz, CH_2O); mass spectrum[15] (70 eV)—211 (6.5), 193 (0.8), 177 (1.0), 167 (2.5), 135 (100) 119 (1.1), 103 (7.3), 93 (17), 77 (74).

Anal. Calcd for $C_9H_{13}N_3OS$: C 51.10; H, 6.18; N, 19.8; S, 15.2. Found: C, 51.10; H, 6.43; N, 19.7; S, 15.1.

N,N′-Bis(phenylthiocarbamoyl)hydrazinoethanol (5).—Solutions of 13.5 g (0.1 mol) of phenyl isothiocyanate in 30 ml of dioxane and 3.8 g (0.05 mol) of hydrazinoethanol in 50 ml of dioxane were treated as in the preparation of **4** to yield 13.8 g (80%) of **5**: mp 114–117°; ir (KBr) 3230 (NH) and 3350 cm^{-1} (OH); nmr δ 10.03 (s, 1, **NH**), 9.62 (s, 1, **NH**), 9.50 (s, 1, NH), 7.31 (m, 10; $2C_6H_5$), 4.30 (s, 1, **OH**), and 3.68 ppm (m, 4, NCH_2CH_2O); mass spectrum[15] (70 ev)—the molecular ion could not be observed even under mildest volatilization conditions (temperature of sample <140°) because of the elimination of H_2S and the formation of compound **9a** or **b**, the resulting spectrum being identical in every respect with that of **9a** or **b**.

Anal. Calcd for $C_{16}H_{18}N_4OS_2$: C, 55.20; H, 5.23; N, 16.2; S, 18.5. Found: C, 55.60; H, 5.54; N, 16.4; S, 17.7.

3-Amino-2-(phenylimino)thiazolidine (6). A. From Treatment of 4 with Concentrated Hydrochloric Acid.—A solution of 2.11 g (0.01 mol) of **4** in 15 ml of concentrated hydrochloric acid was

(13) K. Nakanishi, "Infrared Absorption Spectroscopy-Practical," Holden-Day, Inc., San Francisco, Calif., and Nankodo Co., Ltd., Tokyo, 1962, p 116.

(14) J. C. Howard and G. Klein, *J. Org. Chem.*, **27**, 3701 (1962).

(15) Accurate mass determinations were made from measurements of line positions on ion-detecting photoplates. Relative ion abundance was measured from low resolution scans with an electron multiplier detector. Where elemental compositions are not reported, only the low resolution spectrum was obtained. For high resolution spectra, we list, in addition to the composition and relative intensity, the difference in millimass units between the found mass and the exact mass calculated for an ion of the listed composition. As an example, the molecular ion of **14** has the composition $C_9H_{11}N_3O$ and is the most intense peak in the spectrum; its found mass exceeds that of the calculated mass by 0.5 millimass units; thus, this ion is reported as $C_9H_{11}N_3O$ (100) 0.5. In general, we list the most abundant ion in each 14-mass unit interval ($2 + 14n <$ nominal mass $\leq 16 + 14n$).

heated overnight (100°), diluted with water to 60 ml, filtered, and neutralized with concentrated sodium hydroxide in an ice bath. The oil that separated was washed with cold water and dissolved in a few drops of methanol. Water was added until turbidity persisted. In a few days, 0.5 g (26%) of crystalline **6** was obtained: mp 86–88°; ir (KBr) 1618 (C=N) and 3420 and 3280 cm^{-1} (NH_2); uv max 250 mμ (ε 9980); nmr δ 7.08 (m, 5, C_6H_5), 4.66 (s 2, NH_2), 3.54 (t, 2, J = 7.0 Hz, CH_2N), and 3.10 ppm (t, 2, J = 7.0 Hz, CH_2S); mass spectrum[15] (70 eV)—$C_9H_{11}N_3S$ (85) 0.0, $C_9H_{10}N_2S$ (2.7) −1.3, $C_9H_9N_2S$ (3.0) −0.4, $C_7H_7N_3$ (2.0) 0.5, $C_8H_8N_3$ (5.5) 0.0, C_7H_5NS (27) −0.8, $C_7H_6N_2$ (5.1) −0.2, C_7H_6N (16) −0.8, C_6H_5N (5.5) 0.1, C_6H_5 (100) 0.8.

Anal. Calcd for $C_9H_{11}N_3S$: C, 56.0; H, 5.75; N, 21.8; S, 16.6. Found: C, 55.9; H, 5.74; N, 21.2; S, 16.0.

B. From Treatment of the Monophenylthiocarbamoyl Derivative of 3b with 1 *N* Sodium Hydroxide.—To a solution of 1.42 g (0.01 mol) of **3b** in 40 ml of 50% aqueous dioxane adjusted to pH 8.5–9.0 with 1 *N* sodium hydroxide was added 1.35 g (0.01 mol) of phenyl isothiocyanate in 10 ml of dioxane. The pH was maintained at 8.5–9.0 by the addition of 1 *N* sodium hydroxide to a total of 10 ml (including the amount added initially). After stirring overnight, the solution was evaporated to dryness. The phenylthiocarbamoyl derivative of **5b** was dissolved in methanol and filtered. The filtrate was again evaporated to dryness and the residue was washed with ether, dried, and stirred with 20 ml of 1 *N* sodium hydroxide. The precipitate was collected after a few hours, washed with a small quantity of cold water, and dried yielding 0.5 g (26%) of **6**. Additional material (0.2 to 0.3 g) may be obtained by extracting the aqueous alkaline solution with chloroform.

3-(N-Phenylthiocarbamoylamino)-2-(phenylimino)thiazolidine (7).—To a solution of 1.92 (0.01 mol) **3b** in 30 ml of water and 20 ml of dioxane at pH 8.5–9.0 was added a solution of 5.4 g (0.04 mole) of phenyl isothiocyanate in 20 ml of dioxane with the pH maintained by the simultaneous addition of 1 *N* sodium hydroxide. After addition of the isothiocyanate and at least 20 ml of the base, the temperature was raised to 40°. The pH was adjusted if necessary and the reaction continued overnight. Dilution with 40 ml of water afforded a precipitate which after recrystallization from methanol yielded 1.25 g (38%) of **7**: mp 205–206°; ir (KBr) 1600 (C=N) and 3150 cm^{-1} (NH); uv max (95% C_2H_5OH) 250 mμ (ε 27,200); nmr δ 9.86 (s, 2, HNCSNH), 7.44 (m, 10, 2 C_6H_5), 4.15 (t, 2, J = 7.0 Hz, CH_2N), and 3.85 ppm (t, 2, J = 7.0 Hz, CH_2S); mass spectrum[15] (70 eV)—328 (0.8), 295 (3.2) 261 (0.9) 236 (1.1), 218 (1.0), 210 (0.9), $C_9H_{11}N_3S$ (21) −0.4 $C_9H_{10}N_2S$ (3.7) −0.4, $C_9H_9N_2S$ (4.6) 0.7, 162 (1.7), C_8H_7NS (2.4) 0.0, C_7H_5NS (62) −0.4, $C_7H_6N_2$ (6.2) −0.5, C_7H_8N (14) 0.2, C_6H_7N (27) 0.1, C_6H_5 (100) −0.6.

Anal. Calcd for $C_{16}H_{16}N_4S_2$: C, 58.5; H, 4.91; N, 17.0; S, 19.6. Found: C, 58.5; H, 5.11; N, 16.8; S, 19.4.

2,5-Diphenylimino-3-hydroxyethyl-1,3,4-thiadiazolidine (9a).—Solutions of 0.76 g (0.01 mol) of hydrazinoethanol (**3a**) in 20 ml of dioxane and 2.7 g (0.02 mol) of phenyl isothiocyanate in 20 ml of dioxane were slowly mixed at room temperature and stirred overnight. The solvent was evaporated and the residue (crude **5**) was heated (100°) overnight with 40 ml of concentrated hydrochloric acid. (Alternatively, **5** can be treated directly with concentrated acid, but it is not necessary to isolate pure **5** to convert it into **9a** or **b**.) Dilution of the reaction mixture to 200 ml with water yielded a precipitate which after recrystallization in boiling ethanol furnished 0.4 g (13%) of **9a** or **b**: mp 164–165°; ir (KBr) 1618 (C=N), 1600 (C=N), 3300 (OH), and 3140 cm^{-1} (NH); uv max (95% C_2H_5OH) 232 mμ (ε 16,300) and 257 (19,750); nmr δ 8.25 (s, 1, NH), 7.40 (m, 10, $2C_6H_5$), 4.72 (t, 1, J = 5.7 Hz; CH_2OH), 4.03 (t, 2, J = 6.0 Hz, CH_2N), 3.69 ppm (t, 2, J = 6.0 Hz; CH_2O); mass spectrum[15] (70 eV)—$C_{16}H_{16}N_4OS$ (9.8) 0.7, $C_{16}H_{14}N_4S$ (0.7) 2.3, $C_{15}H_{13}N_4S$ (0.6) −0.5, $C_{14}H_{12}N_4S$ (24) 1.2 $C_{14}H_{10}N_3S$ (0.4) −1.0, $C_{14}H_{11}N_4$ (2.5) 0.5, $C_{13}H_{10}N_3$ (1.7) 0.2, $C_{13}H_{11}N_2$ (3.9) −1.4, $C_{13}H_8N$ (2.2) −0.8, $C_{12}H_9N$ (1.4) 0.5, $C_7H_5N_2S$ (2.9) 1.2, $C_8H_8N_3$ (2.2), 0.2, C_7H_6NS (8.0) −0.5, $C_7H_6N_2$ (29) 0.1, C_7H_6N (12) 0.3, C_6H_6N (13) −1.0, C_6H_5 (100) 0.0.

Anal. Calcd for $C_{16}H_{16}N_4OS$: C, 61.3; H, 5.20; N, 17.9; S, 10.3. Found: C, 61.3; H, 5.40; N, 17.6; S, 11.1.

When the aqueous filtrate above was neutralized with concentrated sodium hydroxide and cooled an oil was formed. The oil was washed several times with cold water, dissolved in methanol, and filtered. Water was added until turbidity persisted. Precipitation of 0.3 g (16%) of **6** occurred in a few days.

2-(*o*-Carboxyphenylamino)-5,6-dihydro-4H-1,3,4-thiadiazine (11a).—Solutions of 3.84 g (0.02 mol) of **3b** in 100 ml of 50% aqueous dioxane (pH 8.5–9.0) and of 3.95 g (0.02 mol) of *o*-methoxycarbonylphenyl isothiocyanate in 10 ml of dioxane were treated as in synthesis B of **6**. The residue [ir (KBr) 1675 cm^{-1} (C=O)] obtained after evaporation of the aqueous dioxane was refluxed overnight in 100 ml of 1 *N* hydrochloric acid. The mixture was evaporated to dryness, the residue was neutralized with 2 *N* sodium hydroxide, and the alkaline solution was filtered. When the filtrate was acidified with hydrochloric acid, a pasty precipitate formed which after crystallization from 50 ml of hot methanol yielded 0.62 g (26%) of **11a** or **b**: mp 185–186°; ir (KBr) 1660 (C=N) 1720, (C=O), 3310 (NH), and 3450 cm^{-1} (OH); uv max (95% C_2H_5OH) 222 mμ (ε 59,100) and 311 (4850); nmr δ 11.52 (s, 1, CO_2H or NH), 7.60 (m, 4, C_6H_4), 6.03 (t, 1, J = 5.0 Hz, $NHCH_2$), 3.30 (s, 1, CO_2H or NH and HDO), 3.11 (t, 2, J = 6.5 Hz, CH_2N), and 2.90 ppm (t, 2, J = 6.5 Hz, CH_2S); mass spectrum[15] (70 eV)—$C_{10}H_{11}N_3O_2S$ (1.0) 0.9, $C_{10}H_9N_3O_2$ (0.9) 0.4, $C_9H_8N_3O_2$ (38) −0.4, $C_8H_7N_3O_2$ (6.7) −0.1, $C_8H_7N_2O_2$ (100) 0.4, $C_9H_4NO_2$ (68) −0.5, $C_7H_5N_2O$ (1.7) 0.3, C_7H_5NO (34) −0.8, C_6H_4NO (3.1) −0.7, C_6H_4O (33) −0.4, C_2H_6NS (7.7) −1.3.

Anal. Calcd for $C_{10}H_{11}N_3O_2S$: C, 50.7; H, 4.65; N, 17.7; S, 13.5. Found: C, 50.9; H, 4.59; H, 17.2; S, 13.0.

Phenylcarbamoylation of Hydrazinoethanol (3a) and Hydrazinoethyl Hydrogen Sulfate (3b). N-Phenyl-N′-hydroxyethyl-N′-aminourea (12).—A solution of 2.38 g (0.02 mol) of phenyl isocyanate in 20 ml of dioxane was added to 1.52 g (0.02 mol) **5a** dissolved in 20 ml of dioxane and stirred overnight. The solvent was evaporated and the residue was dissolved in a minimum amount of acetone. The crystalline product obtained upon addition of anhydrous ether was removed by filtration and the filtrate was evaporated to dryness. A second crop of crystals was obtained when the residue was treated as before, bringing the total yield of **12** to 3.10 g (79%): mp 112–113°; ir (KBr 1645 (C=O), 3310 (NH), and 3400 cm^{-1} (OH); nmr δ 8.90 (s, 1, NH), 7.20 (m, 5, C_6H_5), 4.65 (s, 2, NH_2), 4.60 (t, 1, J = 5.0 Hz, CH_2OH), and 3.50 ppm (m, 4, NCH_2CH_2O); mass spectrum[15] (70 eV)—$C_9H_{13}N_3O_2$ (18) −0.5, C_7H_5O (13) −0.9, C_6H_7N (6.9) −0.5, $C_2H_5N_2O$ (55) −0.4, C_3H_5 (6.7) −0.7, CH_5N_2 (100) −0.3.

Anal. Calcd for $C_9H_{13}N_3O_2$: C, 55.2; H, 6.72; N, 21.6. Found: C, 55.6; H, 6.73; N, 21.7.

N,N′-Bis(phenylcarbamoyl)hydrazinoethanol (13).—A solution of 7.14 g (0.06 mol) of phenyl isocyanate in 40 ml of dioxane was added to 2.28 g (0.03 mol) of **3a** dissolved in 20 ml of dioxane and stirred overnight. The solution was concentrated and anhydrous ether was added to cause precipitation of **13**. A second crop was obtained by reducing the volume and adding ether as before, bringing the total yield of **13** to 8.5 g (90%): mp 180–182°; ir (KBr) 1670 (C=O), 1657 (C=O), 3300 (NH), and 3400 cm^{-1} (OH); nmr δ 8.92 (s, 1, NH), 8.78 (s, 1, NH), 8.10 (s, 1, NH), 7.17 (m, 10, $2C_6H_5$), 4.80 (t, 1, J = 5.0 Hz, CH_2OH), and 3.48 ppm (m, 4, NCH_2CH_2O); mass spectrum[15] (70 ev)—$C_{16}H_{18}N_4O_3$ (3.1) −1.7, $C_{10}H_{11}N_3O_3$ (2.8) −0.6, $C_{10}H_9N_3O_2$ (0.8) −1.1, $C_9H_{13}N_3O_2$ (9.5) −1.6 $C_9H_{11}N_3O$ (10) 0.5, $C_8H_{10}N_3O$ (13) −0.7, $C_7H_8N_2$ (3.0) −0.5, C_7H_5NO (65) −1.0, C_7H_7N (2.0) −0.1, C_6H_7N (100) −1.3, C_6H_5 (35) −1.3.

Anal. Calcd for $C_{16}H_{18}N_4O_3$: C, 61.0; H, 5.78; N, 17.8. Found: C, 61.5; H, 5.84; N, 17.5.

3-Amino-1-phenyl-2-imidazolidinone (14) and 3-(N-Phenylcarbamoylamino)-1-phenyl-2-imidazolidinone (15).—A solution of 1.92 g (0.01 mol) of **3b** in 3–4 ml of water was brought to pH 8.5–9.0 with 10 ml of 1 *N* sodium hydroxide and diluted with 13 ml of dioxane. A solution of 1.19 g (0.01 mol) of phenyl isocyanate in 10 ml of dioxane was added and stirred for 5 hr. The reaction mixture was then diluted to 75 ml with water and allowed to stir an additional 1 hr. Diphenylurea (0.151 g, 0.8 mmol) was removed by filtration and the filtrate was extracted twice with 30-ml portions of chloroform. The aqueous solution was evaporated giving carbamoylated sodium hydrazinoethyl sulfate as an amorphous, hygroscopic solid. The crude salt was dissolved in 25 ml of 1 *N* sodium hydroxide and warmed 3 hr at 55° during which time gas evolved and a solid precipitated. The solid was filtered and the filtrate (A) was set aside. According to tlc on silica gel Gf (methylene chloride:methanol, 24:1), the solid consisted of only two components. The solid was dissolved in hot methanol, filtered, and cooled, producing 0.223 g (8%) (based on **3b**) of **15**: mp 254–256° dec; ir (KBr) 1720 (cyclic C=O), 1642 (C=O), and 3310 cm^{-1} (NH); uv max (CH_3OH) 242 mμ (ε 2900), and 270 and 280 (shoulders); nmr δ 8.76

(s, 1, NH), 8.24 (s, 1, NH), 7.22 (m, 10, $2C_6H_5$), and 3.56 ppm (m, 4, NCH_2CH_2N); mass spectrum[15] (70 eV)—$C_{16}H_{16}N_4O_2$ (3.3) 0.2, $C_{10}H_9N_3O_2$ (7.8) 0.2, $C_9H_{11}N_3O$ (100) −1.1, $C_9H_{10}N_2O$ (17) −0.2, $C_9H_9N_2O$ (2.4) −0.2, $C_8H_{10}N_3$ (1.8) 0.2, $C_8H_7N_2$ (3.7) −1.3, C_7H_5NO (71) 0.0, C_7H_8N (27) −1.5, C_6H_5N (34) −0.8, C_6H_5 (30) −1.5.

Anal. Calcd for $C_{16}H_{16}N_4O_2$: C, 64.9; H, 5.43; N, 18.9. Found: C, 64.7; H, 5.38; N, 19.2.

The mother liquors (B) from crystallization of **15** were evaporated to dryness; the resulting solid was redissolved in a minimum of cold chloroform and preparatively chromatographed as above. The major band (R_f 0.31) was eluted from the plates with methanol in the usual manner yielding 0.213 g of **14**, mp 120–122°.

The basic aqueous filtrate above (A) was extracted twice with 25 ml of chloroform. After drying (anhydrous sodium sulfate) and filtering, the chloroform extract was evaporated to dryness. The residue was recrystallized from chloroform–hexane, yielding 0.530 g of **14**. The total yield of **14** from A and B was 0.743 g (42%): mp 120–122°; ir (KBr) 1715 (C=O) and 3350 cm^{-1} (NH_2); uv max (CH_3OH) 246 mμ (ε 18,500); nmr ($DCCl_3$) δ 7.33 (m, 5, C_6H_5), 4.00 (s, 2, NH_2), and 3.62 ppm (m, 4, NCH_2CH_2N); mass spectrum[15] (70 eV)—$C_9H_{11}N_3O$ (100) 0.5, $C_9H_{10}N_2O$ (4.3) −1.0, $C_9H_9N_2O$ (4.8) −4.0, $C_7H_8N_2$ (3.2) 0.0, C_7H_5NO (18) −0.3, C_7H_7N (30) −0.1, C_6H_5N (23) −0.5, C_6H_5 (90) −1.3.

Anal. Calcd for $C_9H_{11}N_3O$: C, 61.0; H, 6.26; N, 23.7. Found: C, 60.7; H, 6.32; N, 22.2.

3-Isopropylidenamino-1-phenyl-2-imidazolidinone (16). A.—In a separate experiment involving equimolar amounts of phenyl-isocyanate and hydrazinoethyl hydrogen sulfate executed as above, mother liquors (B) were evaporated to dryness and the residue was dissolved in acetone and chromatographed as above, giving rise to several bands. Eluting the major band with acetone and evaporating the solvent produces a solid that, after recrystallization from carbon tetrachloride–hexane, afforded 0.221 g (10%) of **16**: mp 54–56°; ir (KBr) 1725 (C=O) and 1650 cm^{-1} (C=N); uv max (CH_3OH) 248 mμ (ε 4500); nmr (CCl_4) δ 7.16 (m, 5, C_6H_5), 3.52 (s, 4, NCH_2CH_2N), 1.84 (s, 3, CH_3), and 1.96 ppm (s, 3, CH_3); mass spectrum[15] (70 ev)—217 (100), 202 (7.8), 175 (27), 161 (7.3), 147 (6.9), 133 (4.7), 118 (34), 106 (61), 91 (47), 77 (64).

Anal. Calcd for $C_{12}H_{15}N_3O$: C, 66.3; H, 6.96; N, 19.3. Found: C, 66.6; H, 6.89; N, 19.3.

B.—In 2 ml of acetone 51 mg (0.3 mmol) of **14** was dissolved and allowed to stand for 1.5 hr. The acetone was removed and the residue was dissolved in chloroform. Preparative tlc of the mixture yielded 23 mg (40%) of **16**.

Registry No.—Phenyl isocyanate, 103-71-9; **3a**, 109-84-2; **3b**, 3657-48-5; **4**, 18339-72-5; **5**, 18339-61-2; **6**, 18339-62-3; **7**, 18339-63-4; **9a**, 18339-64-5; **11a**, 18339-65-6; **12**, 18339-66-7; **13**, 18339-67-8; **14**, 18339-68-9; **15**, 18339-69-0; **16**, 18339-70-3.

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A New Synthesis of 5-Acyl-2-oxazolin-4-ones and of β-Keto-α-hydroxy Acid Amides from the Reaction of 2,2,2-Trialkoxy-2,2-dihydro-1,3,2-dioxaphospholenes with Acylisocyanates

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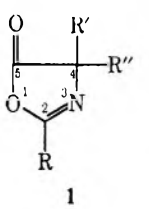
A new reaction leading to 5-acyl-2-oxazolin-4-ones and to the corresponding hydrolysis products, β-keto-α-hydroxy acid amides, is described. The reaction involves two steps: (1) the formation of a 2,2,2-trialkoxy-2,2-dihydro-1,3,2-dioxaphospholene from a trialkyl phosphite and an α-dicarbonyl compound and (2) the reaction of the phospholene with an acylisocyanate to yield the oxazolone and a trialkyl phosphate.

The 2-oxazolin-5-ones ("5-oxazolones" or azlactones[2]) (**1**) have been extensively investigated because of their application in the synthesis of α-amino acids. However, the 2-oxazolin-4-ones (**2**) have received little attention,[3-7] in spite of their potential use in the synthesis of α-hydroxy acid amides.



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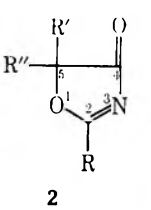

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This paper describes a new reaction whose net effect is to convert an α-dicarbonyl compound (**3**) and an acylisocyanate[8,9] (**4**) into a 5-acyl-2-oxazolin-4-one (**6**), the precursor of a β-keto-α-hydroxy acid amide (**8**). The reagent employed in this reductive condensation is a trialkyl phosphite (**5**), which is first combined with the α-dicarbonyl compound to form a 2,2,2-trialkoxy-2,2-dihydro-1,3,2-dioxaphospholene.[10] Reac-

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Table I

Properties of Acyl Isocyanates and of Their Urea Derivatives

RCONCO					RCONHCONHR′									
R	Compd no.	Bp (mm), °C	Ir, μ[a]	Yield, %	R′	Compd no.	Mp, °C	Molecular formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Ir, μ
C_6H_5[b]	14	62–63 (3.5)	4.48, 5.90	80	[b]										
p-FC_6H_4	15	43–45 (0.7)	4.48, 5.90	95	C_6H_5	18	200–202[c]	$C_{14}H_{11}O_2N_2F$	65.1	4.3	10.8	65.1	4.4	10.7[d]	3.12, 5.90[e]
p-$CH_3OC_6H_4$	16	85–86[f] (0.7)	4.48, 5.90	90[g]	C_6H_5	19	221–223[h]	$C_{15}H_{14}O_3N_2$	66.7	5.2	10.4	66.8	5.2	10.6	5.82[i]
Cl_3C	17	42–43[j] (15)	4.50, 5.75	60	3,4-$Cl_2C_6H_3$	20	171–172[c,k]	$C_9H_6O_2N_2Cl_5$	30.8	1.4	8.0	31.0	1.5	7.5	5.80[i]

[a] In CH_2Cl_2. The isocyanate band was flanked by weak shoulders at 4.30 and 4.60 μ. [b] References 6a and 8. [c] From CH_2Cl_2. [d] F, 7.5% (calcd 7.3%). [e] KBr pellet. [f] Solidified. [g] The CH_3O group had a ^1H nmr signal at τ 6.12. [h] From $HCON(CH_3)_2$. [i] Dilute CH_2Cl_2. [j] Reference 8a gave bp 80–85° (20 mm). [k] Reference 8a gave mp 175°.

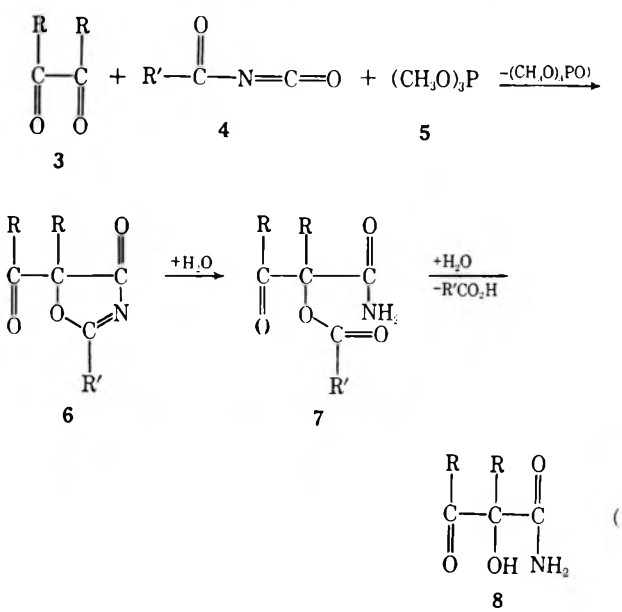
Table II

2-Aryl- and 2-Alkyl-5-acetyl-5-methyl-2-oxazolin-4-ones

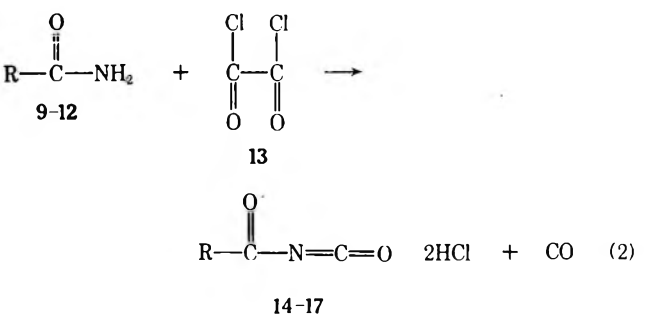
R	Compd no.	Bp (mm) or mp, °C	Molecular formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Yield, %	^1H nmr[a] τ (CH_3CO)	^1H nmr[a] τ (CH_3)	Ir, μ[b]
C_6H_5	23	111–113 (0.04)	$C_{12}H_{11}O_3N$[c]	66.4	5.1	6.4	66.2	5.3	6.1	92	7.75[d]	8.22	5.67, 5.78
p-FC_6H_4	24	76–78[e]	$C_{12}H_{10}O_3NF$	61.3	4.3	5.9	61.5	4.5	5.7[f]	78	7.68[d]	8.12	5.62, 5.78
p-$CH_3OC_6H_4$	25	143–144[g]	$C_{13}H_{13}O_4N$	63.1	5.3	5.6	62.8	5.2	5.6	87	7.76[d,h]	8.23	5.68, 5.78
Cl_3C[i]	27	131–133[e,j]	$C_7H_8O_4NCl_3$[k]	30.4	2.9	5.1	30.3	2.9	5.1	60	7.62,[l] 7.68	8.32	3.10, 5.75,[m] 5.88

[a] Measured at 60 Mcps; nmr values were measured in parts per million *vs.* TMS = 10 (τ values). [b] In CH_2Cl_2 solution. [c] Mol wt (thermoelectric in CH_2Br_2) 214 (calcd 217). [d] In $CDCl_3$ solution. [e] From benzene–hexane. [f] F, 8.2% (calcd 8.1%). [g] From C_6H_6. [h] τ (CH_3O) 6.10. [i] Hydrate of the 2-oxazolin-4-one assumed to be 2-hydroxy-2-trichloromethyl-5-acetyl-5-methyloxazolidine-4-one. [j] Can be sublimed unchanged at 0.05 mm. [k] Mol wt (thermoelectric in dioxane) 272 (calcd 276). [l] In acetone-d_6; insoluble in other nmr solvents. The acetyl signal at τ 7.62 was accompanied by a second, much weaker, closely situated signal. One resolvable CH_3C signal only. The OH signal was broad at *ca.* τ 3.43. There was exchange of H and D with solvent. [m] In KBr pellet. The OH band at 3.10 μ is broad and strong.

tion of the phospholene with the isocyanate produces the oxazolone **6** and a trialkyl phosphate (eq 1).



(1)



(2)

Results

Condensation of Acyl Isocyanates with 2,2,2-Trimethoxy-4,5-dimethyl-2,2-dihydro-1,3,2-dioxaphospholene (21).—The acyl isocyanates **14–17** were made from the corresponding amides **9–12** (eq 2) by the procedure of Speziale and Smith.[8a] The properties of the isocyanates and of the urea derivatives **18–20** are given in Table I. The dioxaphospholene **21** was prepared from biacetyl and trimethyl phosphite as previously described.[10]

The dioxaphospholene **21** reacted with benzoyl isocyanate (**14**) at 30°. The reaction had a 1:1 stoichiometry and produced trimethyl phosphate and 2-phenyl-5-acetyl-5-methyl-2-oxazolin-4-one (**23**) in good yield (eq 3). The properties of the 2-oxazolin-4-one **23** are given in Table II. Note in particular the two carbonyl bands in the infrared (ir) spectrum, and the ^1H nmr signals due to the acetyl and methyl groups on the heterocycle.

No intermediate was detected during the reaction, but we assume that the phospholene added to the isocyanate to form a dipolar adduct **22**, which underwent an intramolecular displacement of trimethyl phosphate by the acyl oxygen to yield the 2-oxazolin-4-one **23**.

The phospholene **21** reacted with aromatic acyl isocyanates having electron-withdrawing and electron-releasing groups, **15** and **16**, respectively, and gave the corresponding 2-oxazolin-4-ones **24** and **25**.

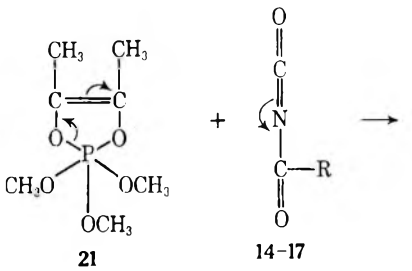
The 2-oxazolin-4-one **26** made from trichloroacetyl isocyanate (**17**) was very sensitive to moisture and was converted into a crystalline monohydrate assumed

TABLE III

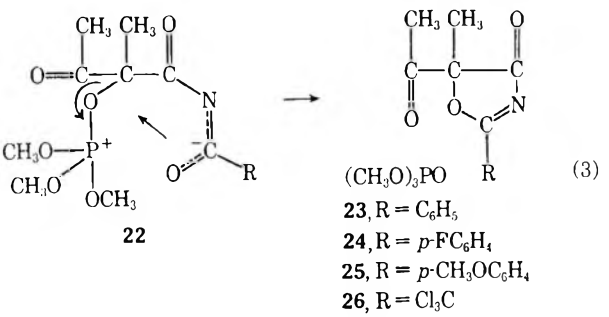
α-METHYL-α-HYDROXYACETOACETAMIDE AND O-ACYL DERIVATIVES $CH_3COC(CH_3)(OR)CONH_2$

R	Compd no.	Mp, °C	Molecular formula	Calcd, % C	H	N	Found, % C	H	N	Yield, %	^{1}H nmr[a] τ (CH_3CO)	τ (CH_3)	Ir, μ
C_6H_5CO	30	135–136[b]	$C_{12}H_{13}O_4N$	61.3	5.5	6.0	61.4	5.5	6.3	45	7.70[c]	8.16	5.81, 5.90,[d] 6.02
p-FC_6H_4CO	31	147–149[b]	$C_{12}H_{12}O_4NF$	56.9	4.7	5.5	57.1	4.8	5.6[e]	70	7.70[f]	8.15	5.78,[g] 5.80, 5.88
H	29	86–88[b]	$C_5H_9O_3N$	45.8	6.9	10.7	46.2	6.9	10.5	45	7.53[h]	8.36	2.85, 2.94, 5.78, 5.90[g]

[a] Nmr values were measured in parts per million *vs.* TMS = 0 (τ values). [b] From benzene. [c] In acetone-d_6. The 2 protons of the amide were at *ca.* τ 1.92. [d] In KBr pellet. [e] F, 7.4% (calcd 7.5%). [f] In $CDCl_3$ solution. [g] In CH_2Cl_2 solution. [h] A broad signal at τ 5.17 is attributed to OH.

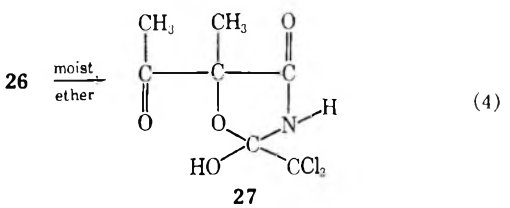


21 14–17



22 23, R = C_6H_5; 24, R = p-FC_6H_4; 25, R = p-$CH_3OC_6H_4$; 26, R = Cl_3C (3)

to be 2-hydroxy-2-trichloromethyl-5-acetyl-5-methyl-4-oxazolidinone (**27**) (eq 4). This material could be

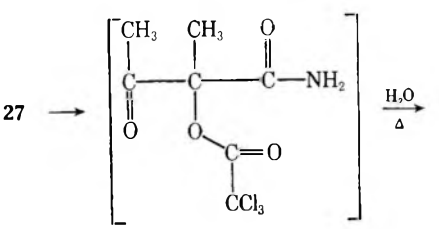


(4)

sublimed *in vacuo* without the loss of water and had a relatively strong band in the infrared at 3.10 μ, in addition to the two expected carbonyl bands (in a KBr pellet). The ^{1}H nmr spectrum and the results of further hydrolysis discussed in the next section are in agreement with structure **27**.

Reaction of 5-Acyl-2-oxazolin-4-ones with Water.—The "hydrate" **27**, of the 2-trichloromethyl-4-oxazolone (**26**), was converted into α-methyl-α-hydroxyacetoacetamide (**29**) by boiling water (eq 5); *cf.* Table III. The formation of other hydrolysis products was not excluded since the amide **29** was isolated only in 45% yield. The O-trichloroacetyl ester, **28**, if formed, was hydrolyzed under these conditions.

The 2-phenyl- and the 2-*p*-fluorophenyl-2-oxazolin-4-ones (**23** and **24**) were converted into the corresponding O-benzoyl and O-*p*-fluorobenzoyl esters **30** and **31**, of the hydroxyacetoacetamide **29** by boiling water (eq 6).



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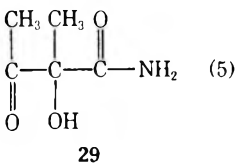

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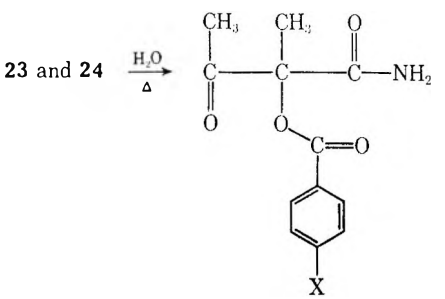
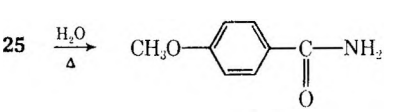


30, X = H; 31, X = F (6)

The behavior of the 2-*p*-methoxyphenyl-2-oxazolin-4-one **25** toward boiling water was rather complex, but approximately 50% of *p*-methoxybenzamide **11** was isolated from this reaction (eq 7). A discussion of

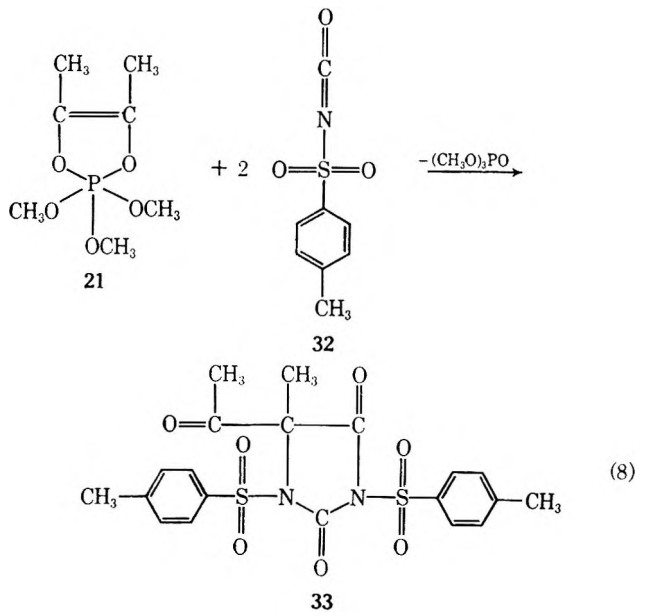


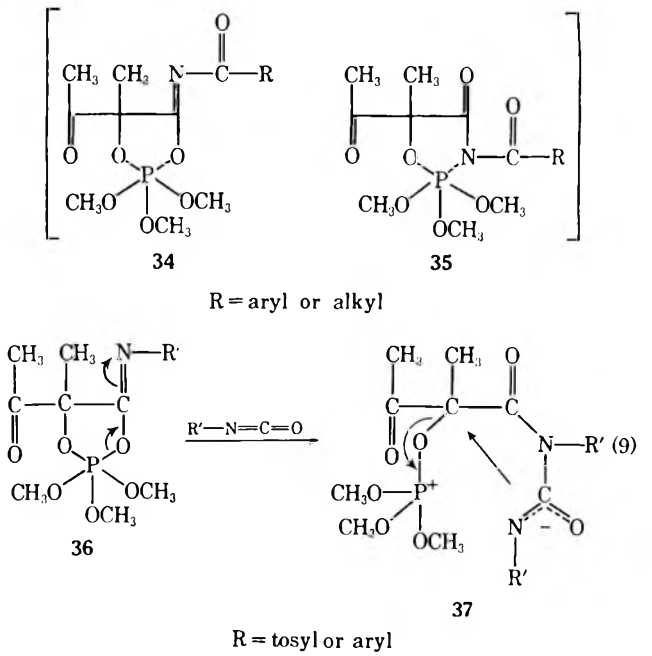
11 (7)

the mechanisms of hydrolysis of 2-oxazolin-4-ones in general[3,6a,7] and of 5-acyl-2-oxazolin-4-ones in particular, at various pH values, will be postponed pending further studies now in progress.

Vigorous hydrolysis of the 2-phenyl-2-oxazolin-4-one (**23**) in aqueous hydrochloric acid gave benzoic acid and acetoin, $CH_3COCH(OH)CH_3$.

Reaction of the Dioxaphospholene with *p*-Toluenesulfonyl Isocyanate.—This reaction occurred at 30°, had a 1:2 phospholeneisocyanate stoichiometry, and yielded trimethyl phosphate and the N,N′-ditosylhydantoin, **33** (eq 8).





A comparison of the behavior of the acyl isocyanates, tosyl isocyanate, and phenyl isocyanate[11] toward the dioxaphospholene is instructive. The presence of an electron-withdrawing group, *i.e.*, R′ = acyl or tosyl (Ts), on the isocyanate, R′—N=C=O, increased its reactivity toward the nucleophilic phospholene.[12,13] However, the 1:1 adducts initially formed in these reactions behaved in different ways. The acyl isocyanate adduct, **22**, did not close to the 2,2,2-trimethoxy-4-imino-1,3,2-dioxaphospholane (**34**) or to the 2,2,2-trimethoxy-4-oxo-1,3,2-oxaazaphospholane (**35**); instead, it underwent an intramolecular displacement of phosphate to give the 2-oxazolin-4-ones **23**–**26**. The tosyl and phenyl isocyanate adducts, however, closed to the 1,3,2-dioxaphospholanes[11] **36**, which were, in turn, capable of nucleophilic addition to isocyanate yielding the 1:2 adducts, **37** (eq 9). The latter formed the hydantoins **33** by intramolecular displacement of phosphate.[11]

Experimental Section

The analyses were performed by the Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

Acyl Isocyanates (Table I). Benzoylisocyanate (14).—Compound **14** was made from oxalyl chloride and benzamide in 1,2-$C_2H_4Cl_2$ solution (10–20 hr at reflux) following the procedure of Speziale and Smith.[8a] The new *p*-fluorobenzoyl isocyanate (**15**) and *p*-methoxybenzoyl isocyanate (**16**) were made as follows. Oxalyl chloride (1.25 molar equiv) was quickly added to a suspension of *p*-fluorobenzamide (**10**) or of *p*-methoxybenzamide (**11**) in CH_2Cl_2 (*ca.* 2.2 *M*) at 20°. The resulting clear solution was kept 12–20 hr at reflux, and the solvent was evaporated. The crude acyl isocyanates, **15** and **16**, were purified by distillation. They were characterized by their ir spectra and by the properties of the solid ureas **18** and **19** made by reaction with 1 molar equiv of aniline in CH_2Cl_2. The application of this procedure to trichloroacetamide (**12**) gave an acyl isocyanate which boiled at a much lower temperature (*ca.* 40°) than that reported[8a] for **trichloroacetyl Isocyanate (17)**. Therefore, we repeated the preparation and the analysis of the urea **20** made from 3,4-dichloraniline and the acyl isocyanate; *cf.* Table I. The separation of trichloroacetylisocyanate (**17**) from solvent CH_2Cl_2 should be carried out by fractional distillation to avoid loss of volatile isocyanate. The acyl isocyanates, in general, must be protected from moisture.

Reaction of 2,2,2-Trimethoxy-4,5-dimethyl-2,2-dihydro-1,3,2-dioxaphospholene (21) with 1 Molar Equiv of Acyl Isocyanates. Preparation of 2-Aryl- and 2-Alkyl-5-acetyl-5-methyl-2-oxazolin-4-ones (23–26) (Table II).—A solution of the phospholene[10-12] **21** in CH_2Cl_2 (1.6–2.5 *M*) was added, dropwise, to a solution of the acyl isocyanate in CH_2Cl_2 (1.6–2.5 *M*, 1 molar equiv) at 20°. The reaction was mildly exothermic, and the solution was stirred 4–10 hr at 20°.

The solvent and the trimethyl phosphate were removed by distillation at 20 and 1 mm, respectively. The oxazolone was purified by distillation (if liquid) or by trituration with cold ether followed by recrystallization from benzene (if solid). The 2-trichloromethyloxazolone **26** was very sensitive to moisture and was converted into the stable, crystalline **2-hydroxy-2-trichloromethyl-5-acetyl-5-methyloxazolidine-4-one (27)** by treatment with moist ether, prior to recrystallization from benzene.

The reaction of the phospholene **21** with *2 molar equiv* of benzoyl isocyanate (**14**) gave the same oxazolone **23** plus unreacted isocyanate.

Hydrolysis of 2-Aryl- and 2-Alkyl-5-acetyl-5-methyl-2-oxazolin-4-ones (Table III).—A suspension of the oxazolone in water was kept 8–12 hr at reflux temperature. The solid which separated on cooling was filtered and was purified by recrystallization from benzene. The **2-phenyl-2-oxazolin-4-one 23** and the **2-*p*-fluorophenyl-2-oxazolin-4-one 24** gave the corresponding O-benzoyl and O-*p*-fluorobenzoyl esters **30** and **31** derived from **α-methyl-α-hydroxyacetoacetamide (29)**. The **2-trichloromethyl-2-oxazolin-4-ones (26 and 27)** gave α-methyl-α-hydroxyacetoacetamide (**29**), under the same conditions. The **2-*p*-methoxyphenyl-2-oxazolin-4-one 25** gave a mixture of products from which *p*-methoxybenzamide (**11**) was isolated in *ca.* 40% yield.

When the 2-phenyl-2-oxazolin-4-one **23** was heated 10 hr with 10% aqueous HCl, benzoic acid and acetoin were produced.

Reaction of 2,2,2-Trimethoxy-4,5-dimethyl-2,2-dihydro-1,3,2-dioxaphospholene (21) with 2 Molar Equiv of *p*-Toluenesulfonyl Isocyanate (32).—A solution of the phospholene **21** (40 g) in CH_2Cl_2 (50 ml) was added dropwise to freshly distilled *p*-CH_3-$C_6H_4SO_2NCO$ (80 g) in CH_2Cl_2 (50 ml). The reaction was exothermic. After 8–10 hr at 20°, the solvent was evaporated and the residue was stirred with cold ether (*ca.* 50 ml) and filtered. The crude hydantoin (50 g, mp 160–170°) was recrystallized from $CHCl_3$–hexane to give 5-acetyl-5-methyl-1,3-di(*p*-toluenesulfonyl)hydantoin (**33**), mp 178–179° (*ca.* 50% yield).

(11) F. Ramirez, S. B. Bhatia, and C. P. Smith, *J. Amer. Chem. Soc.*, **89**, 3030 (1967).

(12) (a) F. Ramirez, N. Ramanathan, and N. B. Desai, *ibid.*, **84**, 1317 (1962); (b) F. Ramirez, H. J. Kugler, and C. P. Smith, *Tetrahedron Lett.*, 3153 (1968); (c) F. Ramirez, H. J. Kugler, A. V. Patwardhan, and C. P. Smith, *J. Org. Chem.*, **33**, 1185 (1968), and references therein.

(13) A. J. Kirby, *Tetrahedron Lett.*, 3001 (1966).

Anal. Calcd for $C_{20}H_{20}O_7N_2S_2$: C, 51.7; H, 4.3; N, 6.0; S, 13.8. Found: C, 51.4; H, 4.4; N, 6.2; S, 13.9.

The ^1H nmr spectrum had signals at τ 7.70 (three acetyl protons), 8.00 (three methyl protons on hydantoin ring), and 7.55 (methyl protons on benzene ring). The ir spectrum (in CH_2Cl_2) had bands at 5.60, 5.73 and 5.81 (sh) μ.

Registry No.—**14**, 4461-33-0; **15**, 18354-35-3; **16**, 4695-57-2; **17**, 3019-71-4; **18**, 18354-38-6; **19**, 18354-39-7; **20**, 6077-66-3; **23**, 18354-41-1; **24**, 18354-42-2; **25**, 18354-43-3; **27**, 18354-44-4; **29**, 18354-48-8; **30**, 18354-45-5; **31**, 18354-46-6; **33**, 18354-47-7.

A γ-Pyran Derivative from Pulegone and Ethyl Acetoacetate. Reformulation of a Bicyclo[3.3.1]nonenone Structure

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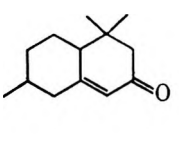
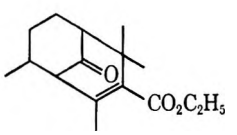
Received August 5, 1968

The crystalline solid isolated from the zinc chloride catalyzed condensation of pulegone and ethyl acetoacetate and previously identified as 3-carbethoxy-2,4,4,8-tetramethylbicyclo[3.3.1]-2-nonen-9-one is now reformulated as 3-carbethoxy-2,4,4,7-tetramethyl-5,6,7,8-tetrahydro-1,4-benzopyran by a reconsideration of its spectral properties and by hydrogenation to a tetrahydro derivative and dehydrogenation to 3-carbethoxy-2,4,4,7-tetramethyl-1,4-benzopyran.

Some time ago it was shown[1] that pulegone acetone, produced by the zinc chloride catalyzed condensation of pulegone with ethyl acetoacetate, has the constitution represented by I rather than three alternative structures proposed by other investigators.[2,3] In the meantime, Chow[4] reported the isolation of another crystalline product from the pulegone condensation, referred to here as compound B, and argued that it possessed structure II.



I



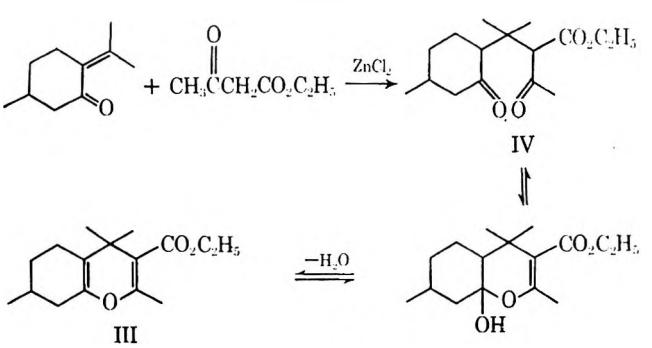
II

The exclusive reduction of the carbethoxy group in compound B by excess lithium aluminum hydride and the alleged formation of a hydrazide rather than a normal 2,4-dinitrophenylhydrazone derivative were but two of the many observations recorded by Chow[4] which do not agree with the behavior expected for a compound such as II. We have reexamined this matter and wish to report that compound B is the carbethoxypyran III and is most likely formed according to the sequence outlined in Scheme I.

When the reaction of pulegone with ethyl acetoacetate was conducted for 10 hr pulegone acetone (I) was the only crystalline product isolated. When the condensation was stopped after 2 hr, column chromatography afforded a new crystalline solid, mp 37–38°, whose physical and spectral properties were essentially identical with those of compound B reported by Chow.[4] There can be no question that the solid that we isolated is identical with the compound described by Chow.[4]

Compound B is converted into pulegone acetone by the action of zinc chloride in acetic acid[4] suggesting that its formation is reversible and that diketo ester IV eventually undergoes an irreversible intramolecular aldol condensation followed by decarbethoxylation to give I. This accounts for the fact that compound B is not found when the condensation is extended for 10 hr. Since the cyclization of IV to III produces water, it was reasoned that the yield of III might be improved if water was removed so as to prevent the hydrolysis of III to IV. When acetic anhydride was added to the reaction mixture, in order to consume the water which formed, the yield of III rose from 5 to 18% and little or no pulegone acetone formed. Unfortunately, the yield of III could not be further improved; the remainder of the material was largely accounted for as a nonvolatile, presumedly polymeric, oil.

SCHEME I

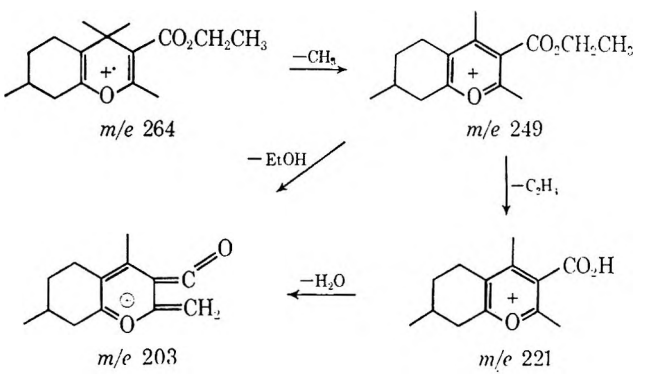


(1) J. Wolinsky and M. A. Tyrell, *Chem. Ind.* (London), 1104 (1960).
(2) P. Barbier, *C. R. Acad. Sci., Paris*, **127**, 870 (1898).
(3) L. G. Jupp, G. A. R. Kon, and E. H. Lockton, *J. Chem. Soc.*, 1639 (1928).
(4) Y. L. Chow, *Tetrahedron Lett.*, 1337 (1964).

Our investigation of compound B began with a spectral examination. The nmr spectrum of compound B displayed singlets at 1.20 and 1.23 ppm accounting for a *gem*-dimethyl group, a singlet vinyl methyl resonance at 1.90 ppm, a triplet and quartet at 1.28 and 4.11 ppm (J = 7 cps) for $-OCH_2CH_3$, and, most significantly, four protons were accounted for in the region (1.9–2.10 ppm) characteristic of allylic hydrogens. The infrared (5.82 and 6.12 μ) and ultraviolet spectra [λ_{max} 212 and 272 mμ (ϵ 2140 and 1480)] were less informative, but are consistent with what might be expected for a carbethoxypyran.[5] The ultraviolet maximum at 272 mμ offers a strong argument against the simple conjugated ester found in Chow's formulation II.

The mass spectrum of compound B showed abundant ions at m/e 249, 221, 219 and 203 in the high mass region. The P − 15 ion at m/e 249 (37% total abundance) completely dominates the spectrum and provides strong support for structure II and its fragmentation to the very stable pyrylium ion pictured in Scheme II.[6]

SCHEME II

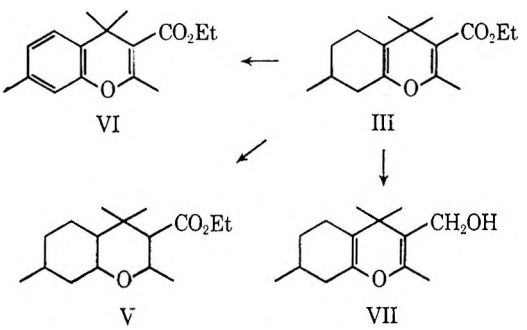


Our experience with a variety of bicyclic ketones[7] would predict that the carbonyl group in compound II would direct its fragmentation and lead to many ions of lower mass.

Compound B displays a plain positive rotatory dispersion curve which confirms the absence of a ketone group. In addition, catalytic hydrogenation gave a tetrahydro derivative, V (parent ion at m/e 268), rather than a dihydro derivative as reported by Chow[4] and demonstrates the presence of two carbon–carbon double bonds.

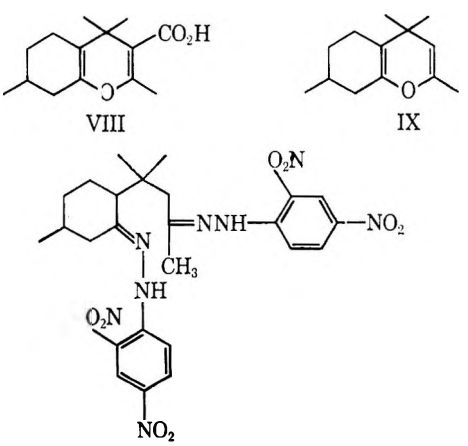
Dehydrogenation of compound B with chloranil gave the benzopyran VI whose infrared spectrum, except for new aromatic peaks, was remarkably similar to that of compound B, suggesting that a minor structural change had occurred during dehydrogenation. The mass spectral fragmentation of compound VI was also very similar to that of compound B. The formation of an aromatic ring under conditions involving minimal structural change provides another definitive argument against Chow's structure II.

Lithium aluminum hydride reduction of III (compound B) gave alcohol VII which displayed infrared



absorption at 5.83 and 6.0 μ. Chow[4] mistook the peak at 5.83 μ for a carbonyl stretching band. The intensity of this peak is too weak to be attributed to a carbonyl group. Doublet absorption at 5.93 and 6.1 μ is characteristic of γ-pyrans[8] and a shift to 5.83 and 6.0 μ would not be unreasonable for a γ-pyran carrying additional substituents at the 3 and 5 positions.

Chow[4] reported the oxidation of alcohol VII to an acid which we now reformulate as VIII. Decarboxylation of this acid gave an olefin which afforded a 2:1 adduct with 2,4-dinitrophenylhydrazine. The olefin and bis-2,4-DNP derivative are now assigned structures IX and X.



Finally, we comment on the reaction of pyran III with 2,4-dinitrophenylhydrazine which affords a 1:1 adduct which still retains the carbethoxy group (CH_3CH_2O– nmr signals) and is not a hydrazide deriva-

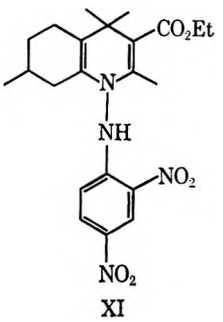
(5) The closest models for an infrared comparison are 3-carbethoxy-5,6-dihydropyrans which show absorption at 1722 and 1660 cm^{-1}; *cf.* loganin, genepin, and related glycosides [K. Sheth, E. Ramstad, and J. Wolinsky, *Tetrahedron Lett.*, 394 (1961); C. Djerassi, T. Nakano, A. N. James, L. H. Zalkow, E. J. Eisenbraun, and J. H. Shoolery, *J. Org. Chem.*, **26**, 1192 (1961)]. Ethyl-3,5-diformyl-4H-pyran [E. Winterfeldt, *Chem. Ber.*, **97**, 1959 (1964)] exhibits λ_{max} 290 mμ (ϵ 5200).

(6) The McLafferty rearrangements shown in Scheme II are documented by strong metastable ions at m/e 196 (249 → 221), 187 (221 → 203), and 166 (249 → 203). These fragmentations provide a strong argument against the necessity of an unpaired electron as a major driving force for the site-specific rearrangement of hydrogen to the carbonyl group in mass spectral reactions [F. W. McLafferty and T. Wachs, *J. Amer. Chem. Soc.*, **89**, 5043 (1967)]. *Cf.* M. Kraft and G. Spiteller, *Chem. Commun.*, 943 (1967), for a similar conclusion.

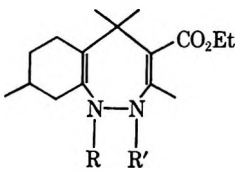
(7) D. R. Dimmel and J. Wolinsky, *J. Org. Chem.*, **32**, 2735 (1967).

(8) M. J. Jorgenson, *J. Org. Chem.*, **27**, 3224 (1962); S. Masamune, *J. Amer. Chem. Soc.*, **84**, 2452 (1962); H. W. Whitlock and N. A. Carlson, *Tetrahedron*, **20**, 2101 (1964).

tive as claimed by Chow.[4] The unique spectral properties of this derivative suggest it has the constitution represented by the dihydropyridine structure XI.

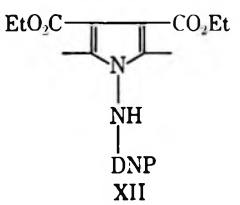


XI



XIII, R = H; R′ = 2, 4-$(NO_2)_2C_6H_3N$-
XIV, R = 2, 4-$(NO_2)_2C_6H_3$; R′ = H

XI exhibits ultraviolet maxima at 256 and 326 mμ which clearly eliminates the possibility that it is the mono-2,4-dinitrophenylhydrazone of diketo ester IV, since 2,4-DNP derivatives of saturated and unsaturated carbonyl compounds display maxima between 348 and 390 mμ.[9,10] On the other hand, the ultraviolet spectrum of XI is nearly identical with the spectra of acyl 2,4-dinitrophenylhydrazides[11] and the pyrrole XII,[12] and it is reasonable to conclude that absorption between 320 and 330 mμ characterizes ArNHN(C=X)- (Ar = 2,4-DNP) systems.



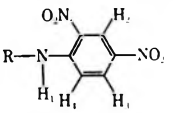
XII

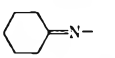
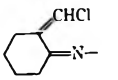
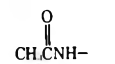
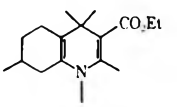
The high-field region of the nmr spectrum of XI is essentially identical with that of pyran III. The aromatic region, however, is quite distinct from that of an ordinary 2,4-DNP derivative as seen in Table I. The NH and C-4 protons are shifted upfield from their normal positions in 2,4-DNP derivatives of aldehydes and ketones, which suggests another method of distinguishing between ArNHN(C=X)- and ArNHN=C< systems.

It is conceivable that the 2,4-DNP derivative of III might be represented alternatively by XIII or XIV. These structures are rejected on the basis that the mass spectrum of the 2,4-DPN derivative displays abundant ions at 262 and 247 (100% relative abundance) attributed to loss of 2,4-DNP–NH[13] and 2,4-DNP–NH plus methyl. Furthermore, the ultraviolet spectrum of the 2,4-DNP derivative undergoes a pronounced bathochromic shift in alkaline solution consistent with the removal of the NH proton in XI and the production of a resonance stabilized anion. Removal of the NH proton in XIII or XIV cannot account for this shift.[14,15]

TABLE I

NMR SPECTRA OF 2,4-DINITROPHENYLHYDRAZINE DERIVATIVES

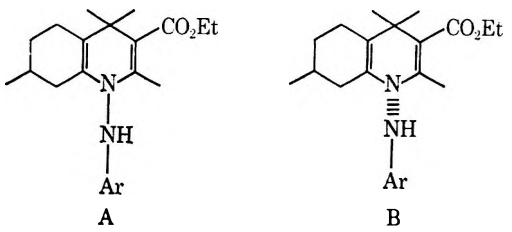


R	Registry no.	H_1	H_2[b]	H_3[c]	H_4
	1589-62-4	11.2	9.1	8.32	7.94
$CH_3CH_2CH{=}N-$		11.13	9.03	8.20	7.88
	3100-86-5	11.3	9.1	8.4	8.04
	2719-07-5	10.36	9.02	8.46	7.4
		9.54	9.02	8.44	7.44

[a] G. J. Karabatsos, B. L. Shapiro, F. M. Vane, J. S. Fleming, and J. S. Ratka, *J. Amer. Chem. Soc.*, 85, 2784 (1963). [b] $J_{2,3}$ = 2.0 cps. [c] $J_{3,4}$ = 9.6–10.0 cps.

The nmr spectrum of XI revealed certain features which are worthy of further consideration. Whereas the $-OCH_2CH_3$ protons appeared as a sharply defined quartet and the H_2 and H_3 aromatic protons were observed as a sharp doublet and a doublet of doublets, the NH resonance was composed of two signals separated by 9 Hz, the aromatic H_4 proton showed four signals instead of the usual two, and the vinyl methyl appeared as a doublet instead of the expected singlet. Long-range spin coupling was eliminated as an explanation for this phenomenon by deuterium-exchange experiments. The NH signals slowly disappeared when a deuteriochloroform solution of XI was stirred with deuterium oxide, but the four-line pattern for H_4 was unaltered. The two signal resonance for the vinyl methyl was not immediately altered, but eventually was reduced in intensity and after 6 days disappeared. Mass spectral analysis of the exchanged derivative indicated as many as six deuterium atoms had been incorporated, suggesting the exchange of two allylic protons as well as the vinyl methyl and NH protons. Stirring a deuteriochloroform solution of deuterated XI with water reversed the process. In this instance the two NH signals appeared very rapidly, whereas complete exchange of the vinyl methyl took *ca.* 9 days. XI could not be broken down into more than one component by crystallization or chromatography, leading to the conclusion that it was composed of a mixture of stable conformers resulting either from restricted rotation[16] about the N–NH bond or from slow inversion[17]

(9) L. A. Jones, J. C. Holmes, and R. B. Seligman, *Anal. Chem.*, **28**, 191 (1956).
(10) C. J. Timmons, *J. Chem. Soc.*, 2613 (1957).
(11) A. C. Thompson and P. A. Hedin, *J. Chromatogr.*, **21**, 13 (1966).
(12) T. D. Binns and R. Brelle, *J. Chem. Soc., C*, 341 (1966).
(13) *Cf.* D. Goldsmith and C. Djerassi, *J. Org. Chem.*, **31**, 3661 (1966), for the observation of an analogous fragmentation of an $N-N(CH_3)_2$ bond in dimethylhydrazone derivatives on electron impact.
(14) G. A. Fleischer and E. C. Kendall, *ibid.*, **16**, 556 (1951); H. Reich and L. Hefle, *ibid.*, **21**, 708 (1956).
(15) F. Bohlmann, *Chem. Ber.*, **84**, 490 (1951); L. A. Jones and N. L. Mueller, *J. Org. Chem.*, **27**, 2356 (1962).
(16) B. H. Korsch and N. V. Riggs, *Tetrahedron Lett.*, 5897 (1966); Y. Shvo, E. C. Taylor, K. Mislow, and M. Raban, *J. Amer. Chem. Soc.*, **89**, 4910 (1967).
(17) A. Loewenstein, G. F. Nevmar, and J. D. Roberts, *J. Amer. Chem. Soc.*, **82**, 3599 (1960); S. G. Brois, *ibid.*, **89**, 4242 (1967); W. N. Speckamp, U. K. Dandit, and H. O. Husiman, *Tetrahedron*, **22**, 2413 (1966).



of the dihydropyridine nitrogen atom giving rise to diastereoisomers A and B.

A temperature dependence study of the nmr of XI demonstrated that NH and vinyl methyl signals collapsed to singlets at 90–100°, but the four-line aromatic H_4 pattern remained unchanged even at 130°. The 2,4-DNP XI was not stable at higher temperature. Attempts to prepare the *p*-nitrophenylhydrazone analog of XI have not met with success and it is not yet certain whether hindered rotation or slow inversion accounts for the properties of XI.

Experimental Section[18]

Reaction of Pulegone with Ethyl Acetoacetate to Give Pyran III.—A mixture of 84 g (0.553 mol) of pulegone and 84.9 g (0.653 mol) of ethyl acetoacetate was added dropwise over a 2-hr period to a vigorously stirred solution of 35.6 g (0.261 mol) of fused zinc chloride in 93 g of acetic acid and 104 g of acetic anhydride. The resulting solution was kept at room temperature for 9 days and was then added to water and extracted with ether. The ether extracts were washed with water, 5% sodium bicarbonate, and saturated salt solution. The ether was dried over anhydrous magnesium sulfate and removed under diminished pressure. Distillation afforded, after a forerun of starting materials, 40.6 g of a liquid, bp 84–103° (0.40 mm), and *ca.* 50 g of undistillable tar. The liquid was chromatographed on an acid-washed alumina column and the fraction eluting with 5% ether in pentane was recrystallized from pentane to give 13.4 g of III: mp 37–38°; ir (Nujol) 5.83 and 6.12 μ; λ_{max}^{EtOH} 212 mμ (ϵ 2140) and 272 (1480); nmr ($CDCl_3$) δ 0.98 (d, 3, $-CHCH_3$), 1.20 and 1.23 (s, 6, $>C(CH_3)_2$), 1.28 (t, 3, $-OCH_2CH_3$), 1.90 (s, 3, $-C{=}CCH_3$), and 4.11 ppm (q, 2, $-OCH_2CH_3$); $[\alpha]^{MeOH}D$ +47.6°; the ORD displayed a plain positive curve, $[\alpha]$ ($cm^{-1} \times 10^{-3}$) 49 (18), 129 (26, 362 (36), and 651° (44); the mass spectrum showed abundant ions at *m/e* 249 (100%), 221 (19%), 219 (9%), and 203 (6%) [lit. mp 37–39°; ir 1712 and 1635 cm^{-1}; λ_{max} 206 mμ (ϵ 5900) and 272 (2500), $[\alpha]D$ +47.8°].[4]

Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.73; H, 9.15. Found: C, 72.91; H, 9.32.

When pulegone, ethyl acetoacetate, and zinc chloride were heated at 90–95° for 2 hr, there was obtained two fractions, bp 70–113° (1.0 mm) and 125–150° (1.5 mm). The first fraction was largely pulegone acetone. Chromatography of the second fraction gave *ca.* 2.0 g of pyran III.

The methyl ester of III was prepared in an identical fashion employing 62.5 g of methyl acetoacetate and 108.0 g of pulegone. The fraction boiling at 86–146° (0.5 mm) was chromatographed on an alumina column to give 19 g of the liquid methyl ester. An analytical sample was obtained by vpc using a DEGS column at 190°. The spectral properties of the methyl ester were almost identical with those of III except for the absence of ethoxyl nmr resonance signals and the appearance of a methoxyl signal at 3.68 ppm. The mass spectrum displayed abundant ions at *m/e* 250 (2%), 219 (7%), 235 (100%), and 203 (55%).

Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.68; H, 9.07.

2,4-Dinitrophenylhydrazine Derivative of III.—A solution of 1.02 g of III in 10 ml of ethanol was added to a solution of 0.86 g of 2,4-dinitrophenylhydrazine and 5 ml of concentrated sulfuric acid in 30 ml of 65% aqueous ethanol. A solid immediately formed which dissolved on addition of 5 ml of ethanol. On standing overnight an orange solid was obtained. Recrystallization from 3:1 ethyl acetate:ethanol gave dark wine-colored crystals: mp 168–170.5°, ir 5.9 μ; λ_{max}^{MeOH} 215 mμ (log ϵ 4.13), 256 (3.92), and 326 (4.17); $\lambda_{max}^{0.1\ M\ NaOH}$ 222 mμ (log ϵ 3.96), 404 (4.05), and 460 (3.87) [lit. mp 178–181°; λ_{max} 326 mμ (log 4.24)].[4] The mass spectrum showed abundant ions at *m/e* 444 (4%), 429 (72%), 248 (84%), 247 (94%), 232 (22%), 220 (37%), 218 (44%), 202 (100%), 201 (75%).

Anal. Calcd for $C_{22}H_{28}N_4O_6$: C, 59.45; H, 6.35; N, 12.60. Found: C, 59.38; H, 6.43; N, 12.61.

The 2,4-DNP derivative of the corresponding methyl ester of III showed mp 171.5–172.5°.

Hydrogenation of Pyran III.—A solution of 126 mg of III in 2.5 ml of acetic acid was hydrogenated for 18 hr at atmospheric pressure using platinum oxide as catalyst. The platinum was removed by filtration and the solvent by distillation under reduced pressure. The residue was purified by vpc on a 10-ft DEGS column at 142° and the pure tetrahydropyran derivative was obtained as a colorless oil: ν_{max} 5.75 μ, showing important ions at *m/e* 268 (25%), 253 (11), 251 (17), 224 (20), 223 (27), 209 (76), 154 (65), 151 (63), 138 (52), 137 (50), 129 (75), 95 (87), 83 (83), 81 (89), 69 (95), 43 (76), and 41 (100%). Overlapping multiplets in the nmr region between 3.2–4.2 ppm accounted for four CHO-type protons. The large number of methyl resonances between 0.82 and 1.25 ppm suggested the tetrahydro derivative was a mixture of stereoisomers.

Anal. Calcd for $C_{16}H_{28}O_3$: C, 71.64; H, 10.45. Found: C, 71.92; H, 10.57.

Dehydrogenation of Pyran III.—A solution of 1.04 g (3.94 mmol) of III and 1.98 g (7.74 mmol) of chloroanil in 30 ml of *o*-xylene was heated at reflux for 2 days under a nitrogen atmosphere. The xylene was removed and pentane was added. A brown solid was removed by filtration and the filtrate was concentrated and chromatographed on an acid-washed alumina column. The fraction eluting with 5% ether–pentane was shown by nmr to be a mixture of III and the aromatic derivative VI. The two pyrans were separated by vpc using a 10-ft DEGS column at 170°. Benzopyran VI was a colorless liquid: ir 5.80 and 6.10 μ; λ_{max}^{MeOH} 215 mμ (log ϵ 3.68) and 258 (3.20); nmr (CCl_4) 6.9 (m, 3, aromatic H), 4.81 (q, 2, $-OCH_2CH_3$), 2.25 (s, 3, $ArCH_3$), 2.07 (s, 3, $C{=}CCH_3$), 1.48 (s, 6, $>C(CH_3)_2$), and 1.30 ppm (t, 3, $-OCH_2CH_3$). The mass spectrum exhibited abundant ions at *m/e* 260 (1%), 215 (15%), 245 (100%), 217 (16%), and 199 (6%).

Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.87; H, 7.95.

Lithium Aluminum Hydride Reduction of III.—A solution of 1.90 g (7.2 mmol) of III in 20 ml of ether was added to a suspension of 0.25 g (6.6 mmol) of lithium aluminum hydride in 20 ml of ether under a nitrogen atmosphere. After heating at reflux for 20 min, saturated ammonium chloride solution was added to the cooled solution. The mixture was filtered and the filtrate distilled to give 1.1 g of an oil which slowly solidified. Sublimation *in vacuo* gave a colorless solid: mp 68–70°; ir 3.05 μ, 5.83 (m) and 6.00 (w); λ_{max}^{MeOH} 240 mμ (sh) (ϵ 2110); nmr (CCl_4) 4.00 (s, 2, $-CH_2O$), 1.83 (s, 3, $C{=}CCH_3$), 1.10 (s, 6, $>C(CH_3)_2$) and 0.98 ppm (d, 3, J = 5 Hz, $>CHCH_3$). The mass spectrum displayed major peaks at *m/e* 222 (1%), 207 (2%), 204 (14%), 189 (100%), and 43 (22%) [lit. mp 80–82.5°;[4] ir 3640, 1710, and 1665 cm^{-1}].

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 74.75; H, 10.15.

Oxidation of Alcohol VII to Acid VIII.—To the cooled chromium trioxide–pyridine complex, prepared by adding 1.55 g (0.0155 mol) of chromium trioxide to 20 ml of pyridine,[19] was added 1.1 g (0.0049 mol) of alcohol VII in 20 ml of pyridine. The resulting mixture was allowed to stir at 0° for 15 min and was

(18) All boiling and melting points are uncorrected. Infrared spectra were measured with Perkin-Elmer Model 221 and 137-B spectrometers. Nmr spectra were determined at 60 Mc with a Varian Associates A-60 spectrometer. Chemical shifts were measured with reference to tetramethylsilane as an internal reference. The mass spectra were measured with a Hitachi RMU-6D mass spectrometer, using an all-glass inlet system heated at 180°, a source temperature of 155°, an ionizing current of 52 μA, and an ionization energy of 75 eV. Ultraviolet spectra were determined with a Bausch and Lomb spectronic 505. The microanalyses were performed by Dr. C. S. Yeh and associates.

(19) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Amer. Chem. Soc.*, **75**, 422 (1953).

then kept at room temperature for 24 hr. The mixture was added to 100 ml of water and extracted with ether. The ether extracts were washed with 10% hydrochloric acid, water, and saturated salt solution. The ether solution was dried over anhydrous magnesium sulfate and the ether was evaporated to give 1.1 g of pyran aldehyde, ir 5.8, 6.0 and 6.2 μ, which was used directly in the next step.

The crude aldehyde was stirred in an open flask for *ca.* 40 hr. The mixture was dissolved in ether, and the ether solution was extracted with sodium bicarbonate solution. The basic extract was acidified with 5% hydrochloric acid and extracted with ether. The ether was removed to leave 0.57 g (48%) of crude acid, which was recrystallized from chloroform: mp 199–200°; ir 5.8 μ (s), 6.0 (m), 6.15 (m), and 6.25 (m); nmr (dilute solution $CDCl_3$) 2.22 (s, 3, $C{=}CCH_3$), 1.43 (s, 6, $>C(CH_3)_2$) and 1.08 ppm (d, 3, $>CHCl_3$). The mass spectrum displayed important ions at *m/e* 236 (2%), 221 (100%), 203 (3%), 43 (13%).

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 70.44; H, 8.37.

A suspension of 100 mg of acid VIII in ether was treated with an ethereal solution of diazomethane. The solvent was evaporated affording an oil whose infrared spectrum was identical with that of the methyl ester of III.

Pyran IX.—A mixture of 0.4 g of acid VIII and 0.4 g of copper powder was heated at 220–300° resulting in the distillation of 0.2 g of liquid: ir 5.8 μ (m) and 6.0 (w); λ_{max}^{MeOH} 211 mμ (log ϵ 3.30) and 2.29 (sh) (3.14); nmr (CCl_4) δ 4.27 (q, 1, J = 1 Hz, =CH), 1.70 (d, 3, J = 1 Hz, *cis*-$CH_3C{=}CH$), 1.05 (s, 6, $>C(CH_3)_2$), and 1.02 ppm (d, 3, $>CHCH_3$). The mass spectrum exhibited important ions at *m/e* 192 (4%), 177 (100%), 135 (9%), 43 (11%).

Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 81.42; H, 10.55.

Registry No.—Pulegone, 15932-80-6; ethyl acetoacetate, 141-97-9; III, 18600-02-7; III (methyl ester), 18588-64-2; XI (methyl ester), 18588-65-5; reduction product of III, 18588-66-4; VI, 18588-67-5; VIII, 18588-68-6; IX, 18588-69-7; XI, 18588-73-3.

The Synthesis of Some Fluoronitrobenzimidazoles and Their Reactivities toward Peptide Nucleophiles

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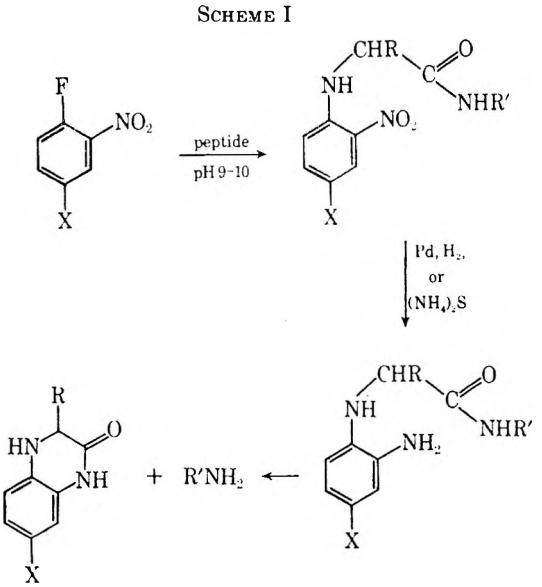
Received July 16, 1968

A series of mononitro- and dinitro-4-fluorobenzimidazoles has been prepared using 2-fluoroacetanilide as starting point. Assignment of position to the nitro groups is based on analyses of nmr hydrogen–fluorine coupling constants. Orientation in nitration is controlled by the fluorine atom rather than by the fused imidazole ring, except where steric factors intercede. At 25°, 5,7-dinitro-4-fluorobenzimidazole is 84 times as reactive as 2,4-dinitrofluorobenzene toward a peptide nucleophile. The enhanced reactivity is attributed primarily to the ability of the fused imidazole ring to participate in stabilization of the Meisenheimer adduct. The corresponding benzimidazole anion, as well as a series of mononitrofluorobenzimidazoles, are unreactive under the same conditions.

A series of investigations in this laboratory on the tertiary structure of proteins[1] created a need for methods for the quantitative determination of N-terminal amino acids in mixtures of polypeptides. Since neither the fluorodinitrobenzene[2] nor the phenyl isothiocyanate[2] method satisfactorily fulfilled our needs for quantitation, efforts were initiated several years ago to develop an alternative procedure.

Of the various possibilities considered, the approach first described by Holley and Holley[3] seemed attractive, primarily by virtue of the mild conditions under which peptide cleavage could be effected. In this method, the peptide is coupled with 1-fluoro-2-nitro-4-X-benzene, in which X = nitro or another electronegative, fluorine-activating substituent. The 2-nitro group of the peptide derivative is subsequently reduced, either catalytically[3] or with sulfide ion,[4] to provide an amino group as a favorably placed nucleophile for intramolecular attack on the amide bond of the N-terminal residue (Scheme I).

SCHEME I



It is obvious that the availability of a reagent with a preexisting nucleophile at position 2 would simplify

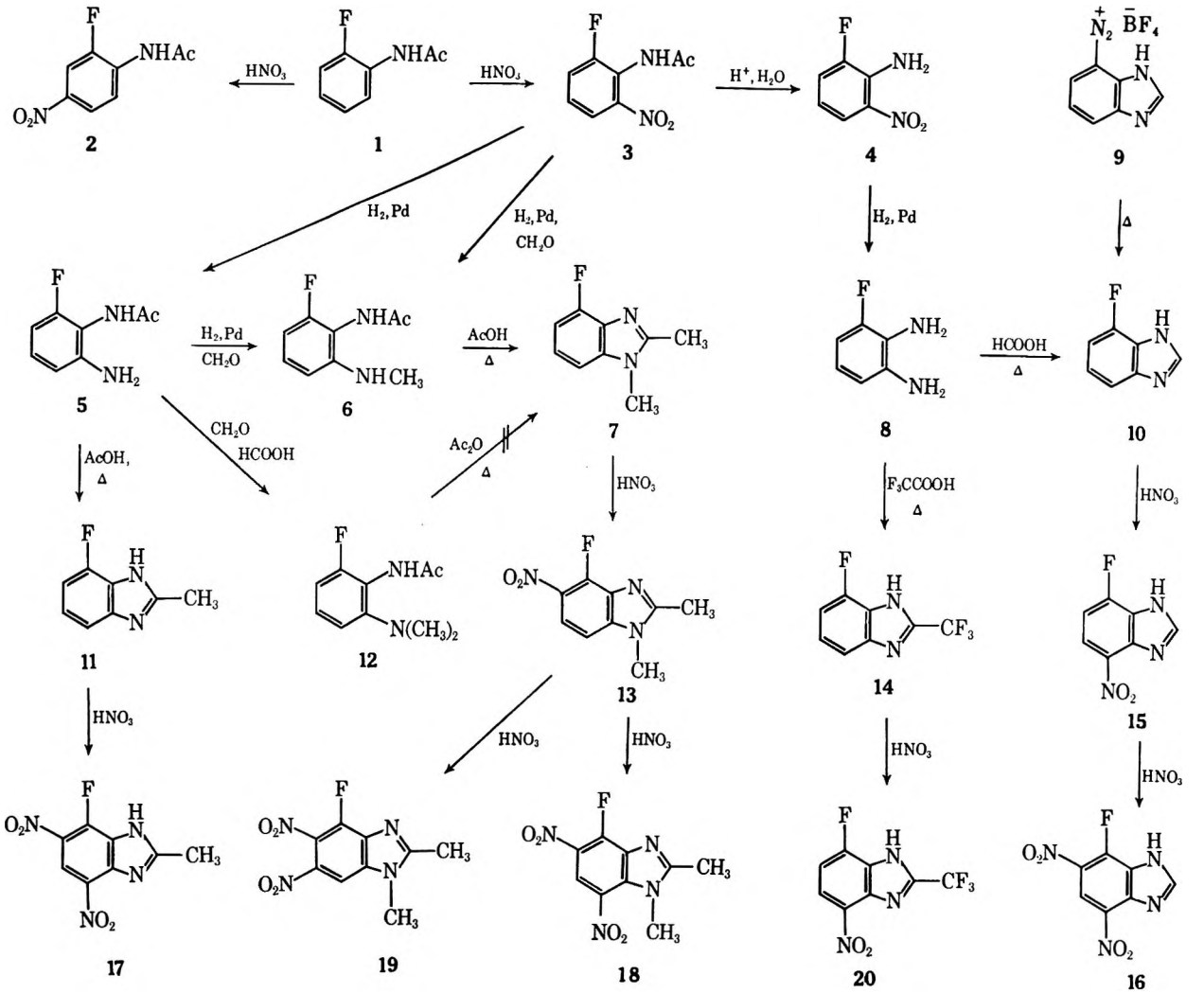
(1) L. Farber and L. A. Cohen, *Biochemistry*, **5**, 1027 (1966); J. G. Wilson and L. A. Cohen, *J. Amer. Chem. Soc.*, **85**, 564 (1963); S. Isoe and L. A. Cohen, *Arch. Biochem. Biophys.*, **127**, 522 (1968).

(2) J. L. Bailey, "Techniques in Protein Chemistry," Elsevier Publishing Co., New York, N. Y., 1962, Chapter 6.

(3) R. W. Holley and A. D. Holley, *J. Amer. Chem. Soc.*, **74**, 5445 (1962).

(4) E. Scoffone, E. Vianello, and A. Lorenzini, *Gazz. Chim. Ital.*, **87**, 354 (1957).

SCHEME II



the procedure measurably, by eliminating the need for a reduction step. Unfortunately, almost any functional group, which might be a reasonable candidate for the role of intramolecular participant, has the undesired effect of deactivating the reagent by electron release into the benzene ring. Guided by the demonstrated nucleophilicity of imidazoles toward activated esters[5] and by the hope that the aromatic character of the imidazole ring would counteract the electron-releasing ability of anilino nitrogen, we prepared a series of dinitro-4-fluorobenzimidazoles for study as bifunctional peptide reagents. The present report deals with the synthetic procedures, structural assignments and kinetics of fluorine replacement. The following paper[6] describes the results of rate studies on the intramolecularly catalyzed hydrolysis of the benzimidazole derivatives of various peptides.

4-Fluorobenzimidazole (**10**) has been prepared in low yield by small-scale pyrolysis of the corresponding diazonium fluoroborate, **9** (Scheme II).[7] Since efforts to expand the reaction scale resulted in even lower yields, an alternative route was developed. Controlled nitration of 2-fluoroacetanilide (**1**) provides a mixture of the *o*- (**3**) and *p*-mononitro (**2**) derivatives, from which 2-fluoro-6-nitroacetanilide (**3**) is readily separated by virtue of its greater alkali solubility.[8] Acid-catalyzed deacetylation of **3** to 2-fluoro-6-nitroaniline (**4**), followed by catalytic hydrogenation, led to 3-fluoro-*o*-phenylenediamine (**8**). When heated in formic acid solution, **8** was converted into 4-fluorobenzimidazole (**10**). Although the over-all yield, at this point, is 25%, large-scale synthesis offers no particular difficulties. Nitration of **10**, under relatively mild conditions, led to the 7-nitro derivative (**15**) while, under more vigorous conditions, the 5,7-dinitro derivative (**16**) was obtained. In either case, no isomeric nitration products were detected. It is noteworthy that benzimidazole, itself, is mononitrated exclusively at C-5; upon further nitration, a mixture of the 5,6-dinitro (54%) and of the 5,7- (or 4,6-) dinitro (21%) isomers is obtained.[9] Evidently, the directive influence of the fluorine atom takes precedence over that of the imidazole ring. Assignment of structure to

(5) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. I, W. A. Benjamin, Inc., New York, N. Y., 1966, Chapter 1.
(6) K. L. Kirk and L. A. Cohen, *J. Org. Chem.*, **34**, 390 (1969).
(7) E. C. Fisher and M. M. Joullié, *J. Org. Chem.*, **23**, 1944 (1958).
(8) B. M. Wepster and P. E. Verkade, *Rec. Trav. Chim.*, **68**, 77 (1949).
(9) G. E. Ficker and D. J. Fry, *J. Chem. Soc.*, 736 (1963).

TABLE I

NUCLEAR MAGNETIC RESONANCE SPECTRAL DATA FOR FLUORONITROBENZIMIDAZOLES[a]

Compd	$\delta_{1\text{-}CH_3}$, ppm	$\delta_{2\text{-}H}$, ppm	$\delta_{2\text{-}CH_3}$, ppm	$\delta_{5\text{-}H}$, ppm	$\delta_{6\text{-}H}$, ppm	$\delta_{7\text{-}H}$, ppm	$J_{HH(ortho)}$, Hz	$J_{HF(ortho)}$, Hz	$J_{HF(meta)}$, Hz	$J_{HF(para)}$ Hz
13	4.18		3.10		8.50 (q)	7.75 (q)	9		6	1
15		9.52		7.67 (q)	8.72 (q)		9	9	4	
20				7.42 (q)	8.60 (q)		9	9	4	
16		9.70			9.30 (d)				6	
17			3.23		9.22 (d)				6	
18	4.30		3.18		9.15 (d)				6	
19	4.30		3.14			8.58 (d)				1.8

[a] Spectra were measured in trifluoroacetic acid as solvent (approximately 0.02 *M*) with tetramethylsilane as internal reference.

these and other nitrobenzimidazoles is based, largely, on analyses of hydrogen–fluorine coupling constants in their nuclear magnetic resonance (nmr) spectra, as discussed below.

By direct hydrogenation of **3**, 2-amino-6-fluoroacetanilide (**5**) was obtained, which was converted into 2-methyl-4-fluorobenzimidazole (**11**) by heating its solution in acetic acid. The product was nitrated directly to 5,7-dinitro-4-fluoro-2-methylbenzimidazole (**17**); no effort was made to prepare a mononitro derivative.

The N-methyl compound, **6**, was obtained by catalytic hydrogenation of **5** in the presence of a small excess of formaldehyde. Direct conversion of **3** into **6** could also be effected by the same technique, although the yield was less satisfactory. By heating a solution of **6** in acetic acid, 1,2-dimethyl-4-fluorobenzimidazole (**7**) was obtained. In earlier experiments, **5** was converted into its N,N-dimethyl derivative, **12**; the conversion of **12** into **7** by boiling its solution in acetic anhydride was attempted. Although there have been several reports on the formation of 1,2-dimethylbenzimidazoles by heating 2-dimethylaminoanilines with acetic anhydride,[10] such conversion could not be effected in the present case. Mononitration of **7** led to the 5-nitro rather than the 7-nitro derivative, evidently the result of steric interference by the 1-methyl group. Upon further nitration of the product, **13**, a mixture of the 5,6-dinitro (**19**) and the 5,7-dinitro (**18**) isomers was obtained, the latter predominating. Separation of the isomers could be effected by column chromatography.

Finally, **8** was converted into 4-fluoro-2-trifluoromethylbenzimidazole (**14**) by heating its solution in trifluoroacetic acid. Nitration of **14** led to the 7-nitro derivative, **20**.

The positions of nitro groups in the mono- and dinitro derivatives were assigned by analysis of aromatic hydrogen–hydrogen and hydrogen–fluorine coupling constants (Table I). The values obtained for the latter ($J_{HF(ortho)}$ = 9 Hz, $J_{HF(meta)}$ = 4–6 Hz, and $J_{HF(para)}$ = 1–2 Hz) are consistent with those observed in other series of fluoroaromatic compounds.[11] It would appear that 4-fluorobenzimidazoles nitrate preferentially at C-7 (**15** and **20**). *ortho* nitration, in the case of **13**, is probably the result of steric interference at C-7 by the 1-methyl group; such interference is readily observed upon examination of space-filling models. The steric effect is evidently sufficient to encourage the formation of the 5,6-dinitro isomer (**19**), in addition to the desired 5,7-dinitro isomer (**18**). The 5,7-dinitro compounds, **16** and **17**, were obtained free of isomeric products.

The imidazole protons in **16** and **17** are fairly acidic. The marked shifts in visible absorption resulting from ionization (Figure 1) permit spectroscopic determination of their dissociation constants. Compound **16** was found to have a pK_a value of 7.97 and compound **17**, 8.18. Clearly, such acidity is the result of resonance stabilization of the negative charge by the nitro substituents (**21**), as well as by the imidazole ring.

The fused imidazole ring has a marked activating effect on aromatic nucleophilic displacement reactions. As may be seen from Table II, the reactivities of **16**, **17**, and **18** extend from 20 to almost 100 times that of

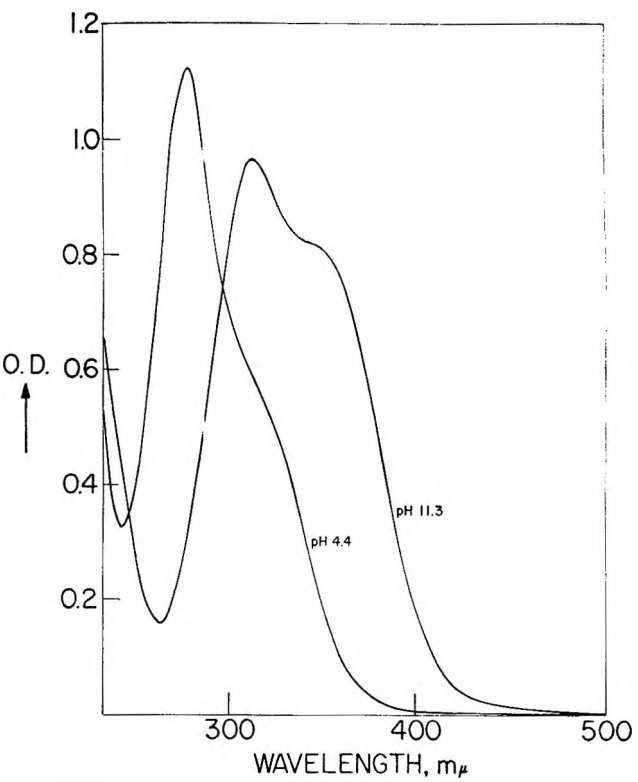
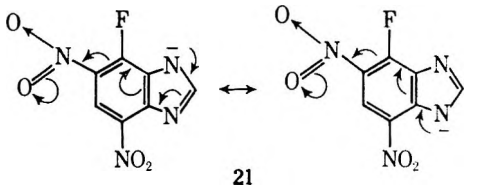


Figure 1.—The uv spectra of 2-methyl-4-fluoro-5,7-dinitrobenzimidazole (**17**) in neutral and alkaline media.

(10) K. Hofman, "Imidazole and Its Derivatives," Interscience Publishers, New York, N. Y., 1953, p 263.

(11) J. A. Pople, W. G. Schneider and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p 324.



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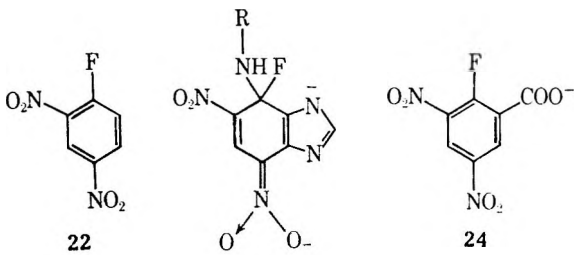
2,4-dinitrofluorobenzene (22) toward alanylglycine. The order of reactivities is consistent with the expected electron-releasing effects of methyl substitution in the imidazole ring. The rate of reaction, in the case of 17,[12] shows a maximum near pH 8, since the protonated peptide is unreactive at low pH and the ionized benzimidazole is unreactive at high pH. The lack of reactivity of the benzimidazole anion may be attributed either to resonance-coupled deactivation of the benzene ring by the negative charge, inability of the Meisenheimer complex (23) to accommodate two negative charges, or electrostatic repulsion between the imid-



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azole anion and the negatively charged dipeptide. We have not attempted to distinguish between the two former possibilities; however, the latter explanation is discounted by the observation that 3,5-dinitro-2-fluorobenzoate anion (24)[13] is significantly more reactive than 2,4-dinitrofluorobenzene toward alanylglycine (Table II).

Two factors, in addition to electronic activation, must be considered as potential contributors to the reactivites of 16, 17, and 18. The first depends on the ability of the reagent to associate with a peptide by hydrogen bonding of the amide group to the imidazole nitrogen prior to nucleophilic attack and, thus, provide the reaction with intramolecular characteristics. To evaluate the importance of this factor, rate data were obtained for a simple amine as nucleophile. Compound 17 is approximately 18 times as reactive as 22 toward methylamine and 38 times as reactive toward alanylglycine (Table II). The enhancement factor of 2 may be the result of hydrogen bonding or may be due to the difference in nucleophilic power of the two amines. At any rate, the factor is too small to be given an important role.

The second pathway for intramolecular assistance depends on hydrogen bonding between the imidazole

(12) Although its pH dependence was not investigated, 16 would be expected to show a similar rate profile.

(13) K. L. Kirk and L. A. Cohen, manuscript in preparation.

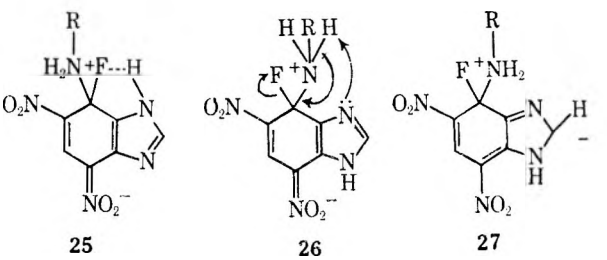
TABLE II

RATES OF REACTION OF ACTIVE FLUORINE COMPOUNDS WITH ALANYLGLYCINE[a]

Compound	pH	k_{obsd}, sec^{-1}	k_2,[b] M^{-1} sec^{-1}	k_2',[c] M^{-1} sec^{-1}	Relative rates
22	7.95	2.92×10^{-5}	6.52×10^{-3}	0.0176	1
16[d]	7.95	2.84×10^{-3}	2.81×10^{-1}	1.48	84.2
17[e]	7.95	1.52×10^{-3}	1.53×10^{-1}	0.656	37.3
17	6.32	8.90×10^{-5}	8.90×10^{-3}	0.664	37.7
17	10.15[f]	6.29×10^{-5}	6.92×10^{-3}	0.660	37.5
18	7.95	1.47×10^{-3}	1.47×10^{-1}	0.397	22.5
19	7.95	1.80×10^{-5}	1.80×10^{-3}	0.00485	0.28
24	7.95	2.41×10^{-3}	2.25×10^{-1}	0.607	34.5
22[g]	8.90[h]	4.10×10^{-4}	4.10×10^{-2}	2.20	125
17[g]	8.90[h]	1.17×10^{-3}	1.10×10^{-1}	39.2	2230

[a] See Experimental Section. [b] $k_2 = k_{obsd}/[alagly]$. [c] $k_2' = k_2$ divided by fraction of peptide present as free base and by fraction of benzimidazole present in neutral form (where applicable). [d] pK_a (NH → N$^-$) = 7.97. [e] pK_a = 8.18. [f] In carbonate buffer (0.2 M). [g] Reaction with methylamine as nucleophile. [h] In borate buffer (0.2 M).

NH and the departing fluorine atom (25) or on intramolecular proton removal by the imidazole nitrogen acting as a general base (26).[14] The former possibility may be excluded by the fact that 18, which should not participate in such a mechanism, shows



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an order of reactivity consistent with its structure, and the latter pathway is rendered unlikely by the very weak basicity of the imidazole nitrogen ($pK < 0$) in these compounds. We conclude that the reactivity of the dinitrofluorobenzimidazole system is due solely, or very largely, to electronic activation of the benzene ring.[15] Such activation may be visualized as resulting from the availability of an additional canonical form for the anion hybrid (27).

The mononitro derivatives show essentially no reactivity toward alanylglycine under the conditions employed, although they are reactive toward the more nucleophilic mercaptans.[16] No effort was made to effect dinitration of the 2-trifluoromethylbenzimidazole (14), since the mononitro compound (20) was already extensively ionized at neutral pH (pK_a = 5.4). As expected, the 5,6-dinitro isomer (19) was considerably less reactive than the 5,7-dinitro compound (18).

(14) B. Capon, M. J. Perkins, and C. W. Rees, "Organic Reaction Mechanisms 1965," Interscience Publishers, New York, N. Y., 1966, Chapter 6.

(15) A lack of proper data prevents evaluation of the inductive contribution of the fused imidazole ring toward activation of the fluorine.

(16) By comparison, 2,4-dinitrofluorobenzene is at least 20,000 times as reactive as 2- or 4-nitrofluorobenzene toward methoxide ion [C. W. L. Bevan and G. C. Bye, *J. Chem. Soc.*, 3091 (1954)].

Experimental Section[17]

2-Fluoro-6-nitroacetanilide (3).—Nitration of 2-fluoroacetanilide was performed on a 1-mol scale, following the published small-scale procedure.[8] Yields of purified material (30–35%) were comparable with those reported. Attempts to increase the yield of the desired *ortho* isomer, by varying reaction time or the strength of nitric acid used, were unsuccessful.

2-Fluoro-6-nitroaniline (4).—A suspension of 10 g (0.05 mol) of 2-fluoro-6-nitroacetanilide (3) in 50 ml of 2 *N* hydrochloric acid was heated at reflux for 3 hr. The reaction mixture was cooled, neutralized with sodium carbonate solution, and chilled. The product was obtained as orange needles, 7.5 g (95%), mp 72.5–74°. The amine has also been obtained by base-catalyzed deacylation of the acetanilide, mp 75–76°.[8]

3-Fluoro-*o*-phenylenediamine (8).—The crude nitroaniline (4, 7.5 g, 0.048 mol) was hydrogenated in ethanol solution, using palladium-on-charcoal catalyst. The theoretical amount of hydrogen was absorbed rapidly at room temperature and atmospheric pressure. Following removal of catalyst and solvent, a reddish oil remained which crystallized upon storage. The product was purified by vacuum sublimation: 5.8 g (95%), mp 40–41°.

Anal. Calcd for $C_6H_7FN_2$: C, 57.13; H, 5.59; F, 15.06; N, 22.21. Found: C, 57.04; H, 5.53; F, 15.02; N, 22.53.

4- (or 7-) Fluorobenzimidazole (10).—A solution of 1.0 g (0.08 mol) of 3-fluoro-*o*-phenylenediamine (8) in 50 ml of 90% formic acid was heated at reflux for 2 hr. Following removal of the solvent, the residue was purified by vacuum sublimation and crystallization from aqueous ethanol to give 0.86 g (80%) of colorless product, mp 188–190° (lit.[7] mp 180–185°).

The product was found to be identical with a sample prepared by pyrolysis of the diazonium fluoroborate (9), by mixture melting point and by comparison of nmr spectra. The nmr spectrum (DMSO-d_6) showed a one-proton singlet at 8.2 (C-2) and an aromatic multiplet at 6.7–7.5 ppm (3 H).

4- (or 7-) Fluoro-2-trifluoromethylbenzimidazole (14).—A solution of 1.0 g (0.08 mol) of 3-fluoro-*o*-phenylenediamine (8) in 25 ml of trifluoroacetic acid was heated at reflux for 2 hr. Following removal of the solvent, the residue was dissolved in ethanol and the solution was decolorized with Norit (hot). After filtration and evaporation of the solvent, the residue was purified by vacuum sublimation to give 1.36 g (83%) of colorless material (mp 183–187°). A portion was crystallized from water and resublimed: mp 188–189°.

Anal. Calcd for $C_8H_4F_4N_2$: C, 47.07; H, 1.98; F, 37.23; N, 13.73. Found: C, 47.18; H, 2.09; F, 37.25; N, 14.04.

The nmr spectrum (DMSO-d_6) showed only an aromatic multiplet at 6.9–7.7 ppm.

2-Amino-6-fluoroacetanilide (5).—A solution of 10 g (0.05 mol) of 2-fluoro-6-nitroacetanilide (3) in 100 ml of ethanol was hydrogenated, using 10% palladium on charcoal. Reduction was complete in 3 hr at room temperature and atmospheric pressure. Following removal of catalyst and solvent, the colorless product (8.4 g, 99%) was crystallized from water and sublimed: mp 154–155°.

Anal. Calcd for $C_8H_9FN_2O$: C, 57.13; H, 5.39; F, 11.30; N, 16.66. Found: C, 56.87; H, 5.58; F, 11.73; N, 16.83.

The ir spectrum (KBr) showed amide absorption at 1675 cm^{-1}. The nmr spectrum (acetone-d_6) exhibited a methyl singlet at 2.12 (3 H) and an aromatic multiplet at 6.2–7.2 ppm (3 H).

4- (or 7-) Fluoro-2-methylbenzimidazole (11).—A solution of 0.50 g (3 mmol) of 2-amino-6-fluoroacetanilide (5) in 20 ml of acetic acid was heated at reflux for 3 hr. Following removal of solvent, the product was purified by sublimation: 0.45 g (100%), mp 210–212°.

Anal. Calcd for $C_8H_7FN_2$: C, 63.99; H, 4.70; F, 12.65; N, 18.66. Found: C, 63.82; H, 4.76; F, 13.14; N, 18.62.

The ir spectrum was devoid of carbonyl absorption. The nmr spectrum (DMSO-d_6) showed a methyl singlet at 2.54 (3 H) and an aromatic multiplet at 6.7–7.4 ppm (3 H).

2-Fluoro-6-N-methylaminoacetanilide (6). A.—To a solution of 5.0 g (0.03 mol) of 2-amino-6-fluoroacetanilide (5) in 50 ml of ethanol was added 2.6 g of 37% formaldehyde solution (approximately 0.032 mol of formaldehyde) and the mixture was hydrogenated using 10% palladium on charcoal. After 36 hr at room temperature and atmospheric pressure, 90% of the theoretical amount of hydrogen had been consumed. Following removal of catalyst and solvent, 5.4 g of crystalline material was obtained. The product was recrystallized from water or ether and sublimed: mp 122–123°.

Anal. Calcd for $C_9H_{11}FN_2O$: C, 59.33; H, 6.09; F, 10.43; N, 15.38. Found: C, 59.63; H, 6.15; F, 10.36; N, 15.41.

The ir spectrum (KBr) showed amide absorption at 1665 cm^{-1}. The nmr spectrum ($CDCl_3$) showed a C-methyl singlet at 2.12 (3 H), an N-methyl singlet at 2.88 (3 H), broad absorption (NH?) at 4.1–4.4 (1 H), and an aromatic multiplet at 6.3–7.7 ppm (3 H).

B.—To a solution of 3.0 g (0.015 mol) of 2-fluoro-6-nitroacetanilide (3) in 50 ml of ethanol was added 1.4 g of 37% formaldehyde solution (approximately 0.017 mol of formaldehyde and the mixture hydrogenated as above. After 2 days, catalyst and solvent were removed, leaving an oil which crystallized slowly upon storage. Thin layer chromatography showed the material to be a mixture of 5 and 6. After two recrystallizations from water and sublimation, a low yield (0.8 g) of the desired N-methyl compound was obtained.

1,2-Dimethyl-4-fluorobenzimidazole (7).—A solution of 1.0 g (5.5 mmol) of 2-fluoro-6-N-methylaminoacetanilide (6) in 25 ml of acetic acid was heated at reflux for 12 hr. Following removal of solvent, 0.88 g (98%) of colorless, crystalline material was obtained. The product was recrystallized from water and sublimed: mp 144–146°.

Anal. Calcd for $C_9H_9FN_2$: C, 65.84; H, 5.53; F, 11.57; N, 17.06. Found: C, 65.73; H, 5.57; F, 11.58; N, 16.82.

The ir spectrum wss devoid of carbonyl absorption. The nmr spectrum (DMSO-d_6) showed a C-methyl singlet at 2.58 (3 H), an N-methyl singlet at 3.68 (3 H), and aromatic multiplet at 6.7–7.4 ppm (3 H).

2-N,N-Dimethylamino-6-fluoroacetanilide (12).—To a solution of 5.0 g (0.03 mol) of 2-amino-6-fluoroacetanilide (5) in 25 ml of formic acid was added 10 ml of formaldehyde solution (37%) and the mixture was heated at reflux for 6 hr. Following removal of solvent, the colorless residue was crystallized from water to give 4.6 g (79%) of dialkylated product, mp 132–135°.

Anal. Calcd for $C_{10}H_{13}FN_2O$: C, 61.21; H, 6.68; F, 9.68; N, 14.27. Found: C, 60.94; H, 6.43; F, 9.78; N, 14.32.

The nmr spectrum (acetone-d_6) showed a C-methyl singlet at 2.10 (3 H), an N-methyl singlet at 2.70 (6 H), and an aromatic multiplet at 6.6–7.4 ppm (3 H).

Several attempts were made to convert 12 into 7 by boiling its solution in acetic anhydride for periods up to 24 hr.[10] In each case, 12 was recovered almost quantitatively.

4- (or 7-) Fluoro-7- (or 4-) nitrobenzimidazole (15).—A solution of 0.25 g of 4- (or 7-) fluorobenzimidazole (10) in 1 ml of concentrated nitric acid was added dropwise to 1 ml of concentrated sulfuric acid with stirring and ice cooling. After storage for 3 hr at 25°, the solution was poured onto ice and the pH of the mixture was adjusted to 5 with saturated sodium bicarbonate solution. The yellow-white solid was collected and dried. Following purification by sublimation, 0.20 g of product, mp 240–247° dec, was obtained, *m/e* 181.03000 (calculated for $C_7H_4FN_3O_2$, 181.03035). Because of difficulty in crystallization of this and other fluoronitrobenzimidazoles, no attempt was made to purify them for combustion analysis. In each case, the composition was ascertained on the basis of parent peaks in the mass spectrum and homogeneity demonstrated by nmr spectra. The uv spectrum (ethanol) showed λ_{max} 316 mμ (ε 7870). For nmr data, see Table I.

1,2-Dimethyl-4-fluoro-5-nitrobenzimidazole (13).—Mononitration of 1,2-dimethyl-4-fluorobenzimidazole (7) was effected by following the general procedure given above. The product was obtained in 88% yield: mp 170–172° (benzene), *m/e* 209.05766 (calculated for $C_9H_8FN_3O_2$, 209.06165). The uv spectrum (ethanol) gave λ_{max} 300 mμ (ε 8870). For nmr data, see Table I.

4- (or 7-) Fluoro-7-(or 4-) nitro-2-trifluoromethylbenzimidazole (20).—Mononitration of 4-fluoro-2-trifluoromethylbenzimidazole (14) yielded 80% of a pale yellow product which was purified by sublimation: mp 120–122°, *m/e* 249.00621 (calculated for $C_8H_3F_4N_3O_2$, 249.02252). The uv spectrum gave $\lambda_{max}^{pH\ 1}$ 316 mμ (ε 9700), $\lambda_{max}^{pH\ 6.3}$ 353 mμ (ε 7950), and $\lambda_{max}^{pH\ 11}$ 335 mμ (ε 8750). On

(17) All melting points were determined on a Kofler block and are uncorrected. Ultraviolet (uv) spectra were measured using a Cary recording spectrophotometer, Model 14, nmr spectra with a Varian A-60 spectrometer, and infrared (μ) spectra with a Perkin-Elmer Infracord spectrophotometer. High resolution mass spectra were measured on an Hitachi double-focusing spectrometer, Model RMU-6E. Microanalyses were performed by Dr. W. C. Alford and his associates of this institute.

the basis of spectral data obtained at several pH values, the pK_a (NH → N^-) was estimated to be 5.4.

5,7- (or 4,6-) Dinitro-4- (or 7-) fluorobenzimidazole (16).—To a solution of 0.47 g of 4-fluorobenzimidazole (10) in 5 ml of concentrated sulfuric acid was added 16 ml of fuming nitric acid (*d* 1.50) and the mixture was heated at 120° (open condenser) for 12 hr. The mixture was cooled and poured onto ice to give a clear yellow solution. Upon neutralization to pH 6 with saturated sodium bicarbonate solution, a pale yellow solid separated: 0.57 g, mp 200° dec, *m/e* 226.01529 (calculated for $C_7H_3FN_4O_4$, 226.01543). On the basis of its nmr spectrum, the dinitro derivative was found to be free of the mononitro compound. The uv spectrum showed $\lambda_{max}^{pH\ 1}$ 275 mμ (ε 16,100), $\lambda_{max}^{pH\ 7.9}$ 300 mμ (ε 11,700), and $\lambda_{max}^{pH\ 10.7}$ 305 mμ (ε 13,700) and 345 (11,000). From spectral data, the pK_a (NH → N^-) was calculated to be 7.97.[18] For nmr data, see Table I.

5,7- (or 4,6-) Dinitro-4- (or 7-) fluoro-2-methylbenzimidazole (17).—Nitration of 4-fluoro-2-methylbenzimidazole (11) was carried out as described above and heating was continued for 20 hr at 120°. The pale yellow product was obtained in quantitative yield: mp *ca.* 250° dec, *m/e* 240.03176 (calculated for $C_8H_5FN_4O_4$, 240.03108). The uv spectral data showed $\lambda_{max}^{pH\ 1}$ 276 mμ (ε 14,600), $\lambda_{max}^{pH\ 7.0}$ 282 mμ (ε 13,400), and $\lambda_{max}^{pH\ 11.7}$ 310 mμ (ε 14,600). From spectral data, the pK_a (NH → N^-) was calculated to be 8.18.[18] Spectra of 17 in neutral and alkaline media are reproduced in Figure 1. For nmr data, see Table I.

1,2-Dimethyl-5,7-dinitro-4-fluorobenzimidazole (18) and 1,2-Dimethyl-5,6-dinitro-4-fluorobenzimidazole (19).—The product obtained by analogous nitration of 1,2-dimethyl-4-fluorobenzimidazole (7) was found, by thin layer chromatography [silica gel, tetrahydrofuran–chloroform (1:1)] to be composed of two isomers. Chromatography of 200 mg of the mixture on a column of silicic acid (Merck) and elution with tetrahydrofuran–chloroform (1:1) led to the recovery of 120 mg of the 5,7-dinitro isomer (18), which was recrystallized from benzene and further purified by sublimation: mp 99–100°, *m/e* 254.04658 (calulated for $C_9H_7FN_4O_4$, 254.04672). The uv spectrum gave $\lambda_{max}^{pH\ 7.9}$ 280 mμ (ε 13,100).

The slower moving 5,6-dinitro isomer (19) was recovered from the column by elution with the same solvent mixture (20 mg) and recrystallized from benzene: mp 164–168° dec, *m/e* 254.04457. The uv spectrum showed $\lambda_{max}^{pH\ 7.9}$ 238 mμ (ε 13,600) and 330 (4600).

Further nitration of the mononitro derivative (13) led, in a similar manner, to a mixture of the dinitro isomers. In addition to their spectral differences, the isomers may be differentiated on thin layer plates by their rates of reaction with ammonia vapor. The 5,7 isomer rapidly forms an intense, deep yellow spot, whereas the 5,6 isomer requires at least 1 hr for reaction with ammonia.

Reaction of Dinitrofluorobenzimidazoles with Alanylglycine.—To a solution of 50 mg (0.34 mmol) of L-alanylglycine in 5 ml of 0.2 *M* sodium bicarbonate–carbonate buffer (pH 9) was added, in one portion, 50 mg (0.22 mmol) of 5,7-dinitro-4-fluoro-2-methylbenzimidazole (17). The mixture was heated at 50° for 30 min, cooled, and acidified to pH 3. The yellow derivative was collected, dried (62 mg, 82%), and crystallized from aqueous ethanol: mp 220–230° dec. The uv spectrum (in 2 *M* KCl–10% ethanol) gave λ_{max} 415 mμ (ε 4680), 370 (8550), 305 (8200), and 228 (9700).[19]

Anal. Calcd for $C_{13}H_{14}N_6O_7$: C, 52.63; H, 3.85; N, 22.95. Found: C, 42.82; H, 3.77; N, 23.04.

The **alanylglycine** derivative of **5,7-dinitro-4-fluorobenzimidazole (16)** was prepared in a similar manner: 74% yield, mp 225–240° dec (aqueous ethanol). The uv spectrum (in 2 *M* KCl–0.02 *N* HCl–10% ethanol) gave λ_{max} 415 mμ (ε 9500), 362 (11,200), 295 (7800), and 228 (7900).

Anal. Calcd for $C_{12}H_{12}N_6O_7$: C, 40.91; H, 3.44; N, 23.86. Found: C, 40.87; H, 3.25; N, 23.92.

The **alanylglycine** derivative of **1,2-dimethyl-5,7-dinitro-4-fluorobenzimidazole (18)** was obtained in 80% yield: mp 195–200° dec (aqueous ethanol). The uv spectrum (in 2 *M* KCl–10% ethanol) showed λ_{max} 425 mμ (sh) (ε 4800), 375 (8350), 250 (9400), and 230 (9150).

Anal. Calcd for $C_{14}H_{16}N_6O_7$: C, 44.21; H, 4.24; N, 22.10. Found: C, 44.39; H, 4.54; N, 21.68.

The dipeptide derivatives were shown to be homogeneous by thin layer chromatography on silica gel GF, using chloroform–*t*-amyl alcohol–acetic acid (70:30:5) as developing agent.

Kinetic Runs with Alanylglycine.—Reaction mixtures were prepared by adding 0.50 ml of an ethanol solution of the appropriate dinitrofluorobenzimidazole (0.08–0.09 m*M*) to 4.5 ml of a solution of alanylglycine (in 0.2 *M* phosphate buffer, pH 7.95). The final concentration of reagent was approximately 0.1 m*M* and that of alanylglycine, 10 m*M*. Samples were maintained at 25° and the progress of the reaction followed by the increase in absorption at 410 mμ. Comparative rates for reaction of alanylglycine with 2,4-dinitrofluorobenzene were followed at 370 mμ. Pseudo-first-order rate constants were obtained from the slope of the plot of $O.D._\infty/(O.D._\infty - O.D._t)$ *vs.* time. Reactions were carried to completion, infinity values and final spectra being in agreement with those obtained from samples of the purified dipeptide derivatives.

Registry No.—**5,** 18645-85-7; **6,** 18645-86-8; **7,** 18645-87-9; **8,** 18645-88-0; **11,** 18645-89-1; **12,** 18645-90-4; **13,** 18645-91-5; **14,** 18645-92-6; **15,** 18645-93-7; **16,** 18645-94-8; alanylglycine derivative of **16,** 18645-99-3; **17,** 18645-95-9; alanylglycine derivative of **17,** 18646-00-9; **18,** 18645-96-0; alanylglycine derivative of **18,** 18646-01-0; **19,** 18645-97-1; **20,** 18645-98-2.

(18) Spectral pK_a values were measured at 25° in 0.2 *M* phosphate buffer containing 10% ethanol.

(19) The uv spectra of peptide derivatives are reproduced in the following paper.[6]

The Hydrolysis of Peptide Bonds by Intramolecular Participation of Benzimidazolium Ions

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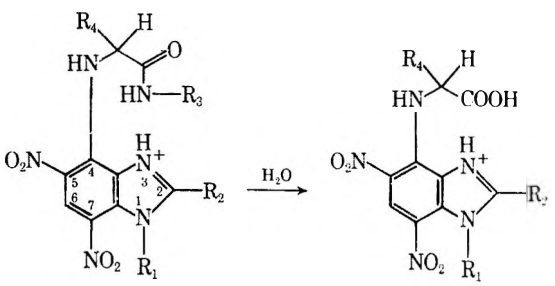
A series of 5,7-dinitrobenzimidazolyl-4 peptides have been prepared and the rates of hydrolysis of the peptide bond determined as a function of acidity and temperature. It is demonstrated that the rate of hydrolysis is dependent on the degree of protonation of a benzimidazole nitrogen atom. The effectiveness of the intramolecular participation varies with the nature of the peptide side chain and with the degree of alkylation of the imidazole ring. No correlation is observed between pK_a and specific rate constant for the various substrates. Heats of ionization and activation parameters are reported for two cases. The compound, 1,2-dimethyl-5,7-dinitrobenzimidazolyl-4-alanylglycine, was found to hydrolyze 65,000 times as rapidly as 2,4-dinitrophenylalanylglycine.

In the preceding paper,[1] we reported on the synthesis of several 5,7-dinitro-4-fluorobenzimidazoles and on the kinetics of displacement of the fluorine atom by simple dipeptides. Using these reagents, we have now prepared a variety of dipeptide derivatives[2] and have studied the rates of peptide bond cleavage as a function of acidity and temperature. This work was undertaken for diverse reasons: we hoped to utilize the bifunctional



1. $R_1 = R_2 = H$
2. $R_1 = H; R_2 = CH_3$
3. $R_1 = R_2 = CH_3$

nature of the reagents as a means of effecting facile, selective, and quantitative removal of N-terminal residues from polypeptides, providing an alternative to currently available methods;[3] secondly, we planned to use this study as an entry into the general problem of intramolecularly facilitated hydrolysis of peptide bonds.

In contrast to the extensive literature on the intramolecularly catalyzed hydrolysis of esters,[4] significantly less work has been done on the analogous hydrolysis of amides. Of the accessory functional groups which have been investigated in the latter case, the principal efforts have involved the hydroxyl[5] and carboxyl[6] groups. Nitrogen participation has been studied in the form of imidazole,[7] pyridine,[8] pyridine N-oxide,[9] aromatic amine,[10] and amide.[11] Sulfur participation has been demonstrated for thioamides,[12a] thioureas,[12b] and dithiocarbamates.[12c]

There is sufficient evidence for a lack of parallelism in the chemistries and hydrolysis mechanisms of esters and amides (particularly in acidic media) to warrant independent investigation of the latter. For example, differences in resonance stabilization, basicity, and conformation are well known. The fact that esters show ^{18}O exchange in acidic media,[13] while amides generally do not,[14] indicates mechanistic differences;

(1) K. L. Kirk and L. A. Cohen, *J. Org. Chem.*, **34**, 395 (1968).

(2) The alternative order of numbering the benzimidazole ring system has been omitted for the sake of simplicity. In tables or figures, standard abbreviations for amino acids have been used: glycine = gly or G; alanine = ala or A; valine = val or V.

(3) J. I. Harris and V. M. Ingram in "Analytical Methods of Protein Chemistry," P. Alexander and R. J. Block, Ed., Pergamon Press, New York, N. Y., 1960, Chapter 12; J. L. Bailey, "Techniques in Protein Chemistry," Elsevier Publishing Co., New York, N. Y., 1962, Chapter 6.

(4) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. I, W. A. Benjamin, Inc., New York, N. Y., 1966, Chapter 1.

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(6) (a) S. J. Leach and H. Lindley, *Trans. Faraday Soc.*, **49**, 915, 921 (1953); (b) M. L. Bender, Y. L. Chow, and F. Chloupek, *J. Amer. Chem. Soc.*, **80**, 5380 (1958); (c) B. Zerner and M. L. Bender, *ibid.*, **83**, 2267 (1961); (d) H. Morawetz and J. Shafer, *ibid.*, **84**, 3783 (1962); (e) E. H. Westhead, Jr., and H. Morawetz, *ibid.*, **80**, 237 (1958); (f) B. Vigneron-Voortman, P. Crooy, and A. Bruylants, *Bull. Soc. Chim. Belges*, **73**, 241 (1964); (g) B. Witkop, *Advan. Protein Chem.*, **16**, 229 (1961).

(7) T. C. Bruice and J. M. Sturtevant, *J. Amer. Chem. Soc.*, **81**, 2860 (1959).

(8) (a) A. Signor and E. Bordignon, *J. Org. Chem.*, **30**, 3447 (1965); (b) A. Signor, E. Bordignon, and G. Vidali, *ibid.*, **32**, 1135 (1967); (c) A. Signor, L. Biondi, and E. Bordignon, *ibid.*, **31**, 1403 (1966).

(9) (a) V. Tortorella and G. Tarzia, *Gazz. Chim. Ital.*, **97**, 1479 (1967); (b) V. Tortorella and G. Bettoni, *ibid.*, **97**, 1487 (1967).

(10) (a) R. W. Holley and A. D. Holley, *J. Amer. Chem. Soc.*, **74**, 3069, 5445 (1952); (b) M. Jutisz, E. Scoffone, and P. de la Llosa, *Bull. Soc. Chim. Fr.*, 1551 (1959); (c) P. de la Llosa, M. Jutisz, and E. Scoffone, *ibid.*, 1621 (1960).

(11) (a) M. Vigneron, P. Crooy, F. Kezdy, and A. Bruylants, *Bull. Soc. Chim. Belges*, **69**, 616 (1960); (b) P. Crooy and A. Bruylants, *ibid.*, **73**, 44 (1964); (c) T. Cohen and J. Lipowitz, *J. Amer. Chem. Soc.*, **86**, 5611 (1964); (d) J. A. Shafer and H. Morawetz, *J. Org. Chem.*, **28**, 1899 (1963); (e) G. R. Stark and D. G. Smyth, *J. Biol. Chem.*, **238**, 214 (1963).

(12) (a) G. C. Barrett, *Chem. Commun.*, 487 (1967); G. W. Kenner and H. G. Khorana, *J. Chem. Soc.*, 2076 (1952); (b) P. Edman, *Acta Chem. Scand.*, **10**, 761 (1956); (c) A. L. Levy, *J. Chem. Soc.*, 404 (1950); J. Leonis, *Bull. Soc. Chim. Belges*, **61**, 524 (1952); D. T. Elmore and P. A. Toseland, *J. Chem. Soc.*, 4533 (1954).

(13) M. L. Bender, *J. Amer. Chem. Soc.*, **73**, 1626 (1951).

(14) (a) M. L. Bender and R. D. Ginger, *ibid.*, **77**, 348 (1955); (b) C. A. Bunton, C. O'Connor, and T. A. Turney, *Chem. Ind.* (London), 1835 (1967).

TABLE I

5,7-DINITROBENZIMIDAZOLYL-4 AMINO ACIDS AND DIPEPTIDES

Compound	Mp, °C[a]	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Yield, %	R_f[b]
1-DL-ala	208–213	$C_{10}H_9N_5O_6$	40.68	3.07	23.73	40.68	3.27	23.98	92	0.79
2-gly	230–238	$C_{10}H_9N_5O_6$	40.68	3.07	23.73	40.82	3.06	23.94	90	0.53
2-DL-ala	222–240	$C_{11}H_{11}N_5O_6$	42.87	3.59	22.65	43.00	3.89	22.59	43	0.83
2-L-val	195–198	$C_{13}H_{15}N_5O_6$	46.29	4.48	20.77	46.33	4.29	20.54	33	0.90
3-gly[c]	215–222	$C_{11}H_{11}N_5O_6$		*m/e* 309			*m/e* 309		97	0.70
3-DL-ala[c]	230–245	$C_{12}H_{13}N_5O_6$		*m/e* 323			*m/e* 323		50	0.84
1-L-alagly	225–240	$C_{12}H_{12}N_6O_7$	40.91	3.43	23.86	40.87	3.25	23.92	73	0.20
2-L-alagly	220–230	$C_{13}H_{14}N_6O_7$	42.62	3.85	22.95	42.82	3.77	23.04	82	0.28
2-gly-DL-ala	220–229	$C_{13}H_{14}N_6O_7$	42.62	3.85	22.95	42.60	4.04	22.66	77	0.27
2-glygly	242–245	$C_{12}H_{12}N_6O_7$	40.91	3.43	23.86	41.20	3.57	23.67	90	0.11
2-L-ala-L-ala	241–245	$C_{14}H_{16}N_6O_7$	44.21	4.24	22.10	44.27	4.52	21.95	76	0.47
2-L-valgly	189–192	$C_{15}H_{18}N_6O_7$	45.68	4.60	21.31	45.39	4.74	21.07	50	0.50
2-L-ala-L-val	240–244	$C_{16}H_{20}N_6O_7$	47.06	4.94	20.58	46.96	4.77	20.49	87	0.76
3-L-alagly	195–200	$C_{14}H_{16}N_6O_7$	44.21	4.24	22.10	44.39	4.54	21.68	79	0.39
3-gly-DL-ala[c]	220–227	$C_{14}H_{16}N_6O_7$		*m/e* 380			*m/e* 380		55	0.38

[a] All compounds melt with decomposition. [b] Tlc on silica gel GF, developed with chloroform–*t*-amyl alcohol–acetic acid (70:30:5). [c] Composition ascertained by parent peak in mass spectrum because of difficulties in crystallization.

furthermore, a dependence of mechanism on the nature of the leaving group has been demonstrated for certain esters.[15] It may be expected that intramolecular hydrolysis will be even more sensitive to structural variations. Finally, the extent to which the mass of data and speculation on the enzymatic hydrolysis of esters[4] is relavant to amide substrates remains uncertain.

Experimental Section[16]

Materials.—Dipeptides (Mann Research Laboratories) were coupled with dinitrofluorobenzimidazoles following the preparative procedure previously reported.[1] Analytical and physical data for these compounds are recorded in Table I. For reference purposes, the corresponding amino acid derivatives were prepared in a similar manner. In each case, recrystallization was effected from aqueous ethanol and homogeneity checked by thin layer chromatography (tlc) (Table I).

pK_a' Measurements.—Standardized hydrochloric acid (2.00 *N*) was diluted as necessary with 2.00 *M* potassium chloride. The solutions were then diluted with ethanol (9:1, v/v) containing *o*-nitroaniline and H_0' values[17] determined spectrophotometrically at 25°.[18] The pK_{BH+} value for the indicator was taken as −0.29, neglecting variations due to the added salt or ethanol. The results are given in Table II; values of H_0 in dilute hydrochloric acid, obtained by interpolation of the data of Paul and Long,[18] are included for comparison.

Using similar procedures and the values of H_0' obtained above, pK_a' (25°) values were determined for peptide derivatives of the several dinitrobenzimidazoles, as recorded in Table III. The uv spectra of the benzimidazole chromophores are quite characteristic, both in the neutral and acidic forms; an example, 2-alanine, is shown in Figure 1. Primarily, the absorbance at 310 mμ, at various values of H_0', was used for pK_a' calculations. Within the range 25–50°, the desired temperature was maintained by circulation of thermostated water through the cell holder.[19]

TABLE II

ACIDITIES OF HYDROCHLORIC ACID SOLUTIONS (μ = 2.00) CONTAINING 10% ETHANOL (BY VOLUME) AT 25°

Acid concentration, mol/l.	H_0'[a]	H_0[b]
0.18	0.54	0.75
0.27	0.40	0.52
0.36	0.27	0.40
0.45	0.14	0.27
0.68	−0.03	0.03
0.90	−0.17	−0.13
1.35	−0.38	−0.39
1.80	−0.51	−0.60

[a] Values determined in this investigation. [b] Values for aqueous hydrochloric acid, based on ref 18.

TABLE III

RATES OF HYDROLYSIS OF 5,7-DINITROBENZIMIDAZOLYL-4 DIPEPTIDES[a]

Compound	pK_a' (25°)	$k_{obsd} \times 10^2$, min^{-1}	$k_u \times 10^2$,[b] min^{-1}	Relative rates
DNP-alagly			0.0021[c]	1
1-alagly	−0.69	5.68	31.9	15200
2-alagly	0.25	18.78	28.7	13700
2-alala	0.15	7.16	11.9	5700
2-glygly	0.62	2.27	2.8	1300
2-glyala	0.59	1.52	1.9	900
2-alaval	0.03	1.84	3.5	1700
2-valgly	0.02	0.65	1.2	600
3-alagly	−0.29	48.10	136.6	65000
3-glyala	0.18	4.87	7.9	3800
2-gly	0.39			
2-ala	0.20			
2-val	−0.10			

[a] At 50°, H_0' = −0.03. [b] Calculated using pK_a' (25°) and eq 2. [c] Based on data of Signor and Bordignon;[8a] rate of hydrolysis measured under (pseudo) first-order conditions, at 60°. For conversion to 50°, E_a was taken as 20 kcal/mol.

In the cases of 2- and 3-alanylglycine, extrapolation to zero time was made prior to calculation, since some hydrolysis occurs at 25°.

Rate Measurements.—Solutions of hydrochloric acid (1.80 ml), at constant ionic strength (2.00 *M*), were placed in glass-stoppered vessels and brought to the desired temperature in a thermostated water bath. Solutions of the substrate in ethanol

(15) J. W. Thanassi and T. C. Bruice, *J. Amer. Chem. Soc.*, **88**, 747 (1966).

(16) Ultraviolet (uv) spectra were measured using a Cary recording spectrophotometer, Model 14. High resolution mass spectra were measured on an Hitachi double-focusing spectrometer, Model RMU-6E. Microanalyses were performed by Dr. W. C. Alford and his associates of this institute.

(17) H_0, and pK_a' refer specifically to media of fixed ionic strength (2.00 *M*) and containing 10% ethanol, as used throughout the present study.

(18) M. A. Paul and F. A. Long, *Chem. Rev.*, **57**, 1 (1957).

(19) No correction was made for the variation of H_0', with temperature. Within the temperature range used, the correction is estimated not to exceed 0.05 H_0 units [A. I. Gelbshtein, G. G. Shcheglova, and M. I. Temkin, *Dokl. Akad. Nauk SSSR*, **107**, 108 (1956)].

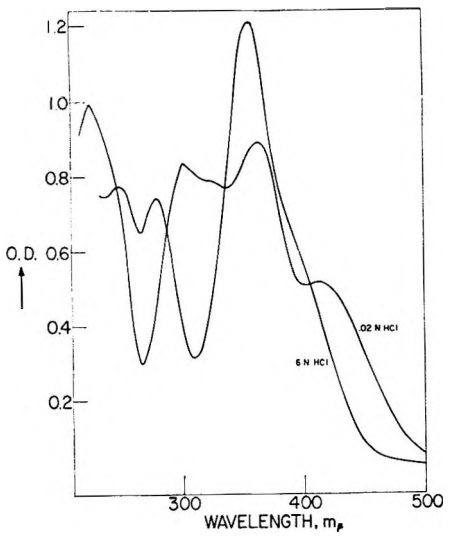


Figure 1.—The uv spectra of 2-alanine in neutral and acidic media.

(0.20 ml, *ca.* 1.5×10^{-2} *M*) were added and 0.10-ml aliquots were withdrawn periodically. The liberated amino acid was assayed by the ninhydrin method,[20] aqueous base being added where necessary to neutralize excess hydrochloric acid. Infinity values were obtained by continuing the hydrolysis runs until the ninhydrin assay gave constant values. Upon completion of a run, the dinitrobenzimidazolylamino acid was the only colored component detectable by tlc. Control experiments showed the dinitrobenzimidazolylamino acids to be completely stable under the conditions of hydrolysis. Dinitrobenzimidazolyl peptides are stable to hydrolysis under alkaline conditions; no peptide bond cleavage was detectable at 50° and pH 10.

Results and Discussion

pK_a' Measurements.—The basicity of the benzimidazole ring system is markedly dependent on the nature of the attached peptide (Table III), as well as on the degree of alkylation of the heterocyclic ring. From the limited cases examined, it would appear that the N-terminal amino acid is the principal determinant of basicity, the pK_a' (25°) values for derivatives of glycyl peptides being 0.4–0.5 units higher than those for alanyl peptides; similar variations are observed in the pK_a' values of the amino acid derivatives. The values bear no relationship, in their order, to the pK_a values of the simple dipeptides and cannot be explained on the basis of inductive effects. More likely, the variation may stem from a combination of electrostatic interactions and the conformational orientation of the peptide side chain, the latter possibly being influenced by the 5-nitro group. In any case, it is clear that, since rates of hydrolysis depend on the degree of protonation of the imidazole nitrogen (see below), variations in basicity must be considered in any comparisons made.

The introduction of a 2-methyl substituent increases benzimidazole basicity by one pK unit (2-alanylglycine *vs.* 1-alanylglycine). Such an enhancement is slightly greater than that observed with simpler benzimidazoles (*ca.* 0.8 unit).[21] The introduction of a 1-methyl substituent normally has little effect on the basicities of benzimidazoles or 2-methylbenzimidazoles. In the present series, the 1,2-dimethyl derivatives (3-alanylglycine, 3-glycylalanine) are less basic than their 2-methyl counterparts by 0.4–0.5 pK units, a phenomenon which may be due to steric interaction between the 7-nitro and 1-methyl groups[1] and the resulting distortion of the imidazole ring.

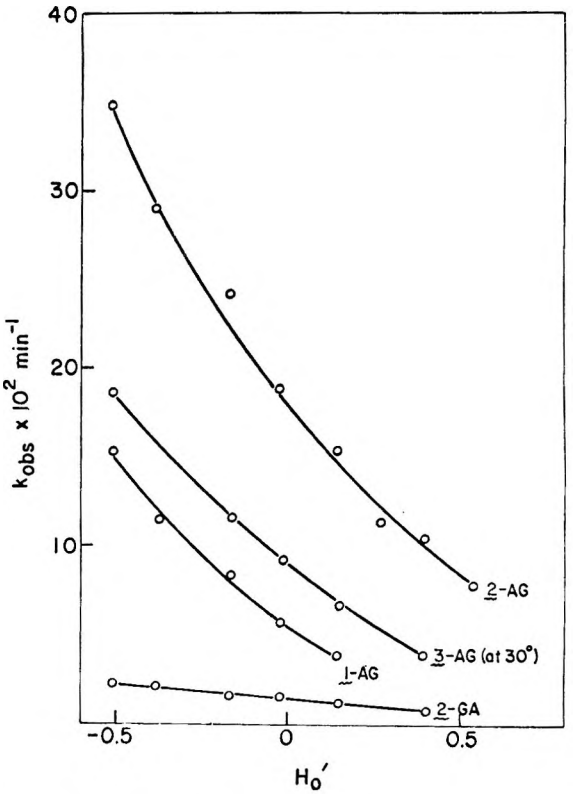


Figure 2.—Dependence of hydrolysis rates on H_0' at 50°.

Rates of Hydrolysis.—The rates of hydrolysis of the various benzimidazolyl dipeptides were followed to 60–90% completion, the first-order rate law being obeyed over the entire range. Observed (pseudo) first-order rate constants are recorded in Table III.[22] The variation of rate with H_0', as shown in Figure 2 for representative compounds, suggests participation by the benzimidazolium species. Since the benzimidazole group can exist in the protonated (ImH^+), neutral (Im), and anionic (Im^-) species (except for series **3**), the total rate may be expressed as a sum of terms (eq 1). Since no peptide bond cleavage was

$$k_{obs}[Im_{tot}] = k_a[ImH^+] + k_n[Im] + k_b[Im^-] \quad (1)$$

observed in alkaline media, $k_b = 0$; the absence of any deviation from linearity in Figure 3 (see below) indicates the acid-independent rate, k_n, to be 0 or negligible. Thus

$$k_{obsd} = k_a[ImH^+/Im_{tot}] = k_a \frac{h_0'}{h_0' + K_a'} \quad (2)$$

(20) D. H. Spackman, W. H. Stein, and S. Moore, *Anal. Chem.*, **30**, 1190 (1958).

(21) K. Hofmann, "Imidazole and Its Derivatives," Interscience Publishers, New York, N. Y., 1953, p 251.

(22) All rate constants and other slope values were calculated by the method of least squares.

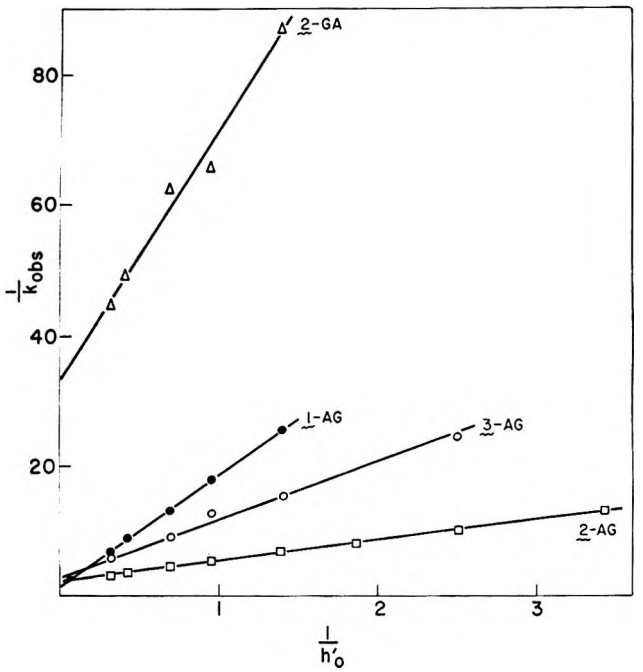


Figure 3.—Plot of $1/k_{obsd}$ *vs.* $1/h_0'$ as a test for kinetic dependence on protonated benzimidazole.

and

$$1/k_{obsd} = 1/k_a + K_a'/k_a \times 1/h_0' \quad (3)$$

where k_a = the specific rate constant for the acid-catalyzed reaction and K_a' = the apparent dissociation constant for the equilibrium 4.

$$-NH^+ \overset{K_a'}{\rightleftharpoons} -N + H^+ \quad (4)$$

For each compound studied, the linearity of a plot of $1/k_{obsd}$ *vs.* $1/h_0'$ (Figure 3) demonstrated a kinetic dependence on the concentration of protonated benzimidazole.[23] No attempt was made to derive values of k_a or K_a' from eq 3 and the slopes of the lines in Figure 3, since such values are highly sensitive to slight variations in slope. Approximate values of k_a (Table III) were calculated from k_{obsd} and pK_a' (25°). For two compounds, 2-alagly and 2-glyala, the variation of pK_a' with temperature was determined spectrophotometrically; the results, together with thermodynamic functions, are shown in Table IV. The values are in accord with those obtained for other very weak bases, such as *o*- and *p*-nitroaniline.[24] The error in k_a (50°), introduced by neglecting the difference between pK_a' (25°) and pK_a' (50°), would amount to 10–15% and would not significantly affect the conclusions drawn from these results.

A Brønsted plot of log k_a (50°) *vs.* pK_a' (25°) (Figure 4) fails to show any general dependence of hydrolysis rate on basicity, except for the three 2-alanyl-X compounds, which obey a linear relationship. On the other hand, the specific rates for 3-alanylglycine and 3-glycylalanine show an inverse dependence on benzimidazole basicity. The order of hydrolysis rates for the series of 2 dipeptides bears no relationship to that for hydrolysis of the simple dipeptides,[25] possibly because the intramolecular reaction is governed principally by conformational alignment of the side chain, rather than by steric accessibility to water.

Variation in the benzimidazole portion of the molecule similarly fails to demonstrate any trend. Of the three alanylglycine derivatives studied, 3-alanylglycine hydrolyzes most rapidly, although its pK_a' value falls between those for the corresponding 1- and 2-alanylglycine derivatives. Although 2-methylimidazoles and 2-methylbenzimidazoles are significantly less nucleophilic than their unsubstituted counterparts,[26] presumably for steric reasons, such a factor is not obvious in the present study. It is well known, however, that steric hindrance is far less of a deterrent to intramolecular than to intermolecular reactions.[27] Furthermore, while the benzimidazole anion is a better nucleophile than the neutral species toward *p*-nitrophenyl acetate,[26] it is ineffective toward amide substrates.

Effect of Temperature.—Rates of hydrolysis at a series of temperatures were determined for 2-alanylglycine and 2-glycylalanine. Based on heats of ionization, values of pK_a' at each temperature were calculated and, in turn, values of k_a from k_{obsd} and pK_a' (eq 2).[19]

TABLE IV
APPARENT HEATS OF IONIZATION OF BENZIMIDAZOLYL DIPEPTIDES

Compound	pK_a' (25°)	pK_a' (50°)[a]	$\Delta H'_{ioniza.}$ cal/mol	$\Delta S_{ioniza.}$ eu
2-alagly	0.25	0.12	2600	7.4
2-glyala	0.59	0.38	3600	9.4

[a] pK_a' was also determined at several intermediate temperatures.

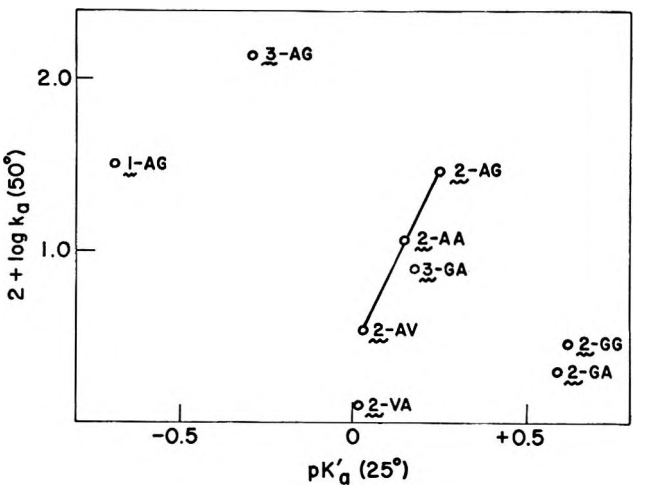


Figure 4.—Variation of specific rate constants (k_a) with basicities of benzimidazoles.

(23) For most of the acid concentrations used, the deviation of h_0 from $a_{H_3O^+}$ is small.

(24) Thus, *o*-nitroaniline (pK_a = −0.26) shows ΔH = 1710 cal/mol and ΔS = 6.9 eu and *p*-nitroaniline (pK_a = 1.00), ΔH = 3130 cal/mol, and ΔS = 5.9 eu [A. I. Biggs, *J. Chem. Soc.*, 2572 (1961)].

(25) R. L. Hill, *Advan. Protein Chem.*, **20**, 37 (1965).

(26) T. C. Bruice and G. L. Schmir, *J. Amer. Chem. Soc.*, **80**, 148 (1958).

(27) (a) E. L. Eliel, "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley & Sons, Inc., New York, N. Y., 1956, p 119; (b) R. M. Topping and D. E. Tutt, *J. Chem. Soc., B*, 1346 (1967).

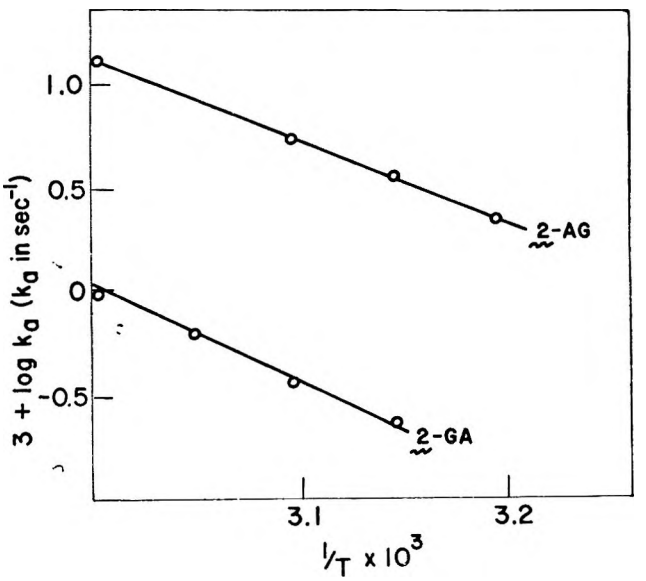


Figure 5.—Effect of temperature on specific rate constants for hydrolysis ($H_0' = -0.03$).

Plots of log k_a *vs.* $1/T$ were linear (Figure 5), and provided the activation parameters summarized in Table V. The small negative entropies of activation are indicative of the intramolecular nature of the rate-determining step in the hydrolytic reaction and, possibly, of the noninvolvement of water in that step.[28]

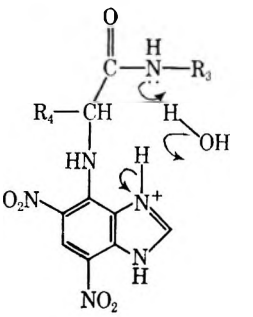
TABLE V

ACTIVATION PARAMETERS FOR BENZIMIDAZOLYL DIPEPTIDES[a]

Compound	E_a, kcal/mol	$\Delta H^{\ddagger}$, kcal/mol	$T\Delta S$, kcal/mol	$\Delta F^{\ddagger}$, kcal/mol
2-alagly	18.7	18.2	−3.3	21.4
2-glyala	21.4	20.7	−4.2	24.9

[a] Calculated for 50°.

Reaction Mechanism.—It would be premature to attempt to select from the various mechanisms which may be considered for the intramolecular facilitation of hydrolysis by the benzimidazolium species. Geometrical limitations do not favor the benzimidazolium ion acting as a general acid (**4**). The formation of cyclic acyl intermediates has neither been demonstrated nor excluded: the fact that **3**-alanylglycine and **3**-glycylalanine hydrolyze 4–5 times as rapidly as 2-alanylglycine and 2-glycylalanine, respectively, makes



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consideration of an acylbenzimidazole intermediate difficult; on the other hand, the dimethylbenzimidazole series may operate by a pathway different from that of the less alkylated series. Regardless of the detailed mechanism, the facilitation effect includes the entropy advantage of an intramolecular reaction, an increase in the local concentration of protons, and, possibly, some conformational control in the proton-transfer process. Of the cases examined, that of **3**-alanylglycine is most impressive, its k_a being 65,000 times as great as that of 2,4-dinitrophenylalanylglycine.

Registry No.—1-DL-ala, 18646-22-5; 1-L-alagly, 18645-99-3; 2-gly, 18646-24-7; 2-DL-ala, 18646-25-8; 2-L-val, 18646-26-9; 2-L-alagly, 18646-00-9; 2-gly-DL-ala, 18646-28-1; 2-glygly, 18646-29-2; 2-L-ala-L-ala, 18646-30-5; 2-L-valgly; 18646-31-6; 2-L-ala-L-val, 18646-32-7; **3**-gly, 18646-33-8; **3**-DL-ala, 18646-34-9; **3**-L-alagly, 18646-01-0; **3**-gly-DL-ala, 18646-36-1.

(28) *Cf.* E. Gaetjens and H. Morawetz, *J. Amer. Chem. Soc.*, **82**, 5328 1960), and J. W. Thanassi and T. C. Bruice, *ibid.*, **88**, 747 (1966).

Participation of the Anilino Group in Peptide Bond Cleavage. The Use of *t*-Butyl 3,5-Dinitro-2-fluorocarbanilate as a Peptide Reagent

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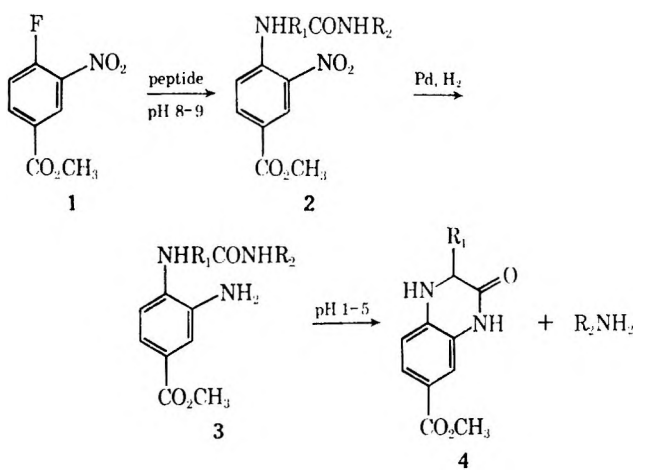
Picramyl fluoride (3,5-dinitro-2-fluoroaniline) has been prepared by the stannous chloride reduction of picryl fluoride and by the Curtius rearrangement of 3,5-dinitro-2-fluorobenzoyl azide. Reaction of picramyl fluoride with peptides (at pH 8) results in replacement of the fluorine atom by the peptide nitrogen. Coupling is followed by rapid intramolecular attack of the anilino group on the neighboring peptide bond (even at pH 8), resulting in cleavage of that bond and the formation of a dihydroquinoxalone derivative of the N-terminal amino acid. By use of the *t*-BOC derivative of picramyl fluoride (*t*-butyl 3,5-dinitro-2-fluorocarbanilate), the coupling and cleavage steps can be separated. Removal of the blocking group by trifluoroacetic acid is followed by rapid cyclization, both reactions proceeding quantitatively. Sequencing of a polypeptide (*e.g.*, oxidized insulin A chain) provides steadily decreasing yields of N-terminal derivatives, owing to benzimidazolone formation during the coupling step. By kinetic analysis, it is shown that the benzimidazolone (**17**) arises from attack of the 2,4-dinitroaniline anion (**16**) on the adjacent *t*-butyl carbanilate group.

The cleavage of amide bonds can be achieved by intramolecular participation of a variety of both nucleophilic and electrophilic species.[1] The protonated forms of pyridine[2] and of benzimidazole[1] nitrogen have been found to be particularly effective, but earlier work of Holley and Holley[3] and of others[4] has suggested than anilinium ions might be even more potent.

Holley and Holley coupled a variety of peptides with 4-carbomethoxy-2-nitrofluorobenzene (**1**) and formed the aniline derivatives (**3**) by catalytic hydrogenation of the nitro group in **2** (Scheme I). A

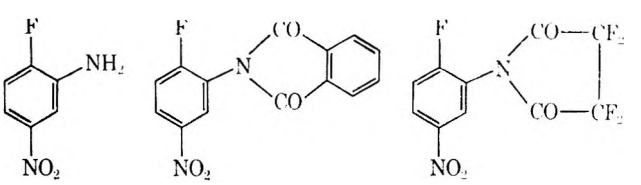
SCHEME I



facile and rapid conversion of **3** into the dihydroquinoxalone **4**, and a shorter peptide, could then be effected under mildly acidic conditions. In subsequent extensions of the principle, the coupling reagent was modified by variation of the 4 substituent.[4] By use of sulfide ion, the readily accessible 2,4-dinitrophenyl peptide could be reduced selectively at the 2-nitro group.[4a] Despite the ease and efficiency of the cyclization procedure, the method has failed to achieve wide acceptance in the practice of sequential degradation of polypeptides. Principally, the obstacle has been the requirement of a reduction step, which could provide complications, particularly in the case of sulfur-containing peptides or proteins.

A logical alternative would be the use of a reagent with a preexisting anilino or potential anilino group. Such a goal is immediately thwarted by the electron-releasing and fluorine-deactivating properties of the anilino nitrogen. Thus, 2-fluoro-5-nitroaniline (**5**) is inert to peptide nucleophiles under any reasonable reaction conditions, nor does acylation of the nitrogen atom negate the deactivating effect.[5] In cyclic diacylimide derivatives, such as **6** and **7**, the imide carbonyl is more susceptible to nucleophilic attack than the fluorine-bearing carbon atom.[6]

Since it has been shown[7] that 2,4-dinitrofluorobenzene is considerably more reactive toward nucleophiles than 2- or 4-nitrofluorobenzene, we considered the possibility that an additional nitro group in **5** might counteract the negative effect of the anilino function. Earlier work also suggested that an *o*-nitro substituent may have a significant effect in promoting a favorable orientation of the amide bond for hydrolysis.[1,2] A



(1) For an extensive bibliography, see K. L. Kirk and L. A. Cohen, *J. Org. Chem.*, **34**, 390 (1969).

(2) A. Signor and E. Bordignon, *ibid.*, **30**, 3447 (1965); A. Signor, E. Bordignon, and G. Vidali, *ibid.*, **32**, 1135 (1967).

(3) R. W. Holley and A. D. Holley, *J. Amer. Chem. Soc.*, **74**, 5445 (1952).

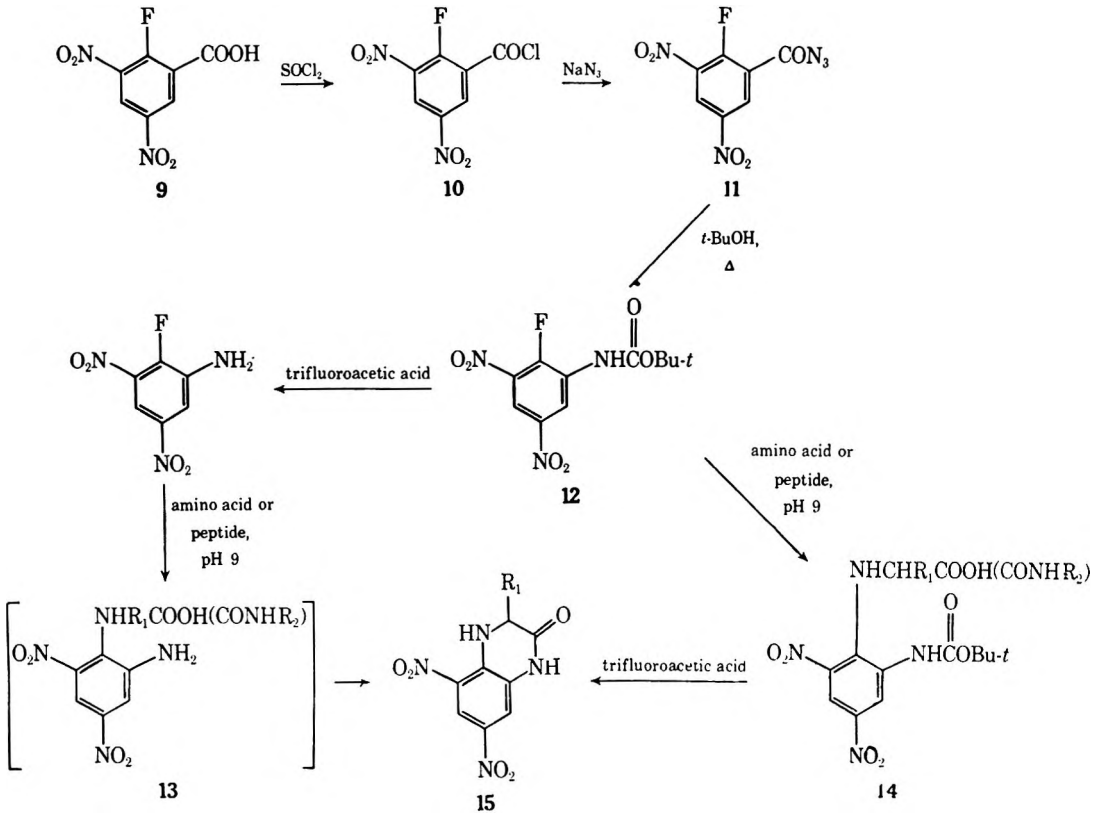
(4) (a) E. Scoffone, E. Vianello, and A. Lorenzini, *Gazz. Chim. Ital.*, **87**, 354 (1957); (b) L. Scarso, E. Scoffone, and D. Chillemi, *ibid.*, **87**, 1348 (1957); (c) P. de la Llosa, M. Jutisz, and E. Scoffone, *Bull. Soc. Chim. Fr.*, 1621 (1960).

(5) Similarly, acylation fails to negate the *ortho–para*-directing influence of aniline in electrophilic substitution [H. C. Brown and Y. Okamoto, *J. Amer. Chem. Soc.*, **80**, 4979 (1958)].

(6) L. A. Cohen and W. M. Jones, unpublished observations.

(7) C. W. L. Bevan and G. C. Bye, *J. Chem. Soc.*, 3091 (1954).

SCHEME II



first approach to the synthesis of 3,5-dinitro-2-fluoroaniline (picramyl fluoride) (**8**) was based on the stannous chloride reduction of picryl fluoride. Although a small yield of **8** was obtained, following chromatography of the complex reaction mixture, the method was unsatisfactory for preparative purposes.

In an alternative procedure, 2-fluorobenzoic acid was nitrated to form 3,5-dinitro-2-fluorobenzoic acid (**9**),[8] which, in turn, was converted into the acid chloride (**10**) and the azide (**11**) (Scheme II). Despite the reactivity of the activated fluorine atom in **10**, the acyl azide was the principal product formed in the presence of equimolar amounts of azide ion. Curtius rearrangement of the azide, by heating its solution in *t*-butyl alcohol, provided the protected aniline derivative, *t*-butyl 3,5-dinitro-2-fluorocarbanilate (**12**). The blocking group was readily removed by brief exposure of **12** to trifluoroacetic acid at room temperature. Following this sequence, picramyl fluoride (**8**) was obtained in an over-all yield of 50%; the preparation of **8** *via* **12** was preferred over the direct Curtius rearrangement of **11** in aqueous media. Nmr spectra supported the structures assigned to both **8** and **12** (see Experimental Section).

Although somewhat less reactive than 2,4-dinitrofluorobenzene, picramyl fluoride (**8**) coupled readily with peptide nucleophiles, as we had hoped. When alanylglycylglycine was treated with excess reagent for 3 hr at 35° and pH 8, the dihydroquinoxalones (**14**) corresponding to alanine and glycine were isolated, in 67 and 44% yield, respectively, *prior* to acidification of the reaction mixture. In earlier studies with 2-amino-4-methanesulfonylphenyl derivatives of peptides, it was found that the rate of cyclization decreased sharply above pH 6.[4b,c] In the present series, participation and cyclization proceeded readily, even at pH 8. In more alkaline media, the reaction was complex and led to intractable materials. When **8** was coupled with simple amino acids, such as alanine, the amino acid derivative, **13**, could not be obtained, cyclization to the dihydroquinoxalone occurring even at the pH of the coupling reaction.

To effect a separation of coupling from cyclization, the N-protected derivative, **12**, was utilized. In the reaction with alanylglycine at pH 8 (25°), **12** was found slightly more reactive than 2,4-dinitrofluorobenzene, the second-order rate constants being 7.1×10^{-3} and 6.5×10^{-3} M^{-1} sec^{-1}, respectively. Subsequent to coupling and removal of excess reagent, the anilino group was liberated by exposure of **15** to trifluoroacetic acid for 15 min at room temperature. Under these conditions, cyclization proceeded rapidly and quantitatively.

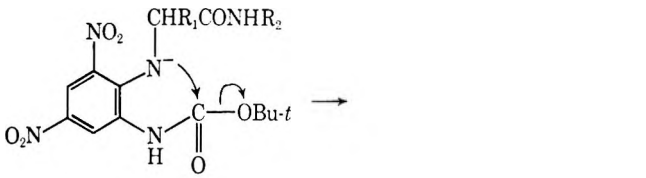
In contrast to the ease of oxidation of other dihydroquinoxalones,[9] those of the dinitro series were stable during isolation and thin layer chromatography (tlc); the unalkylated **14**, derived from glycine, showed a slight tendency to darken on thin layer plates. On the basis of their infrared (ir) spectra (5.9 μ, KBr), the dihydroquinoxalones are properly formulated as lactams, rather than the enolic lactims.[10]

(8) H. Goldstein and A. Giddey, *Helv. Chim. Acta*, **37**, 1121 (1954).

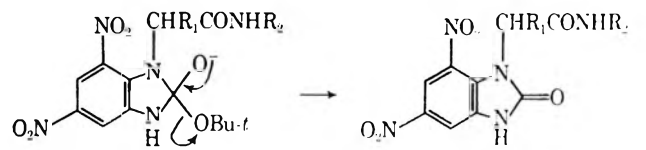
(9) J. C. E. Simpson, "Condensed Pyridazine and Pyrazine Rings," Interscience Publishers, New York, N. Y., 1953, Chapter 37.

(10) D. G. O'Sullivan and P. W. Sadler, *J. Chem. Soc.*, 2916 (1957).

Application of the protected reagent, **12**, to the degradation of several peptides, including oxidized insulin A chain, led to dihydroquinoxalone recoveries which were significantly less than quantitative. In the latter case, the first three degradation cycles gave recoveries of the glycine, isoleucine, and valine derivatives in yields of 72, 55, and 40%, respectively. Since removal of the blocking group and the cyclization reaction had been shown to proceed to completion in trifluoroacetic acid, the efficiency of the coupling reaction was reexamined. When the coupled derivative, **15**-glycylalanine, was exposed to media more alkaline than pH 8, the peak at 370 mμ disappeared and the yellow color of the solution faded. The product of the reaction was found to be the benzimidazolone, **17**.



16



17

The reaction may proceed by nucleophilic attack of the nitrogen anion of **16** on the urethan carbonyl, with displacement of *t*-butoxide ion. An alternative pathway to **17**, involving collapse of the *t*-butyl carbanilate to an isocyanate *via* β elimination, followed by addition of the neighboring anilino nitrogen, was partially excluded by the demonstration that both **12** and **15**-proline were stable under the same alkaline conditions. However, the possibility remains that isocyanate formation is initiated by intramolecular proton transfer from the carbanilate nitrogen to the nitrogen anion of **16**.

Based on the two relationships which follow, eq 1

$$\mathrm{ArNHR} \underset{}{\overset{K_a}{\rightleftharpoons}} \mathrm{ArN^-R} + \mathrm{H^+} \text{ and } \mathrm{ArN^-R} \xrightarrow{k_{rate}} \text{products}$$

$$1/k_{obsd} = 1/k_{rate} + [\mathrm{H^+}]/K_a k_{rate} \qquad (1)$$

may be formulated as shown below. The linearity of a plot of $1/k_{obsd}$ *vs.* H^+ (Figure 1) confirmed the assumption that the cyclization reaction depends on a rate limiting concentration of **16**. Once benzimidazolone formation has occurred, participation and cleavage of the peptide bond are no longer possible.

Although further modification of the reagent will be necessary to eliminate such side reactions in coupling, the facility and completeness of the cyclization step, as well as the ease of indentifying and assaying the resulting amino acid derivative, are features which indicate that further effort is warranted.

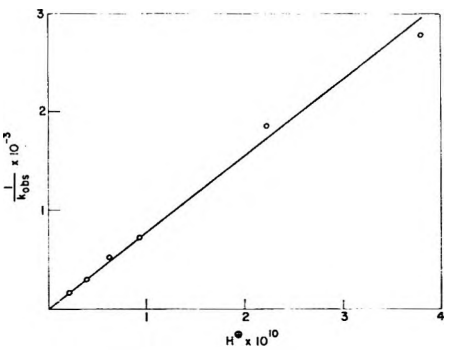


Figure 1.—Rate of benzimidazolone formation as a function of pH.

Of additional interest is the facility with which lactam formation occurs between the 3,5-dinitroanilino and carboxyl groups and the facility of peptide bond cleavage, *even* in mildly alkaline media. Assuming, as previous work has suggested,[4b,c] that the anilinium ion is the reactive species, and considering the low basicity of the nitrogen atom in **15** (pK_a = 1–2), the specific rate constants for such reactions should be impressive; appropriate kinetic studies are in progress.

Experiment Section[11]

3,5-Dinitro-2-fluoroaniline (**8**).—Anhydrous stannous chloride (9.5 g)[12] was dissolved in 80 ml of glacial acetic acid by saturation with hydrogen chloride at 25° and with exclusion of moisture. Dilution to 100 ml with acetic acid provided a reducing reagent which was 0.5 *M* in stannous chloride.

To a stirred solution of 462 mg (2.0 mmol) of picryl fluoride[13] in 5 ml glacial acetic acid was added 13 ml (6.5 mmol) of stannous chloride reagent dropwise over 5 min at room temperature. The original yellow color of the solution was transformed to green and finally to red. After 4 hr, the solvent was removed *in vacuo* and the residual material taken up in water. Colored material was extracted with several portions of chloroform; the combined extracts were dried and evaporated giving 483 mg of red oil. The material was purified by chromatography on 50 g of silica gel and elution with benzene. The desired compound was located in the yellow fractions by exposure of thin layer samples to ammonia vapor; the rapid transformation of a spot from yellow to red revealed the presence of **8**. Appropriate fractions were combined to give 105 mg (26%) of yellow crystals which were recrystallized from benzene–cyclohexane: mp 105–106°, λ_{max}^{EtOH} 375 mμ (ε 2150).

Anal. Calcd for $C_6H_4FN_3O_4$: C, 35.83; H, 2.00; F, 9.45; N, 20.89. Found: C, 35.88; H, 1.93; N, 20.82; F, 9.74.

(11) Melting points are uncorrected. The uv spectra were measured on a Cary recording spectrophotometer, Model 14, nmr spectra with a Varian A-60 spectrometer, and ir spectra with a Perkin-Elmer spectrophotometer, Model 421. Mass spectra were measured on an Hitachi double-focusing spectrometer, Model RMU-6E. Microanalyses were performed by Dr. W. C. Alford and his associates of this institute.

(12) H. Stephen, *J. Chem. Soc.*, 2786 (1930).

(13) G. Olah, A. Pavlath, S. Kuhn, and G. Varsanyi, *Acta Chim. Acad. Hung.*, **7**, 431 (1955); S. J. Kuhn and G. A. Olah, *J. Amer. Chem. Soc.*, **83**, 4564 (1961). For other methods of preparation, see G. C. Shaw and D. L. Seaton, *J. Org. Chem.*, **26**, 5227 (1961); R. E. Parker and T. O. Read, *J. Chem. Soc.*, 9 (1962); N. N. Vorozhtsov, Jr., and G. G. Yakobson, *Zh. Obshch. Khim.*, **31**, 3705 (1961); J. Murto, *Acta Chem. Scand.*, **20**, 303 (1966); H. L. Sharma, V. N. Sharma, and R. L. Mital, *Can. J. Chem.*, **44**, 1327 (1966).

TABLE I

PROPERTIES OF DIHYDROQUINOXALONES[a]

Amino acid	Yield, %	Mp, °C	m/e[b]	λ_{max}^{EtOH}, mμ (ε)	R_f[c]
Glycine	98	225–250 dec	238	374 (10,800), 266 (14,100)	0.37
Alanine	95	206–235 dec	252	374 (9,800), 264 (13,500)	0.56
Isoleucine	92	184–187	294	374 (10,000), 265 (13,300)	0.78
Valine	87	175–180	280	374 (10,200), 268 (13,800)	0.70
Proline	98	205–209 dec	278	392 (9,500), 276 (10,900)	0.65

[a] All of the dihydroquinoxalones show an ir band (KBr) at 5.9 μ (carbonyl). [b] Composition was confirmed by m/e of parent peak in mass spectrum. [c] On silica gel GF, with ether as solvent.

The nmr spectrum ($CDCl_3$) showed two quartets (area 1:1) centered at 8.11 and 7.71 ppm (J_{HH} = 3 Hz and J_{HF} = 5 Hz).

3,5-Dinitro-2-fluorobenzoyl Azide (11).—The nitration of 2-fluorobenzoic acid and conversion of the dinitro derivative (9) into the acid chloride (10) were performed according to published procedures.[8] Comparable yields (60–70%) were obtained on a fivefold scale. The acid chloride was converted into the acid azide by exchange with azide ion. A sample of crude acid chloride (2.75 g, 11 mmol) was dissolved in 10 ml of glacial acetic acid and to the stirred solution was added 0.73 g (11 mmol) of powdered sodium azide over 15 min.[14] The mixture was kept an additional 45 min at room temperature and poured onto ice. Crystallization was induced by scratching. The pale yellow solid was filtered, washed with water, and dried, to give 2.08 g (75%) of 11, which was used directly for Curtius rearrangement. Attempts to purify the material were unsuccessful. The compound began to melt at 55° with gas evolution.

The ir spectrum ($CHCl_3$) showed azide bands at 4.50 (w) and 4.65 (s), carbonyl absorption at 5.85, and nitro bands at 6.48 and at 7.43 μ.

***t*-Butyl 3,5-Dinitro-2-fluorocarbanilate (12).**—A solution of 2.00 g (7.8 mmol) of crude azide in 20 ml of anhydrous *t*-butyl alcohol was heated slowly and maintained at reflux for 1 hr. Following removal of solvent *in vacuo*, the partially crystalline material was purified by chromatography on 70 g of silica gel and elution with benzene, to give 1.72 g (73%) of pale yellow crystals. The product was recrystallized from benzene–cyclohexane: mp 149–151°; λ_{max}^{EtOH} 330 mμ (ε 2240).

Anal. Calcd for $C_{11}H_{12}FN_3O_6$: C, 43.86; H, 4.02; F, 6.31; N, 13.95. Found: C, 44.05; H, 3.82; N, 13.75; F, 6.80.

The ir spectrum ($CHCl_3$) was devoid of azide bands and showed carbonyl absorption at 5.78 μ ($CHCl_3$). The nmr spectrum ($CDCl_3$) showed a singlet at 1.57 (*t*-butyl) and two quartets centered at 8.47 and 9.30 ppm (J_{HH} = 3 Hz and J_{HF} = 6 Hz).

3,5-Dinitro-2-fluoroaniline (8).—To a solution of 200 mg of the carbanilate (12) in 5 ml of benzene was added 2 ml of trifluoroacetic acid. The mixture was kept at room temperature for 3 hr and the solvent was removed *in vacuo* to give 137 mg (97%) of crystalline material which was recrystallized from benzene–cyclohexane: mp 105–106°. On the basis of chromatographic behavior, nmr spectrum and mixture melting point, the product was identical with that prepared by partial reduction of picryl fluoride.

Preparation of 3-Substituted 3,4-Dihydro-5,7-dinitro-2(1H)-quinoxalones (15). A.—The following general procedure was used to couple the N-protected reagent (12) with amino acids and to generate the dihydroquinoxalones therefrom. A mixture of 10 mg of 12 and 15 mg of amino acid in 0.4 ml of dioxane–0.2 *M* sodium carbonate buffer (pH 9.2) (1:1) was kept at 45° for 1 hr. At this point, tlc indicated the total consumption of reagent. The solution was cooled, diluted with 0.5 ml of water, and acidified to pH 3 with 1 *N* hydrochloric acid. The mixture was extracted with ethyl acetate and the extract was dried and evaporated. The residual material, 14, was shown to be homogeneous by tlc but was not characterized further. The product was dissolved in 5 ml of trifluoroacetic acid, the solution was kept at room temperature for 15 min, and the solvent was removed, providing 15 as a yellow crystalline solid. Properties of dihydroquinoxalones, prepared in this manner, are recorded in Table I.

B.—To a solution of 10 mg of alanine in 0.2 *M* sodium bicarbonate was added 5 mg of 3,5-dinitro-2-fluoroaniline (8). The mixture was kept at 60° for 30 min; tlc indicated the formation of the dihydroquinoxalone derivative of alanine. Upon cooling of the solution, yellow needles separated. The ir spectrum of the material (KBr) was identical with that of 15-alanine prepared above.

Reaction of 12 with Glycylalanine.—A mixture of 50 mg of glycylalanine and 25 mg of 12 in 2 ml of dioxane–0.2 *M* phosphate buffer (pH 8.0) (1:1) was kept at 45° for 1 hr. The solution was cooled, diluted with 5 ml of water, and acidified to pH 3 with 1 *N* hydrochloric acid. The mixture was extracted with several portions of ethyl acetate until the organic layer remained colorless. The combined ethyl acetate extracts were dried and evaporated to give 35 mg (96%) of a yellow solid: mp 102–123° dec; λ_{max}^{EtOH} 354 mμ (ε 9800). The product, 14-glycylalanine, was shown to be homogeneous by tlc. For analysis, the compound was dried at 50° *in vacuo*.

Anal. Calcd for $C_{16}H_{21}N_5O_9$: C, 44.96; H, 4.95; N, 16.39. Found: C, 45.21; H, 4.95; N, 16.49.

Reaction of 3,5-Dinitro-2-fluoraniline (8) with Alanylglycylglycine.—To 10 mg of reagent (8) in 0.2 ml of dioxane was added 2.5 mg of alanylglycylglycine in 0.2 ml of 0.2 *M* phosphate buffer (pH 8) and the mixture was maintained at 35° for 3 hr. The reaction mixture was cooled, diluted with 1 ml of water, and extracted with portions of ethyl acetate until the extract remained colorless. The combined extracts were dried and evaporated to yield a solid yellow residue. In addition to excess reagent, tlc showed two yellow spots, corresponding to 15-alanine and 15-glycine. Following purification of the dihydroquinoxalones by preparative tlc, the yields of the alanine and glycine derivatives, based on optical density at 374 mμ, were 67 and 44%, respectively. Work-up of the aqueous phase, by evaporation and exposure to trifluoroacetic acid, provided less than 5% additional material.

Reaction of 12 with Alanylglycylglycine.—To a solution of 2.4 mg of alanylglycylglycine and 18 mg of 12 in 0.5 ml of dioxane–water (1 : 1) was added 0.5 ml of 2,6-lutidine and the mixture was maintained at 40° for 2 hr. The solvent was evaporated and the residue was dissolved in 5 ml of trifluoroacetic acid. After 15 min at room temperature, the solvent was removed and the residue was extracted with ethyl acetate. Tlc showed the ethyl acetate extract to contain 15-alanine and picramyl fluoride (8). The yield of 15-alanine, following preparative thin layer purification, was 63%.

Partial Sequential Degradation of Oxidized Insulin A Chain.—Conditions for coupling with 12 and cleavage were the same as those used for alanylglycylglycine. Prior to treatment with trifluoroacetic acid, the residue was washed with ethyl acetate to remove excess reagent. The yield of 15-glycine, following thin layer purification, was 72%. Repetition of the cycle gave 15-isoleucine in 55% yield, and a second repetition gave 15-valine in 40% yield. In each cycle, the dihydroquinoxalone derivative was devoid of contamination by derivatives of other amino acids.

Formation of Benzimidazoione (17) from 14-Glycylalanine.—A solution of 30 mg of 14-glycylalanine in 5 ml of 0.2 *M* sodium carbonate buffer (pH 10.2) was stored at room temperature for 20 min, during which time the yellow color of the solution faded. Tlc ($CHCl_3$–*t*-amyl alcohol–acetic acid, 70:30:5) on silica gel GF revealed the total disappearance of starting material and the formation of a new, colorless product. The reaction mixture was acidified with 1 *N* hydrochloric acid, precipitating a pale yellow solid, which was collected and dried: 17 mg (95%); mp 243–245°; $\lambda_{max}^{pH\ 10.07}$ 380 mμ (sh) (ε 5000) and 310 (10,000), λ_{max}^{EtOH} 350 mμ (ε 6900) and 275 (8800).

Anal. Calcd for $C_{12}H_{11}N_5O_8$: C, 40.79; H, 3.14; N, 19.83. Found: C, 41.07; H, 3.32; N, 19.62.

The ir spectrum (KBr) showed carbonyl bands at 5.85 and 5.95 μ. The nmr spectrum showed a loss of the *t*-butyl peak at 1.5 ppm.

Rate of Reaction of 12 with Alanylglycine.—A 500 μl aliquot of a 6.7×10^{-4} *M* solution of 12 in ethanol was diluted to 4.50 ml with 0.2 *M* phosphate buffer (pH 7.95). To this solution was added 500 μl of 1.07×10^{-2} *M* alanylglycine in the same phosphate buffer. The rate of reaction, at 25°, was followed by the increase in optical density at 370 mμ. The observed second-

(14) The use of excess sodium azide led to partial replacement of the fluorine atom as well.

order rate constant was found to be 7.09×10^{-3} l. mol^{-1} sec^{-1}; under the same conditions, the second-order rate constant for the reaction of alanylglycine with 2,4-dinitrofluorobenzene was 6.52×10^{-3} l. mole^{-1} sec^{-1}.

Kinetics of Benzimidazolone (17) Formation.—Aliquots (500 μl) of a solution of 2.091 mg of 14-glycylalanine in 10 ml of ethanol were diluted to 5.00 ml with 0.2 *M* carbonate buffer at various pH values. Benzimidazolone formation was followed at 25°, by the decrease in optical density at 370 mμ. Observed first-order rate constants for benzimidazolone formation follow (pH, $k \times 10^3$ in sec^{-1}): 9.42, 0.36; 9.65, 0.54; 10.04, 1.41; 10.20, 1.96; 10.41, 3.52; 10.68, 5.70.

Registry No.—**8**, 18646-02-1; **11**, 18646-13-4; **12**, 18646-03-2; **14**-glycylalanine, 18646-04-3; **15**-glycine, 18646-05-4; **15**-alanine, 18646-06-5; **15**-isoleucine, 18646-07-6; **15**-valine, 18646-08-7; **15**-proline, 18646-09-8; **17**, 18646-10-1.

1,4 Additions of Phosphorus Trichloride to Cyclic α,β-Unsaturated Ketones[1a,b]

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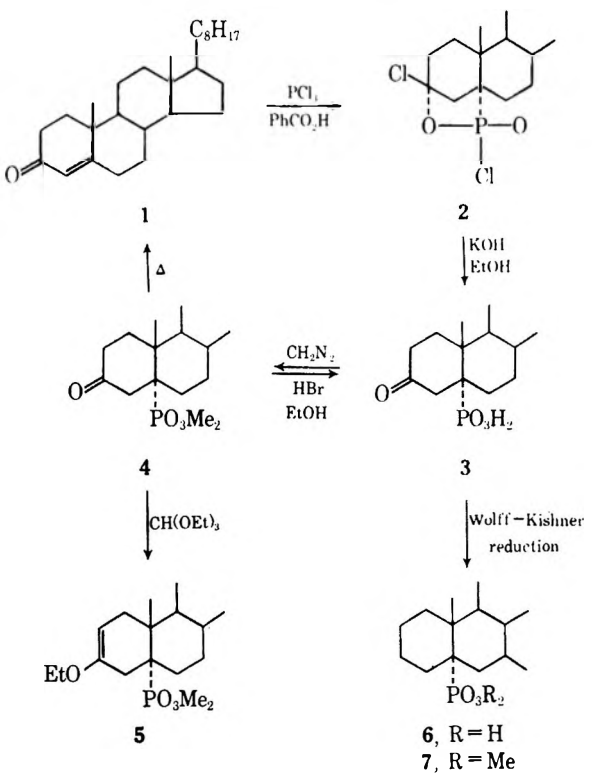
Phosphorus trichloride reacts with 4-cholesten-3-one in the presence of benzoic acid to provide a stable, crystalline intermediate in the normal 1,4-addition reaction of this reagent. Chemical and spectral evidence support the assignment of phostonyl chloride structure 2 to this intermediate with the phosphorus atom in the 5α position. An analogous product (**11**) is obtained from 2-keto-10-methyl-$\Delta^{1,9}$-octalin. A mechanism is proposed involving an initial electrophilic attack of the phosphorus atom on the carbonyl oxygen.

The reactions of phosphorus trichloride with ketones provide methods for forming carbon–phosphorus bonds which we have investigated for use in preparing steroidal phosphonic acids. We have found that the course of the reactions of this reagent with Δ^4-3-keto steroids is dependent upon the reaction conditions, thus the use of acetic acid as the solvent leads to 3-chloro-3,5-dienes, whereas acetic anhydride causes the formation of 3-acetoxy-3,5-dienes.[2] Substituting crystalline phosphorous acid for the acetic acid and using phosphorus trichloride in excess provides 3,5-dien-3-ylphosphonic acids by 1,2 addition of the phosphorus reagent.[3] We now report that the use of benzoic acid in phosphorus trichloride as the solvent allows the isolation of 1,4-addition products of 4-cholesten-3-one and 2-keto-10-methyl-$\Delta^{1,9}$-octalin which are the first fully characterized intermediates obtained from the normal 1,4-addition reaction of this reagent with α,β-unsaturated ketones to give γ-ketophosphonic acids. In addition to providing a route to steroidal C_5-phosphonic acids, therefore, these intermediates have significance in providing evidence about the mechanism of the reaction.

The nonhydrolytic work-up of a solution of 4-cholesten-3-one (**1**), phosphorus trichloride, and benzoic acid allows the isolation in 20–25% yield of a crystalline phosphorus-containing steroid, mp 206–208°, in addition to the major product, 3-chloro-3,5-cholestadiene. The elemental analysis and molecular weight of this new compound are consistent with the molecular formula $C_{27}H_{45}Cl_2O_2P$. On the basis of these and the following data, structure **2** is proposed for this compound (Scheme I).[4]

SCHEME I



(1) (a) Abstracted from the Ph.D. Dissertation of M. D. Martz, University of Missouri, Jan 1967. Presented in part at the First Midwest Regional Meeting of the American Chemical Society, Kansas City, Mo., Nov 1965. (b) Journal Series Paper No. 5457. Approved by the Director of the Missouri Agriculture Experiment Station. (c) To whom all correspondence should be addressed at the Department of Plant Pathology, University of Missouri, Columbia, Mo. 65201.

(2) J. A. Ross and M. D. Martz, *J. Org. Chem.*, **29**, 2784 (1964).

(3) J. A. Ross and S. S. Wasson, Abstracts of Papers Presented at the First Midwest Regional Meeting of the American Chemical Society, Kansas City, Mo., Nov 4–5, 1965, p 31.

(4) The Chemical Abstracts name for **2** is (3β-chloro-3-hydroxy-5α-cholestan-5-yl)phosphonochloridic acid intramolecular ester. We shall refer to it as a "phostonyl chloride" following Conant's original suggestion: *cf.* A. Eberhard and F. H. Westheimer, *J. Amer. Chem. Soc.*, **87**, 253 (1965).

The infrared, ultraviolet, and nmr spectra of phostonyl chloride **2** corroborate the absence of hydroxyl, carbonyl, and olefinic groups. The infrared spectrum is quite complex with multiple bands centered at 1280 and 890 cm^{-1} assigned to the P–O and P–OR groups, respectively. Phostonyl chloride **2** is surprisingly stable to alcohols, amines, and aqueous acids. Treatment of the compound with ethanolic potassium hydroxide, however, provides the ketophosphonic acid **3**, the normal 1,4-addition product expected from the reaction of phosphorus trichloride with cholestenone.

The 3-keto group of **3** is indicated by its infrared absorption at 1715 cm^{-1} and the formation of a 2,4-dinitrophenylhydrazone. Ketophosphonic acid **3** is smoothly converted into the dimethyl ester **4** by diazomethane. The complete esterification is shown by the doublet in its nmr spectrum at δ 3.71 (J_{PH} = 11 Hz) having an area corresponding to six protons. This ester can be completely hydrolyzed to the ketophosphonic acid **3** by refluxing in ethanolic hydrobromic acid. The 3-keto group of **4** reacts normally in the formation of a 2,4-dinitrophenylhydrazone and by reaction with ethyl orthoformate to give the enol ether **5**.

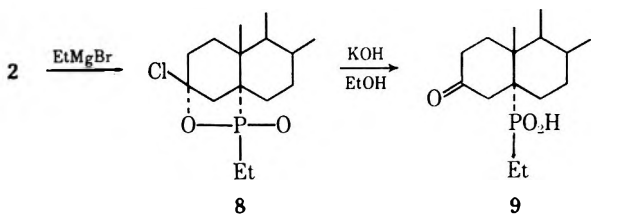
The absence of any deep-seated structural change during these reactions is shown by the pyrolysis of the dimethyl ketophosphonate **4** to 4-cholesten-3-one (**1**). This reaction, which is similar to the Cope elimination of amine oxides or the Kraft ester pyrolysis, is unusual for phosphonates and has been reported previously only in the case of certain α-phosphonoaldehydes.[5] The ease of the carbon–phosphorus cleavage in this case is apparently due to the presence of the acidic α-hydrogen (relative to the ketone) which allows the elimination of dimethylphosphonate.

The dimethyl ketophosphonate **4** proved to be resistant to Wolff–Kishner reduction, but the free acid **3** is readily reduced under these conditions to cholestan-5α-ylphosphonic acid (**6**). Reaction of this acid with diazomethane yields the dimethyl ester **7**.

Although phostonyl chloride **2** is very stable to a number of nucleophilic reagents, it does react with an excess of ethylmagnesium bromide to give a new compound **8** in which one of the chlorine atoms is replaced by an ethyl group and the phostone ring is retained. The infrared spectrum of this product is very similar to that of the parent phostonyl chloride with complex bands in the 1300–600-cm^{-1} region. The phosphoryl oxygen absorption is found at 1265 cm^{-1}, a 20-cm^{-1} shift from that of **2**. This is in fair agreement with the 38-cm^{-1} shift calculated for the substitution of an alkyl group for chlorine in this series.[6]

Basic hydrolysis of **8** opens the phosphorus ring to give a ketophosphinic acid **9** as shown by its infrared spectrum. This compound could not be obtained analytically pure, but its 2,4-dinitrophenylhydrazone gave acceptable analytical data to complete its characterization.

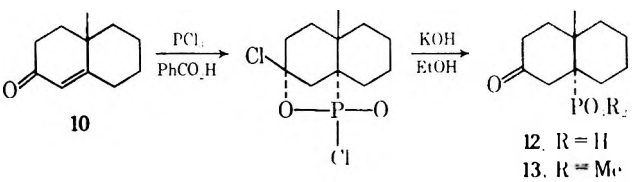
The stepwise removal of the chlorine atoms provides



8 **9**

conclusive evidence for their assignment at C_3 and on the phosphorus atom. The C_5 assignment of the phosphorus atom is based on the previously known mode of reaction of phosphorus trichloride with α,β-unsaturated ketones, the ease of elimination of dimethyl phosphonate from **4**, and the spectral evidence described below.

The bicyclic analog of cholestenone, 2-keto-10-methyl-$\Delta^{1,9}$-octalin (**10**), was also found to form a phostonyl chloride (**11**) in low yields when allowed to react with phosphorus trichloride and benzoic acid. The spectral properties of **11** are similar to those of **2**, and it is readily cleaved by basic hydrolysis to the ketophosphonic acid **12**. When **12** was treated with diazomethane in a solution of chloroform, dioxane, and N,N-dimethylformamide and the solvents were subsequently evaporated under reduced pressure, a yellow oil was obtained which was shown by its infrared spectrum to be a mixture of the expected dimethyl ester **13** and the unsaturated ketone **10**. The latter was probably a product of heating **13** during the



10 **11**

12, R = H
13, R = Me

evaporation of the solvents. Distillation of the crude reaction mixture failed to achieve separation of the two compounds, and glpc analysis of the distillate showed that the ketophosphonate was contaminated with 5% of **10**. Characterization of **13** was achieved by means of its 2,4-dinitrophenylhydrazone, which could be obtained free of contamination.

The 5α assignment of the phosphorus groups in compounds **2**–**9** and **10**–**13** is supported by their nmr data. Arguments can be advanced that there is no *a priori* assumption that the phosphorus atom must be at the angular position *trans* to the methyl group, and it is necessary, therefore, to exclude substitution at C_4 and C_6 (steroids) or at C_1 or C_8 (decalins). All other sites of substitution are excluded by the pyrolysis of the dimethyl ketophosphonate **4** to cholestenone.

The half-height widths $W_{h/2}$ for the angular methyl group resonances were obtained according to the methods of Robinson[7] and of Williamson, Howell and Spencer[8] and are shown in Table I. All of the $\Delta W_{h/2}$

(5) R. H. Churi and C. E. Griffin, *J. Amer. Chem. Soc.*, **88**, 1824 (1966).
(6) J. V. Bell, J. Heisler, H. Tannenbaum, and J. Goldenson, *ibid.*, **76**, 5185 (1954).
(7) M. J. T. Robinson, *Tetrahedron Lett.*, 1685 (1965).
(8) K. L. Williamson, T. Howell, and T. A. Spencer, *J. Amer. Chem. Soc.*, **88**, 325 (1966).

TABLE I

NMR DATA OF ANGULAR METHYL GROUPS[a]

Compd	Chemical shift, ppm (Hz)	$\Delta W_{h/2}$ (rel to $W_{h/2}$ of TMS), Hz	Multiplicity
2	1.34 (80.4)	1.02	d (J = 0.8 Hz)
4	1.27 (76.2)	1.24	d (J = 0.8 Hz)
7	1.08 (64.8)	1.52	s
5	1.13 (67.8)	1.38	d (J = 0.8 Hz)
11	1.40 (84.0)	1.29	s
12	1.36 (81.5)	1.50	s

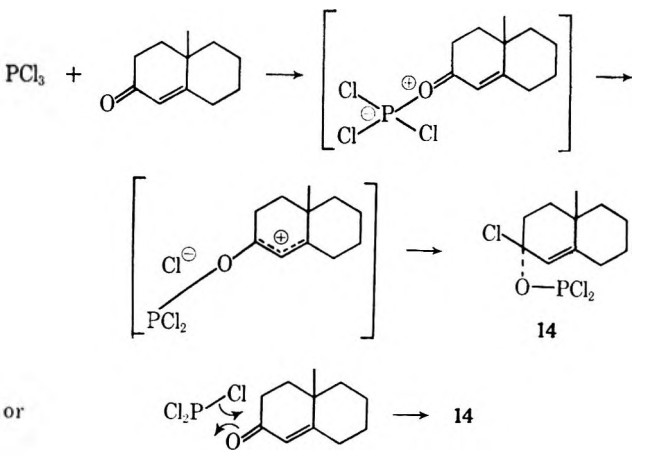
[a] The C_{19}-proton resonance of **3** disappeared into the methylene envelope.

values are larger than the average for *trans*-fused steroids (0.84 Hz[8]) or for *trans*-decalins (0.80 Hz[8]), and indicate a greater degree of coupling of the methyl protons than is found in the latter compounds. This coupling is further borne out by the splitting of the C_{19} proton resonances of **2**, **4** and **5** into doublets with coupling constants of 0.8 Hz. To our knowledge no other four-bond proton–phosphorus coupling through single bonds to carbon has been reported, but this coupling constant seems reasonable for these compounds. A phosphorus atom at C_1 or C_6 would require coupling through five σ bonds, and in neither case would the stereochemistry be so favorable.

The chemical shifts of the C_{19} protons are also in agreement with the 5α assignment. By use of the substituent additivity rules of Zürcher[9] the substituent effect of the dimethoxyphosphinyl group of **7** is calculated to be 18.3 Hz.[10] This value is consistent with the 10-Hz downfield shift of the 1α-dialkoxyphosphinyl group reported by Harvey, DeSombre, and Jensen.[11] The calculated chemical shift for the 3-keto derivative **4** is 79.3 Hz[12] whereas its observed value is 76.2 Hz, or 3.1 Hz higher field than calculated. This is similar to the 3.0 ± 0.5 Hz upfield shift, relative to the calculated values, observed for 5α-cyano steroids.[13] This deviation was explained in terms of a dipole–dipole interaction between the cyano group and the 3-keto group causing a distortion of ring A which in turn causes the C_{19} protons to be relatively shielded by the carbonyl group. The close agreement of the dimethoxyphosphinyl steroid value to the cyano steroid figure undoubtably is a result of the same kind of distortion effect.

Mechanism.—The reactions of phosphorus trichloride with carbonyl compounds have been widely used to prepare α-hydroxyphosphonic acids from saturated aldehydes or ketones and γ-ketophosphonic acids from α,β-unsaturated ketones.[14] Numerous mechanisms have been proposed for these reactions, based in part on proposed structures of labile, incompletely characterized intermediates obtained before the final hydrolysis to the isolated products.[15,16]

SCHEME II



Early workers, considering the unshared pair of electrons on the phosphorus atom, proposed nucleophilic addition of the reagent across the unsaturated system.[17] This same type of mechanism was proposed again recently to explain the reaction of phosphorus trichloride with dibenzoylethylene.[18]

Although such nucleophilic attack by phosphorus appears reasonable in view of the many well-known additions of nitrogen compounds and of trialkyl phosphines and phosphites to carbonyl derivatives, current knowledge about the reactions of halogen-containing trivalent phosphorus compounds indicates they have considerable electrophilic character due to the electronegativity of the halogens.[19] These compounds readily undergo reactions involving transition states which are stabilized by *d*-orbital interactions. Thus trivalent phosphorus chlorides undergo facile nucleophilic displacement of chlorine atoms by the oxygen atoms of water, alcohols and epoxides.[19] Similar nucleophilic attacks on the phosphorus atom have been proposed to explain the carbonyl reactions of phosphorus trichloride.[20–22] In these mechanisms the phosphorus atom is initially bonded to the carbonyl oxygen atom, and subsequent rearrangements leading to the carbon–phosphorus bond are proposed.

The isolation of stable intermediates **2** and **11** now provides strong evidence for initial electrophilic attack by the phosphorus atom on the carbonyl oxygen of the systems studied. We propose that the first step of the reaction is an electrophilic 1,2 addition of the reagent to the carbonyl group (Scheme II). Subsequent stages of the reaction must then involve the partial hydrolysis of the phosphorus substituent, the addition of this group to the double bond, and the protonation of C_4 to

(9) R. F. Zürcher, *Helv. Chim. Acta*, **46**, 2054 (1963)

(10) 18.3 Hz = 64.8 Hz (**7**) − [47.5 Hz (5α,14α-androstane)[9] − 1.0 Hz (17β-C_8H_{17})[9]].

(11) R. G. Harvey, E. R. DeSombre, and E. V. Jensen, *Steroids*, **9**, 101 (1967).

(12) 79.3 Hz = 64.8 Hz (**7**) + 14.5 Hz (3-oxo).[9]

(13) A. D. Cross and I. T. Harrison, *J. Amer. Chem. Soc.*, **85**, 3223 (1963).

(14) K. Sasse in Houben Weyl's "Methoden der organischen Chemie," E. Müller, Band XII/1, Georg Thieme, Stuttgart, Germany, 1963, pp 361–365.

(15) J. B. Conant and A. A. Cook, *J. Amer. Chem. Soc.*, **42**, 830 (1920).

(16) C. E. Griffin and J. T. Brown, *J. Org. Chem.*, **26**, 853 (1961).

(17) J. B. Conant and V. H. Wallingford, *J. Amer. Chem. Soc.*, **46**, 192 (1924), and references therein.

(18) F. Ramirez, O. P. Madan, and C. P. Smith, *J. Org. Chem.*, **30**, 2284 (1965).

(19) A. J. Kirby and S. G. Warren, "The Organic Chemistry of Phosphorus," Elsevier Publishing Co., Amsterdam, The Netherlands, 1967, Chapter 8.

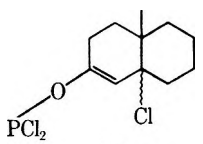
(20) H. J. Page, *J. Chem. Soc.*, **101**, 423 (1912).

(21) F. R. Atherton, V. M. Clark, and A. R. Todd, *Rec. Trav. Chim. Pays-Bas*, **69**, 295 (1950).

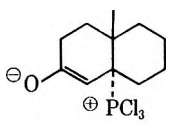
(22) M. I. Kabachnik and T. Ya. Medved, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 540 (1952); *Chem. Abstr.*, **47**, 4848 (1953).

yield 2 or 11. The exact sequence of these latter steps is not clear and a number of alternative routes can be written.

The initial 1,2 addition finds precedent in the mechanism proposed for the reaction of benzaldehyde with the reagent,[21] but differs from previously proposed 1,4 additions to α,β-unsaturated ketones.[20,22] In our examples initial 1,4 addition would lead to intermediates (*e.g.*, **15**) in which C_3 is planar, precluding ring closure in subsequent steps except by tortuous rearrangements or attack by another chlorinating agent. Similar reasoning argues against nucleophilic 1,4 addition leading to intermediates such as **16**.



15



16

This mechanism not only accounts for the products obtained in this investigation, but also for the partially characterized intermediates obtained from the reaction of phosphorus trichloride with benzalacetophenone.[15] In the latter case the initially formed phostonyl chloride would undergo facile elimination of hydrogen chloride to provide the observed unsaturated product.

Experimental Section[23]

(3β-Chloro-3-hydroxy-5α-cholestan-5-yl)phosphonochloridic Acid Intramolecular Ester (2).—A solution of 50.2 g (0.131 mol) of 4-cholesten-3-one (**1**) in 200 ml of phosphorus trichloride was allowed to stand at room temperature for 3 hr. Benzoic acid (16.5 g, 0.135 mol) was added to the solution with stirring, and the mixture was allowed to stand for an additional 26 hr. The excess phosphorus trichloride was then distilled under reduced pressure, and the resulting pasty residue was treated with 250 ml of ether. The mixture was cooled in an ice bath, filtered, and washed with ethanol to give 9.52 g of product, mp 204–206.5°. A second crop, mp 203–205°, was obtained to bring the total yield to 9.64 g (14.7%). Recrystallization of the crude product from chloroform–95% ethanol provided 8.95 g of pure **2**: mp 206.5–208.5°; $[\alpha]^{27}D$ +35.8° (c 1.59, $CHCl_3$); no absorption in the uv to 205 mμ; ir (Nujol) 1280 (=PO), 1245, 1120, and 890 cm^{-1} (POC); nmr ($CDCl_3$) δ 1.35 (d, J_{PH} = 0.8 Hz, C_{19} protons), 3.4 (d, 1, J = 13 Hz).

Anal. Calcd for $C_{27}H_{45}Cl_2O_2P$: C, 64.40; H, 9.01; Cl, 14.08; P, 6.15; mol wt, 503. Found: C, 64.28; H, 9.07; Cl, 14.30; P, 6.24; mol wt, 496 (CCl_4, Cottrell boiling point apparatus).

Treatment of **2** with *p*-toluidine, N,N-diethylaniline, phenol, sodium methoxide in methanol, or aqueous acids resulted only in the recovery of the starting material.

The chilled filtrate from the second crop above was treated with methanol until the foaming had subsided. The solution was concentrated under reduced pressure, and the resulting crystalline solid was collected by filtration and washed successively with cold 95% ethanol, 5% aqueous $NaHCO_3$, and water. This material was recrystallized from ether–95% ethanol to give 21.2 g of crude 3-chloro-3,5-cholestadiene (identified by ir spectrum).

The yields of **2** varied from 10 to 21% in various experiments with the best yield being obtained by using 2 molar equiv of benzoic acid and allowing 48 hr to elapse before working up the reaction.

(3-Oxo-5α-cholestan-5-yl)phosphonic Acid (3).—A mixture of 2.00 g (3.98 mol) of **2** and 100 ml of 5% ethanolic KOH was refluxed for 2.5 hr under nitrogen. After the solution had cooled to room temperature, 100 ml of water was added to give a clear solution. This solution was acidified with 6 *N* hydrochloric acid, and the resulting white, crystalline precipitate was collected by filtration. Recrystallization of the crude product from acetonitrile–1 *N* hydrochloric acid provided 1.12 g (61%) of the ketophosphonic acid **3**: mp 237–240°; $[\alpha]^{27}D$ +35° (*c* 1.65, $CHCl_3$); ir (Nujol) 3530 (OH), 3380 (OH), 1715 (C=O), 1665 (C=O, not present in $CHCl_3$), 1225 (=PO), 1185, and 1005 cm^{-1}.

Anal. Calcd for $C_{27}H_{47}O_4P$; C, 69.49; H, 10.15; P, 6.61; mol wt, 467. Found: C, 69.62; H, 10.31; P, 6.50; neut equiv, 468.

2,4-Dinitrophenylhydrazone had mp 150–163°.

Anal. Calcd for $C_{33}H_{51}N_4O_7P$: C, 61.28; H, 7.95; N, 8.66; P, 4.79. Found: C, 61.27; H, 8.24; N, 8.57; P, 4.65.

Dimethyl (3-Oxo-5α-cholestan-5-yl)phosphonate (4).—Diazomethane prepared from 3.05 g (14.2 mmol) of N-methyl-N-nitroso-*p*-toluenesulfonamide[24] was distilled into a slurry of 2.00 g (4.27 mmol) of ketophosphonic acid **3** in 70 ml of anhydrous ether. Enough chloroform was then added to dissolve the remaining solid, and the solution was washed successively with dilute hydrochloric acid, water, and saturated aqueous NaCl. The ether–chloroform solution was dried ($MgSO_4$), filtered, and evaporated under reduced pressure to give 1.56 g (73%) of the dimethyl ester **4**, mp 191–201°. Recrystallization from acetone (twice) and ethyl acetate (twice) provided an analytical sample: mp 204–209°; $[\alpha]^{27}D$ +30° (*c* 1.64, $CHCl_3$); ir (Nujol) 1720 (C=O), 1235 (=PO), 1185 (POMe), 1055, 1010, 810 and 785 cm^{-1}; nmr ($CDCl_3$) δ 3.71 (d, 6, J_{PH} = 11 Hz, $POCH_3$), 1.27 (d, J_{PH} = 0.8 Hz, C_{19} protons).

Anal. Calcd for $C_{29}H_{51}O_4P$: C, 70.41; H, 10.39; P, 6.26. Found: C, 70.61; H, 10.58; P, 6.27.

2,4-Dinitrophenylhydrazone had mp 231–233°.

Anal. Calcd for $C_{35}H_{55}N_4O_7P$: C, 62.30; H, 8.22; N, 8.30; P, 4.59. Found: C, 62.36; H, 8.35; N, 8.32; P, 4.67.

Hydrolysis of Dimethyl (3-Oxo-5α-cholestan-5-yl)phosphonate (4).—A solution of 0.10 g (0.2 mmol) of the dimethyl ketophosphonate **4** in 13 ml of 95% ethanol and 11 ml of 42% hydrobromic acid was refluxed for 7 hr. Additional ethanol (*ca.* 5 ml) was added to dissolve the resulting precipitate, and the refluxing was continued for 1 additional hr. The slightly cloudy solution was allowed to cool to room temperature, and crystallization was completed at 15°. The resulting white solid was collected by filtration, washed with dilute hydrochloric acid, and dried over KOH to yield 0.09 g (96%) of crude ketophosphonic acid **3**, mp 229–236°. Recrystallization from acetone–6 *N* hydrochloric acid gave 0.06 g (67% recovery) of **3**: mp 235–239°; mmp with authentic **3** 235–240°; ir identical with that of authentic **3**.

Dimethyl (3-Ethoxy-5α-cholest-2-en-5-yl)phosphonate (5).—A mixture of 2.00 g (4.05 mmol) of dimethyl phosphonate **4**, 0.74 g (5.0 mmol) of triethyl orthoformate, 63 ml of absolute ethanol, and 10 drops of 8% ethanolic HCl was stirred at 80° for 1 hr. The clear, colorless solution was allowed to stand at room temperature for 11 hr and was then made alkaline with ethanolic NaOH. This solution was poured into 125 ml of water to give a heavy suspension of a white solid. This precipitate was collected by filtration, and a second crop was obtained by the addition of water to the filtrate. The ir spectrum of this crude product (1.72 g) indicated it was a mixture of starting material and the desired enol ether. This material was heated again for 40 min at 80° with 1.48 g (10 mmol) of redistilled triethyl orthoformate and 6 drops of 8% ethanolic HCl in 50 ml of absolute ethanol. Work-up as before provided 1.38 g (65%) of crude, waxy product, mp 139–145°. Recrystallization of this material from acetonitrile afforded a first crop of 0.93 g of enol ether **5**: mp 144–147°;

(23) All melting points and boiling points are uncorrected. Infrared spectra were determined on a Perkin-Elmer Model 237B Infracord spectrophotometer. Ultraviolet spectra were determined on a Beckman Model DB spectrophotometer. Nuclear magnetic resonance spectra were obtained on a Varian A-60 spectrometer with tetramethylsilane as the internal reference. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

(24) Th. J. de Boer and H. J. Backer in "Organic Syntheses," Coll. Vol. 4, N. Rabjohn, Ed., John Wiley & Sons, Inc., New York, N. Y., 1963, p 250.

$[\alpha]^{29}D$ +83° (*c* 1.97, $CHCl_3$); ir (CCl_4) 1660 (C=C), 1240 (≡PO), 1200 (POMe), 1120, and 1060–1035 cm^{-1} (d); nmr ($CDCl_3$) δ 4.14 (d, 1, *J* = 3 Hz, C=CH), 3.77 (q, 2, *J* = 7 Hz, $COCH_2$), 3.70 (d, 6, J_{PH} = 10.5 Hz, $POCH_3$), 1.30 (t, *J* = 7 Hz, OCH_2CH_3), 1.13 (d, J_{PH} = 0.8 Hz, C_{19} protons).

A second crop, mp 140–145°, was obtained to bring the total recovery of **5** to 1.12 g (81%).

Anal. Calcd for $C_{31}H_{55}O_4P$: C, 71.22; H, 10.61; P, 5.93. Found: C, 71.23; H, 10.75; P, 6.00.

Pyrolysis of Dimethyl (3-Oxo-5α-cholestan-5-yl)phosphonate (4).—The dimethyl ketophosphonate **4** (0.50 g, 1 mmol) was heated at 225–231° (oil bath temperature) under vacuum (0.5 mm) using a Dry Ice trap for 6.5 hr. The resulting yellow melt was cooled to room temperature and dissolved in ether. A small amount of insoluble material was removed by filtration, and the ether filtrate was washed with 10% aqueous NaOH. This treatment caused the formation of an oil which was insoluble in ether and aqueous base and which was discarded. The ether solution was then washed with water and saturated aqueous NaCl, dried ($MgSO_4$), and evaporated to a yellow oil. The ir spectrum of this crude material showed it to be mainly 4-cholesten-3-one (**1**), but it could not be induced to crystallize. The 2,4-dinitrophenylhydrazone of **1** was then prepared from this product by the usual procedure. The final yield of this derivative was 0.03 g (23%): mp 230–232°; mmp with authentic 4-cholesten-3-one DNP 230–233°; uv max ($CHCl_3$) 286 mμ (log ε 4.38), 290 (4.02), 256 (4.20) [lit. mp 233–234°[25]; uv max ($CHCl_3$) 292 mμ (log ε 4.06), 281 (4.20), 256 (4.33)[26]].

From the Dry Ice trap was isolated 0.08 g (70%) of dimethyl phosphonate (identified by ir spectrum).

5α-Cholestan-5-ylphosphonic Acid (6).—The Huang-Minlon modification of the Wolff–Kishner reduction was used.[27] A mixture of 1.00 g (2.2 mmol) of ketophosphonic acid **3**, 5 ml of absolute ethanol, 70 ml of freshly distilled diethylene glycol, 8.0 g of KOH, and 10.5 ml (18 mmol) of 85% hydrazine hydrate was refluxed for 30 min. The temperature of the mixture was then raised to 204° over a 2-hr period by removing the condensate. The temperature was maintained at 204–208° for an additional 2 hr. The solution was allowed to cool to room temperature and was acidified with hydrochloric acid to give a white precipitate. This material was filtered, washed with water, and dried to give 0.92 g of crude product, mp 155–165° dec. Recrystallization from ether–methanol–concentrated hydrochloric acid yielded 0.69 g (71%) of phosphonic acid **6**: mp 242–247°; $[\alpha]^{28}D$ +21° (*c* 1.57, $CHCl_3$–MeOH); ir (Nujol) 1130 (broad, ≡PO), 1000–985 (broad), 950, and 920–900 cm^{-1} (d).

Anal. Calcd for $C_{27}H_{49}O_3P$: C, 71.64; H, 10.91; P, 6.84. Found: C, 71.65; H, 11.07; P, 6.73.

Dimethyl 5α-Cholestan-5-ylphosphonate (7).—Diazomethane prepared from 1.00 g (4.65 mmol) of N-methyl-N-nitroso-*p*-toluenesulfonamide[24] was distilled into a solution of 0.30 g (0.66 mmol) of phosphonic acid **6** in 200 ml of CH_2Cl_2–$CHCl_3$ (1:7, v/v). The resulting yellow solution was washed with dilute H_2SO_4, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl. The CH_2Cl_2–$CHCl_3$ solution was dried ($MgSO_4$) and evaporated under reduced pressure to a yellow-green oil which crystallized after standing at room temperature for several days. This crude product was chromatographed on 10 g of silica gel using $CHCl_3$ as the eluent to give 0.24 g (75%) of the dimethyl ester **7**: mp 95–100°; $[\alpha]^{27}D$ +23° (*c* 2.18, $CHCl_3$); ir (Nujol) 1240 (≡PO), 1185 (POMe), 1070–1030 (d), 810, 785, and 740 cm^{-1}; nmr ($CDCl_3$) δ 3.69 (d, 6, J_{PH} = 11 Hz, $POCH_3$) and 1.08 (s, C_{19} protons).

Anal. Calcd for $C_{29}H_{53}O_3P$: C, 72.46; H, 11.11; P, 6.44. Found: C, 72.55; H, 11.12; P, 6.26.

(3β-Chloro-3-hydroxy-5α-cholestan-5-yl)ethylphosphinic Acid Intramolecular Ester (8).—To a stirred mixture of 3.00 g (5.97 mmol) of phostonyl chloride **2** in 25 ml of anhydrous ether was added a solution of ethylmagnesium bromide prepared from 0.85 g (7.8 mmol) of ethyl bromide in 12 ml of anhydrous ether. As the addition proceeded, the slurry thickened and ether was added until the solid dissolved (final volume *ca.* 75 ml). This solution was stirred at room temperature for 3 hr and then refluxed for 4 hr. A colorless solid was deposited during the reflux period. After cooling, the mixture was filtered, and the filtrate was evaporated under reduced pressure to give a colorless dry foam. Trituration of this foam with 95% ethanol provided 1.15 g (39%) of crude **8**, mp 192–196°. Recrystallization of the crude product from methanol gave 0.92 g (80% recovery) of the intramolecular ester **8**: mp 202.5–205.5°; mmp with starting material 201–208.5°. Two additional recrystallizations provided an analytical sample: mp 206–209°; $[\alpha]^{27}D$ +23° (*c* 2.02, $CHCl_3$); ir (Nujol) 1265 (≡PO), 1230, 1050, and 900 cm^{-1}; nmr ($CDCl_3$) δ 4.21 (m, 0.6, *J* = 7 Hz, impurity[28]), 1.37 (s, broad, C_{19} protons).

Anal. Calcd for $C_{29}H_{50}ClO_2P$: C, 70.06; H, 10.14; Cl, 7.13; P, 6.23. Found: C, 69.75; H, 10.22; Cl, 6.90; P, 6.21.

(3-Oxo-5α-cholestan-5-yl)ethylphosphinic Acid (9).—A mixture of 0.50 g (1.0 mmol) of intramolecular ester **8** and 25 ml of 5% ethanolic KOH was flushed with nitrogen for 10 min and refluxed under nitrogen for an additional 15 min. The hot yellow solution was acidified with 25 ml of dilute hydrochloric acid and allowed to stand at room temperature for 24 hr. Since no crystallization occurred during this period, the mixture was extracted with $CHCl_3$. The $CHCl_3$ extract was dried ($MgSO_4$) and evaporated under reduced pressure to a dry foam. Addition of methanol to the foam caused the formation of a white precipitate which was collected by filtration. This solid (0.10 g), mp 139–220°, appeared to be a mixture of starting material and the desired product by its ir spectrum. The methanol filtrate was evaporated under reduced pressure, and the residue was crystallized over a period of 3 months from ethyl acetate–acetonitrile to give 0.12 g (25%) of the ketophosphinic acid **9**: mp 190–205°; $[\alpha]^{27}D$ +35° (*c* 2.02, $CHCl_3$); ir (CCl_4) 3450–3390 (OH), 2670–2630 (=PO_2H), 1720 (C=O), 1685–1650 (=PO_2H), 1175 (broad, ≡PO), 1040, and 960 cm^{-1}; nmr ($CDCl_3$) δ 7.41 (s, 1.5, OH), 4.10 (m, 1.3, *J* = 7 Hz), 2.15 (s, 1), 1.29 (s, C_{19} protons).

No satisfactory analysis could be obtained for this material, but the residue obtained by evaporation of the ethyl acetate–acetonitrile filtrate above provided a satisfactory 2,4-dinitrophenylhydrazone, mp 150–152°.

Anal. Calcd for $C_{35}H_{55}N_4O_6P$: C, 63.81; H, 8.42; N, 8.50; P, 4.70. Found: C, 63.58; H, 8.06; N, 8.47; P, 4.58.

***trans*-[3-Chlorooctahydro-3-hydroxy-8a-methyl-4a(2H)-naphthyl]phosphonochloridic Acid Intramolecular Ester (11).**—A solution of 21.5 g (0.131 mol) of 2-keto-10-methyl-$\Delta^{1,9}$-octalin (**10**)[29] in 125 ml of phosphorus trichloride was allowed to stand at room temperature for 3 hr. Benzoic acid (16.5 g, 0.135 mol) was added, and the solution was allowed to stand at room temperature for an additional 2 days. The excess phosphorus trichloride was evaporated under reduced pressure, and the residue consisting of an oil and a solid was treated with 50 ml of anhydrous ether to give a colorless precipitate. After filtration the colorless solid became yellow. The material was slurried in ether and kept at ice-bath temperature overnight. Filtration then provided 6.95 g of the product, mp 152–157°, in the first crop and 2.35 g, mp 146–152°, in the second crop (total yield 25%). Recrystallization of the first crop from $CHCl_3$–petroleum ether (bp 60–70°) and the second crop from cyclohexane provided 8.57 g (92% recovery) of the phostonyl chloride **11**: mp 147–152°; ir (Nujol) 1310, 1300, 1285 (≡PO), 1200, 1125, 1025, 940–935 (d), 910, 895–885 (d), 865 and 775 cm^{-1}; nmr ($CDCl_3$) δ 3.32 (d, 1, J_{PH} = 13 Hz, C_1-β proton?) and 1.40 (s, 3, CCH_3).

Anal. Calcd for $C_{11}H_{17}Cl_2O_2P$: C, 46.66; H, 6.05; Cl, 25.04; P, 10.94; mol wt, 283. Found: C, 46.56; H, 6.34; Cl, 25.16; P, 10.92; mol wt, 290 (CCl_4, Cottrell boiling point apparatus).

***trans*-[Octahydro-8a-methyl-3-oxo-4a(2H)-naphthyl]phosphonic Acid (12).**—Phostonyl chloride **11** (2.00 g, 7.07 mmol) was stirred in 100 ml of 5% ethanolic KOH under nitrogen for 100

(25) E. Josephy and F. Radt, Ed., "Elsevier's Encyclopedia of Organic Chemistry," Series III, Vol. 14, Elsevier Publishing Co., Inc., Amsterdam, The Netherlands, 1940, p 121.

(26) F. Radt, Ed., "Elsevier's Encyclopedia of Organic Chemistry," Series III, Vol. 14 supplement, Springer-Verlag, Berlin, Germany, 1956, p 2434s.

(27) Huang-Minlon, *J. Amer. Chem. Soc.*, **71**, 3301 (1949).

(28) This impurity is apparently the product of displacement of the phosphoryl chlorine of **2** by OC_2H_5 formed by oxidation of the Grignard reagent. The appearance and chemical shift of the δ 4.21 band are similar to the methylene proton resonances of other phosphorus ethyl esters. The presence of this impurity is also indicated in the mass spectrum of **8** by a small one-chlorine isotopic cluster at *m/e* 512–514, 16 mass units above the molecular ion cluster of **8**. A striking feature of this mass spectrum and the mass spectrum of **2** is a high abundance one-chlorine cluster at *m/e* 402–404 formed by loss of H_2PO_2Et and H_2PO_2Cl, respectively.

(29) N. C. Ross and R. Levine, *J. Org. Chem.*, **29**, 2341 (1964).

min at room temperature (the temperature increased slightly during the initial mixing). Water was added until the mixture was homogeneous, and the solution was poured into 80 ml of 6 *N* hydrochloric acid. When no crystallization occurred in 7 hr, the solution was adjusted to pH 2 and was extracted with four 65-ml portions of $CHCl_3$. Drying ($MgSO_4$) and evaporation of the combined extracts under reduced pressure gave a thick syrup. This material was crystallized from CH_2Cl_2–cyclohexane (1:1, v/v) to provide 0.70 g of product, mp 225–232° dec [second crop, 0.16 g, mp 217–226° dec (49% total)]. Recrystallization of the combined crude product from CH_2Cl_2–methanol gave 0.56 g (65% recovery) of ketophosphonic acid **12**: mp 224–230° dec; ir (Nujol) 1700 (C=O), 1200 (very broad, ≡PO), 1000, and 925 cm^{-1}; nmr (MeOH) δ 1.36 (s, CCH_3).

Anal. Calcd for $C_{11}H_{19}O_4P$: C 53.65; H, 7.78; P, 12.58; mol wt, 246. Found: C, 53.47; H, 7.86; P, 12.50; neut equiv, 252.

2,4-Dinitrophenylhydrazone had mp 203–208°.

Anal. Calcd for $C_{17}H_{23}N_4O_7P$: C, 47.89; H, 5.44; N, 13.14; P, 7.26. Found: C, 47.70; H, 5.60; N, 12.92; P, 7.19.

Dimethyl *trans*-[Octahydro-8a-methyl-3-oxo-4a(2H)-naphthyl]-phosphonate (13).—Diazomethane prepared from 5.80 g (27.2 mmol) of N-methyl-N-nitroso-*p*-toluenesulfonamide[24] was distilled into a solution of 2.00 g (8.12 mmol) of ketophosphonic acid **12** in 75 ml of a $CHCl_3$–dioxane–DMF mixture. The resulting solution was washed successively with dilute H_2SO_4, water, and saturated aqueous NaCl. Drying ($MgSO_4$) and evaporation of the solution under reduced pressure gave a yellow oil, the ir spectrum of which indicated was a mixture of the desired dimethyl ester and **10**. Distillation of this oil gave 0.65 g of product: bp 145–150° (1 mm); ir (neat) 1720 (C=O), 1675, 1620, 1235 (≡PO), 1180 (POMe), 1055–1035 (d, PO–alkyl), 815, and 775 cm^{-1}. Glpc analysis (Micro-Tek GC 2000-R, twin SE 30 columns, column temperature 210°, flame ionization detector) indicated that the product was contaminated with *ca.* 5% of the unsaturated ketone **10**.

Since no satisfactory separation of these compounds could be accomplished, the 2,4-dinitrophenylhydrazone, mp 124–127°, of **13** was prepared from the mixture by the usual procedure.

Anal. Calcd for $C_{19}H_{27}N_4O_7P$: C, 50.22; H, 5.99; N, 12.33; P, 6.82. Found: C, 50.02; H, 6.12; N, 12.12; P, 6.54.

Registry No.—**2**, 18554-19-3; **3**, 18554-20-6; **3** (2,4-dinitrophenylhydrazone derivative), 18554-21-7; **4**, 18554-22-8; **4** (2,4-dinitrophenylhydrazone derivative), 18554-23-9; **5**, 18554-24-0; **6**, 18554-25-1; **7**, 18554-26-2; **8**, 18554-27-3; **9**, 18554-28-4; **9** (2,4-dinitrophenylhydrazone derivative), 18554-29-5; **11**, 18554-30-8; **12**, 18554-31-9; **12** (2,4-dinitrophenylhydrazone derivative), 18554-32-0; **13**, 18554-33-1; **13**, (2,4-dinitrophenylhydrazone derivative), 18554-34-2; phosphorus trichloride, 7719-12-2.

Photochemical Reactions of Resin Acids. Photochemically Initiated Addition of Methanol to Abietic Acid[1a]

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Irradiation of abietic acid or methyl abietate in methanol or benzene–methanol mixture gave rise to two epimeric ethers **6** and **7** along with products of decarboxylation, disproportionation, isomerization and polymerization. The structures of the two photoadducts **6** and **7** were proved by chemical degradation and nmr and mass spectra. The addition is nonstereospecific at C_{13} and seems to be a bimolecular process,[2c] in which a photoexcited polar species abstracts a proton from methanol to give an intermediate carbonium ion, which then coordinates with solvent. No bicyclobutane intermediate could be isolated under the conditions used for photolysis.

Photochemical transformations of the diene systems in the steroids have been extensively studied[2] but only a few reports have been made on the diterpene resin acids. Photolytic valence isomerizations of levopimaric and palustric acids have been reported.[3,4] Irradiation of abietic acid in ethanol has been reported to give hydroxy acids.[5] The purpose of the present investigation was to study the photolysis of abietic acid and methyl abietate in methanol.

In contrast to the results in ethanol,[5] irradiation (2537 Å) of abietic acid or methyl abietate in absolute methanol or in benzene–methanol gave little if any alcoholic product. The major monomeric products (35% by glpc) were two ethers, photoadducts I and II, obtained in a 9:1 ratio. Isomerization, disproportionation, and, in the case of the acid, decarboxylation products were also obtained. Both ethers could be isolated by preparative glpc of the methyl esters. Thick layer or column chromatography separated the methyl esters of the adducts from the other products but not from each other. Fractional crystallization of the mixed ethers gave pure photoadduct I.

Reduction of photoadduct I with lithium aluminum hydride followed by dehydrogenation with palladium

(1) (a) Presented at the 156th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 8–13, 1968. (b) Resident Postdoctoral Research Associate under the auspices of the National Academy of Sciences, National Research Council. (c) One of the laboratories of the Southern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture.

(2) (a) J. Pusset and R. Beugelmans, *Tetrahedron Lett.*, 3249 (1967); (b) P. G. Gassman and W. E. Hymans, *Chem. Commun.*, 795 (1967); *Tetrahedron*, **24**, 4437 (1968), and the references cited therein; (c) G. Just and V. Di Tullio, *Can. J. Chem.*, **42**, 2153 (1964); G. Bauslaugh, G. Just, E. Lee-Ruff, *Can. J. Chem.*, **44**, 2837 (1966), and the references cited therein; (d) W. G. Dauben and W. T. Wipke, *Pure Appl. Chem.*, **9**, 539 (1964); W. G. Dauben, *Chem. Weekbl.*, **60**, 381 (1964), and the references cited therein; (e) G. J. Fonken, "Organic Photochemistry" Vol. 1, O. L. Chapman, Marcel Dekker, Inc., New York, N. Y. 1967, p 197, and the references cited therein.

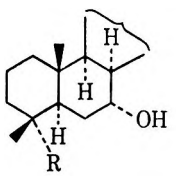
(3) W. H. Schuller, R. N. Moore, J. E. Hawkins, and R. V. Lawrence, *J. Org. Chem.*, **27**, 1178 (1962).

(4) W. G. Dauben and R. M. Coates, *J. Amer. Chem. Soc.*, **86**, 2490 (1964); *J. Org. Chem.*, **29**, 2761 (1964).

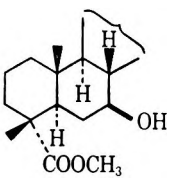
(5) R. F. Brown, G. B. Bachman, and S. J. Miller, *J. Amer. Chem. Soc.*, **65**, 623 (1943).

on charcoal gave retene, indicating that the abietic carbon skeleton was retained in the adduct. This was also supported by the pyrolysis of photoadduct I, which gave mainly methyl abietate. The nmr spectrum of photoadduct I showed a broad one-proton vinyl signal at 315 cps similar in shape and position to the C_7 proton signal of methyl abietate, a three-proton methoxyl signal at 189 cps, no HCO signal, and a two-proton singlet at 133 cps. This suggests that photoadduct I has a C_7–C_8 double bond and a methoxyl group at C_{13}.

Hydroboration–oxidation[6,7] of isopimaric and related $\Delta^{7,8}$ resin acids is known to give predominantly C_7 alcohols. Hydroboration–oxidation of photoadduct I by the LAH–BF_3 method[8] gave as the major product a diol (**1**) which was isolated in 65% yield as its *p*-



1, R = CH_2OH
2, R = $COOCH_3$



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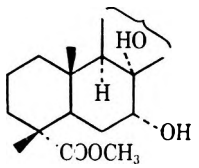
nitrobenzoate. Attempts to analyze the crude diol by glpc were unsuccessful. Use of the sodium borohydride–BF_3 method[6] with limited reagent gave a product containing 93% **2** and 6% of another hydroxy ester, presumably **3**. The C_7-α assignment for the hydroxyl in **1** and **2** is confirmed by the position and shape of the carbinol proton band. In each case it is a one-proton peak, at 226 cps (calcd[9a] 220 cps) with a half-height[10] width of 6 cps characteristic of an equatorial carbinol proton.[6,7,9,10] In the *p*-nitrobenzoate of **1** it shifts to 307 cps. The α assignment for the C_8 proton follows from the known *cis* hydroboration[11] and is confirmed by the deshielding of the C_{17} protons.[12]

The final proof of the C_7–C_8 double bond position was obtained by the osmium tetroxide–oxidation[8b,13] reaction sequence to give the ketoaldehyde (**5**). The intermediate diol (**4**) showed a clean one-proton triplet at 210 cps ($J_{e,e}$ = 2.5 cps and $J_{a,e}$ = 3.5 cps)[14a] for the equatorial C_7-β proton, and the C_{10} methyl (C_{17} protons)



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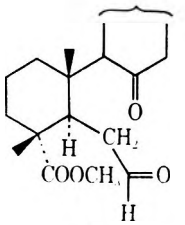

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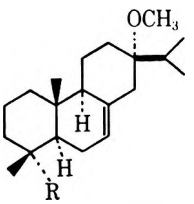
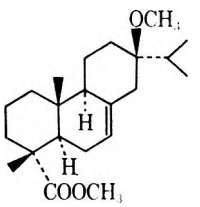
was deshielded. The *cis* mode of addition[13] for osmium tetroxide is known, so the diol is **4**. The ketoaldehyde showed a triplet at 581 cps (J = 1.8 cps) characteristic of aldehydes[14b] having two protons in the α-carbon atom. An aldehyde derived from C_{14} could not have two α protons so the aldehyde proton must be at C_7 coupled with the two C_6 protons.

With the double bond position fixed the methoxyl must be at C_{13} giving either **6** or **7** as the structure of



6, R = $COOCH_3$
6a, R = CH_2OH



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photoadduct I. As shown in Table I, photoadduct II has an nmr spectrum which is very similar to that of photoadduct I. In particular, the position and shape of the olefinic proton signal and deshielded methylene (C_{14}) proton signal together with the absence of an HCO signal strongly suggests that photoadduct II is the C_{13} epimer of photoadduct I.

TABLE I

CHEMICAL SHIFTS[a] (CPS) OF PHOTOADDUCT I (6) AND PHOTOADDUCT II (7)

Protons at	Photoadduct I (6)	Photoadduct II (7)
C_7	315 (diffused d, 1 H)	321 (b, 1 H)
C_{15}-OCH_3	216 (s, 3 H)	219 (s, 3 H)
C_{13}-OCH_3	189 (s, 3 H)	185 (s, 3 H)
C_{14}	133 (s, 2 H)	127 (s)
C_{16}	76 (s)	76 (s)
C_{19} and C_{20}	52 (d, J = 6.5)	52 (s, J = 6.5)
C_{17}	51 (s)	54 (s)

[a] Downfield relative to TMS as internal standard taken in $CDCl_3$.

Photolysis of 3-methylcholesta-3,5-diene in ethanol is reported[2c] to yield the unsaturated ether which would result from attack by the ethoxyl group on the less hindered side of the diene molecule. In the case of the resin acids the α side is less hindered;[7,15] therefore

(6) E. Wenkert, P. W. Jeffs, and J. R. Mahajan, *J. Amer. Chem. Soc.*, **86**, 2218 (1964).

(7) W. Herz, D. Melchior, R. N. Mirrington, and P. J. S. Pauwels, *J. Org. Chem.*, **30**, 1873 (1965).

(8) (a) S. Wolfe, M. Nassium, Y. Mazur, and F. Sondheimer, *ibid.*, **24**, 1034 (1959); (b) D. K. Black and G. W. Hedrick, *ibid.*, **32**, 3758 (1967).

(9) (a) E. L. Eliel, M. H. Gianni, Th. H. Williams, and J. B. Stothers, *Tetrahedron Lett.*, 741 (1962); (b) J. C. Sircar and A. I. Meyers, *J. Org. Chem.*, **32**, 1248 (1967).

(10) B. E. Cross and P. L. Myers, *J. Chem. Soc., C*, 471 (1968).

(11) H. C. Brown, "Hydroboration," W. A. Benjamin, Inc., New York, N. Y., 1962, pp 145, 146.

(12) J. W. Huffman, T. Kamiya, L. H. Wright, J. J. Schmid, and W. Herz, *J. Org. Chem.*, **31**, 4128 (1966).

(13) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," John Wiley & Sons, Inc., New York, N. Y., 1967, p 759.

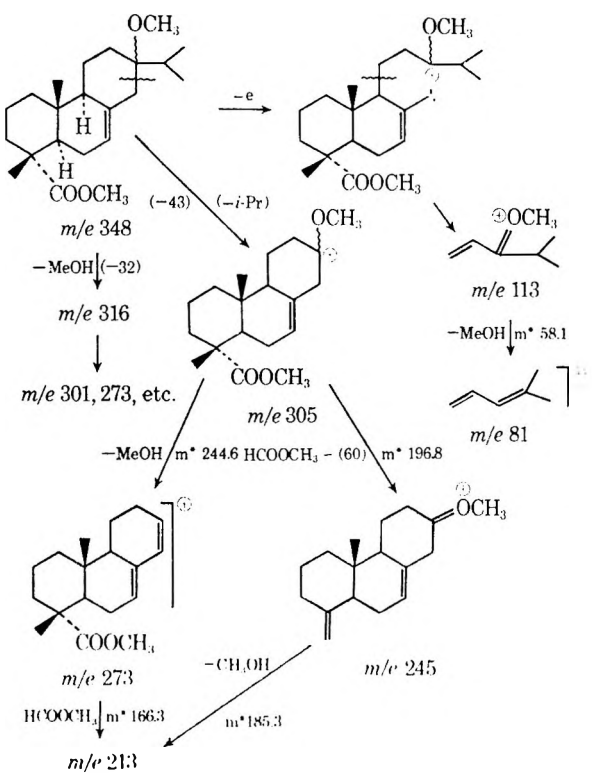
(14) (a) N. S. Bhacca and D. H. Williams, "Application of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, p 77; (b) *ibid.*, p 76.

(15) H. Kanno, W. H. Schuller, and R. V. Lawrence, *J. Org. Chem.*, **31**, 4138 (1966), and the references cited therein.

photoadduct I, being the major product, should have the α-methoxy structure (6).

Further proof of the epimeric relationship of the two photoadducts and strong support for the structural assignments is provided by the mass spectra of the adducts. The two spectra are qualitatively identical (*i.e.*, all major peaks are common to both spectra) but differ significantly in the relative abundance of certain fragments. Origin of the major ions is outlined in Scheme I. In each case only one possible

SCHEME I

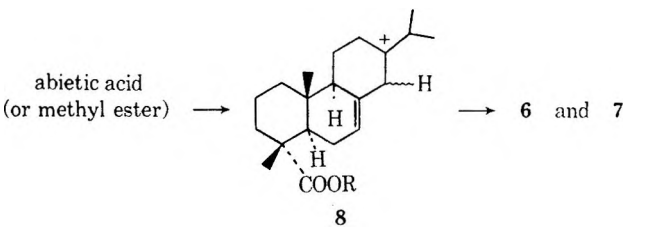


contributing structure is indicated. Formation of *m/e* 316 ions (M − 32) by α cleavage with rearrangement[16a] and further fragmentation to give the same ions obtained from the resin acids[16b] is to be expected regardless of the position of the methoxyl so these fragments have no qualitative significance. Ions arising from loss of an isopropyl group (M − 43) are not very abundant in the mass spectra of resin acid methyl esters[16b] unless the loss is facilitated by some neighboring group. Hence, the appearance of the *m/e* 305 as a major peak in the adduct spectra strongly supports the C_{13} position for the methoxyl in both adducts. Final proof that both have C_{13} methoxyls is provided by the *m/e* 113 ions which loses methanol to give the *m/e* 81 ion (metastable ion peak (m*) observed at *m/e* 58.1). The initial C_{13}–C_{14} and the final C_9–C_{11} cleavages are favored because they are β to the double bond.

(16) (a) F. W. McLafferty, *Anal. Chem.*, **29**, 1782 (1957); (b) C. A. Genge, *ibid.*, **31**, 1751 (1959).

Bieman[17] has pointed out that when epimers differ in steric crowding, the intensity of the molecular ion is higher for the less crowded isomer. Furthermore, in the case of alcohols and their acetates the intensity of the $M^+ - ROH$ ion is lower for the less crowded isomer. Examination of molecular models of **6** and **7** shows that **7** is less crowded than **6** even if the C ring in **6** has a twist-boat conformation. Since photoadduct II gives five times as much M^+ as photoadduct I and only one-third as much $M^+ - CH_3OH$ and derived fragments, it has structure **7**.

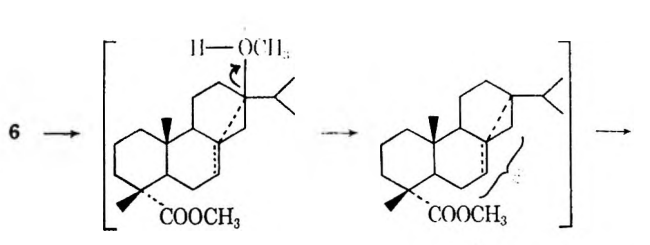
Since no cyclopropyl ring protons were evident in the nmr of the crude irradiation product, the formation of **6** and **7** probably takes place *via* the intermediate **8**, nonstereospecifically by a bimolecular



process.[18] The isolation of both the C_{13}-epimeric ethers **6** and **7** lends support to this mechanism and is in agreement with the results reported for 3-substituted cholest-3,5-dienes.[2c,2d,18]

In an attempt to enhance the reaction and to avoid poly(di?)merization of the abietic acid or methyl abietate, the irradiation was carried out in methanol containing 0.1 equiv of perchloric acid.[18] No photoadduct I could be detected in the glpc. The treatment of the photoadduct I with a solution of methanol–perchloric acid at room temperature for 10–15 min resulted in the regeneration of the methyl abietate (60%). This probably occurs by protonation of the methoxyl group followed by the elimination of methanol *via* the homoallylic carbonium ion,[18b] **9**, which rearranges to methyl abietate (Scheme II). The whole photochemical transformation

SCHEME II



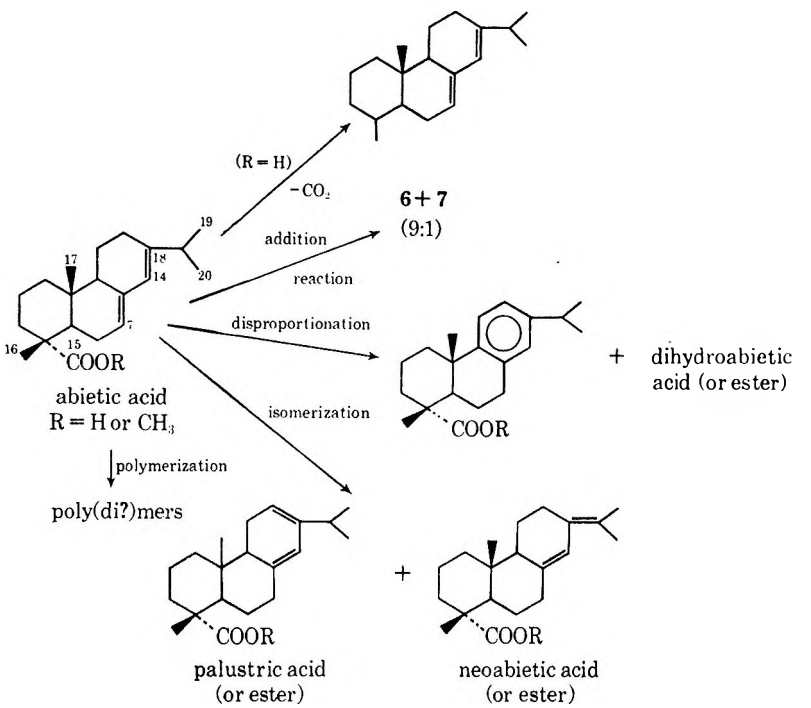
of abietic acid may then be represented as in Scheme III.

Photolysis of abietic acid or methyl abietate in other protic media is currently under active investigation and the results will follow soon. Neoabietic acid and

(17) K. Biemann, "Mass Spectrometry, Organic Chemical Applications," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 144.

(18) (a) G. Bauslaugh, G. Just, and E. Lee-Ruff, *Can. J. Chem.*, **44**, 2837 (1966), and the references cited therein. (b) G. Just and C. C. Lezoff, *ibid.*, **42**, 79, 2801 (1964).

SCHEME III



the other resin acids are also being investigated and the results will be published at a later date.

Experimental Section[19]

13-β-Isopropyl-13-α-methoxypodocarp-7-en-15-oic Acid Methyl Ester (6) and 13-α-Isopropyl-13-β-methoxypodocarp-7-en-15-oic Acid Methyl Ester (7).—Abietic acid[20,21] (9.15 g, $[\alpha]^{25}D$ −105–106°) was dissolved in absolute methanol (AR, 450 ml) and the solution degassed five times alternately introducing dry nitrogen in the quartz vessel. The solution was photolyzed with 2537-Å light[22] until the absorption went down to 10–15% of the original value. Analyses were also done by glpc,[23a] converting the acids to methyl esters with tetramethylammonium hydroxide (TMAH). When the photoadduct peak was the only major peak, the reaction was stopped (138 hr). The methanol was removed under vacuum and the residue analyzed as follows: (a) neutral volatile products, 4%[23b]; (b) total volatile products, 51%; (c) photoadducts, 28.5%, (d) other products such as dehydroabietic, abietic, etc., 22.5%. The neutralization equivalent (383.2) indicated polymerization and decarboxylation.

The product was esterified with diazomethane and chromatographed over Woelm neutral alumina (activity I, 210 g). Elution with hexane (400 ml) and 5% ether–hexane (200 ml) gave the resin-acid mixtures (1.62 g) containing methyl palustrate, methyl dehydroabietate, methyl abietate, two unknown peaks and the early peaks (the decarboxylated products). All known compounds were identified by glpc and the ir. Further elution with 5% ether–hexane (200 ml), 7.5% ether–hexane (200 ml) and 10% ether–hexane (400 ml) gave the solid photoethers (3.99 g, 37%) which were recrystallized from methanol to give the photoadduct I (6): 2.0635 g, 18.5%; mp 81–83°. One additional recrystallization gave the analytical sample: mp 84°; $[\alpha]^{26}D$ +12.1°; ir ($CHCl_3$) 5.84 (C=O), 7.25, 7.35 (isopropyl), 8.10, 8.45 and 8.76 (COC ester), 9.28 (COC ether) and 12.10 μ (>C=CH); nmr (see Table I); mass spectrum *m/e* (%Σ 40) 348 (0.1), 316 (11.6), 305 (9.1), 301 (10.5), 273 (22.4), 257 (3.0), 256 (2.1), 245 (1.0), 241 (1.1), 213 (2.8), 113 (2.7), 81 (1.1).

Anal. Calcd for $C_{22}H_{36}O_3$; C, 75.86; H, 10.34. Found: C, 76.04; H, 10.56.

The mother liquor, concentrated in the photoadduct II, and the resin acid esters were used in the preparative gas chromatography (5% Versamid-900; 20 ft × 3/8 in., 120 ml/min, 245°). The unknown peak (α 1.70) ahead of palustric was collected: ir (film) 5.80, 7.25, 8.10, 8.80, and 9.10 μ; no uv max. The other resin acid esters were also collected and identified by ir.

The photoadduct II (7) was collected separately as a viscous oil: ir (film) 5.81 (C=O), 7.25, 7.35 (isopropyl), 8.10, 8.46, 8.76 (COC ester), 9.26 (COC ether), 12.10 μ (>C=CH); nmr (see Table I); mass spectrum *m/e* (%Σ 40) 348 (0.5), 316 (3.8), 305 (9.2), 301 (1.9), 273 (6.3), 257 (1.4), 256 (1.1), 245 (0.8), 241 (3.0), 213 (2.2), 113 (6.9), 81 (2.3).

Anal. Calcd for $C_{22}H_{36}O_3$; C, 75.86; H, 10.34. Found: C, 75.68; H, 10.27.

Photolysis of Abietic Acid in Methanol–Benzene.—Abietic acid (0.807 g) in methanol (64 ml, AR) and benzene (16 ml, AR) was irradiated for 33 hr with 2537-Å light and the reaction was followed by glpc. Evaporation of the solvent gave a brown oil which was esterified with diazomethane solution and the photoproducts 6 and 7 were isolated together by preparative gas chromatography (20% S.E.-30 on Chromosorb W at 255°; 12 ft × 3/8 in. helium flow, 120 ml/min; retention time, 16 min).

Photolysis of Methyl Abietate in Methanol.—A solution of methyl abietate [prepared from abietic acid (0.5 g) with excess diazomethane in ether] in methanol (50 ml, AR) was irradiated with 2537-Å light for 26 hr and the reaction followed quantitatively both by uv and glpc. No early peaks, *i.e.*, decarboxylated abietic acid, were evident and the formation of the photoadducts

(19) Melting points are uncorrected. Infrared spectra were obtained with a Perkin-Elmer Infrared spectrophotometer, Model-21. Ultraviolet spectra and rotations were determined in 95% ethanol. Analytical gas chromatographic analyses were performed on a Varian Aerograph Model 1200 using 3/16-in. columns of specified length packed with 5–10% Versamid-900 on 60–80 mesh Chromosorb W. Methyl arachidate was used as an internal standard for determination of relative retention times (α) and for quantitative analyses. Nuclear magnetic resonance spectra were determined in deuteriochloroform, unless otherwise stated, with a Varian A-60A spectrometer, using tetramethylsilane as an internal standard. The multiplicities are s = singlet, d = doublet, t = triplet, m = multiplet and b = broad. Mass spectra were measured on an A.E.I. M.S.-9 spectrometer at 70 eV, using a direct inlet system. Analyses were carried out by Galbraith Laboratories, Inc., Knoxville, Tenn. The mention of firm names or trade products does not imply that they are endorsed or recommended by the Department of Agriculture over others not mentioned.

(20) Prepared from levopimaric acid, kindly supplied by Dr. W. H. Schuller of our laboratory, after initial purification.

(21) W. H. Schuller, H. Takeda, and R. V. Lawrence, *J. Chem. Eng. Data*, **12**, 283 (1967).

(22) Rayonet preparative photochemical reactor, Type RS, was used, having four 15-W modules as light source, available from the Southern New England Ultraviolet Co., Middletown, Conn. 06457.

(23) (a) N. M. Joye, Jr., and R. V. Lawrence, *J. Chem. Eng. Data*, **12**, 279 (1967); (b) analyzed without TMAH.

6 and 7 increased with time; but at the same time, considerable amounts of disproportionation products were formed. After 27 hr the sample analyzed as follows: volatile matter (57.8%), composed of palustrate, dihydroabietates, etc. 6.6%, dehydroabietate 27.6%, abietate 20%, neoabietate 0.66%, and photoadducts, 45.8%.

13-β-Isopropyl-13-α-methoxypodocarp-7-en-15-ol (6a).—To a solution of photoadduct I (**6**, 195 mg) in dry ether (12 ml) was added lithium aluminum hydride (117 mg) in ether (25 ml). The mixture was then refluxed for 4 hr, cooled, decomposed with a saturated solution of sodium sulfate (0.5 ml) and the ether solution filtered, dried (Na_2SO_4) and the solvent removed to give a solid (**6a**, 192 mg), mp 88–90°. This was recrystallized from *n*-pentane and had mp 91–93°. It showed a single peak in glpc: ir (film) 3.02, 7.27, 7.32, 8.0, 8.95 and 9.25 μ.

Anal. Calcd for $C_{21}H_{36}O_2$: C, 78.75; H, 11.25. Found: C, 78.79; H, 11.32.

Heating of **6a** with Pd–C for 4 hr at 220–245° yielded retene which was identified by its glpc retention time and uv spectrum.

7α-Hydroxy-13β-isopropyl-13α-methoxy-8α-podocarpan-15-ol (1).—To the stirred ice-cold solution of the photoadduct I (**6**, 525 mg) in dry ether (20 ml) was added slowly in installments the powdered LAH (216 mg). After stirring for 30 min at 0°, freshly distilled boron trifluoride etherate (0.7 ml) in dry ether (10 ml) was added slowly during a period of 1 hr and the mixture left at room temperature for 16 hr. It was decomposed with a saturated solution of sodium sulfate (1.2 ml) and the ether layer was filtered off. Removal of solvent gave a solid residue which was dissolved in 80% aqueous alcohol (40 ml) containing sodium hydroxide (0.6 g), followed by the slow addition of 30% hydrogen peroxide (4 ml). The mixture was stirred at room temperature for 2 hr and then refluxed on a steam bath for 4 hr, before diluting with brine and extracting with ether. The total ether extract was washed thoroughly with brine and was dried (Na_2SO_4) and the solvent stripped off to give (532 mg) of **1**: mp 60–75°; ir (Nujol) 3.02, 9.30, 9.65, 9.95 and 11.85 μ; nmr 226 (b, 1, $W_{1/2}$ = 6 cps, equatorial C_7-β proton), 191 (two d, center of C_{15} AB system, 2, J = 11 cps, $\delta_B - \delta_A$ = 34 cps, δ_A = 173 cps and δ_B = 208 cps), 186 (s, 3, CH_3O), 203 cps (b, 2, exchangeable with D_2O and unmasked the other peaks on addition of D_2O, 2 OH; in DMSO-d_6, C_7-α-OH appeared at 240 (d, 1, J = 2 cps) and C_{15}-OH appeared at 193 (b, $W_{1/2}$ = 5 cps), 65 (s, C_{17} protons), 51 (d, J = 6.5 cps, C_{19} and C_{20} protons), and 43 cps (s, C_{16} protons). This could not be recrystallized from many solvents.

***p*-Nitrobenzoate of Diol 1.**—To the ice-cold solution of diol **1** (440 mg) in dry pyridine (3 ml) was added in several installments the recrystallized *p*-nitrobenzoyl chloride (1.0 g, mp 73°) with constant shaking. After the addition was over, the lumps were broken with a spatula and the mixture was allowed to stand at room temperature for 2 more hr, occasionally shaking the mixture. It was heated on a steam bath for 10 min, then poured onto the ice–sodium bicarbonate mixture. The benzoate crystallized out as the trihydrate. It was filtered, washed thoroughly with sodium bicarbonate solution and water and dried. The crude product was recrystallized from 95% ethanol to give 525 mg (65%) of the ester, mp 218–222°. It was further recrystallized from chloroform–alcohol to give the analytical sample, mp 225°.

Anal. Calcd for $C_{35}H_{44}O_9N_2 \cdot 3H_2O$; C, 60.87; H, 7.25; N, 4.06. Found: C, 60.79; H, 7.27; N, 4.06.

Recrystallization and redrying of the sample at 100° (0.2 mm) over Drierite for 14 hr gave the monohydrate: mp 225°; ir ($CHCl_3$) 5.82, 6.23, 6.56, 7.44, 7.85, 8.98, 9.10 and 9.35 μ; nmr 480 (m, 8, aromatic), 307 (b, 1, $W_{1/2}$ = 6.5 cps, equatorial C_7-β proton), 240 (two d-AB type, J = 10 cps, $\delta_B - \delta_A$ = 20 cps, C_{15} protons), 187 (s, 3, CH_3O), 73 (s, C_{17} protons), 61 (s, C_{16} protons), 53 cps (d, J = 6.5 cps, C_{19} and C_{20} protons); integrated protons ≃ 44.

Anal. Calcd for $C_{35}H_{44}O_9N_2 \cdot H_2O$: C, 64.22; H, 7.03; N, 4.24. Found: C, 64.69; H, 6.70; N, 4.18.

7α-Hydroxy-13β-isopropyl-13α-methoxy-8α-podocarpan-15-oic Acid Methyl Ester (2).—Freshly distilled boron trifluoride etherate (1.25 g) was added dropwise at 0° with stirring to a solution of the photoadduct I (**6**, 1.012 g) and sodium borohydride (330 mg) in dry tetrahydrofuran (AR, 16 ml) over a period of 40 min. Stirring was continued at 0° for a further period of 2 hr. Excess borane was destroyed by stirring for 20 min with a saturated sodium sulfate solution (1 ml). Sodium hydroxide solution (3 *N*, 2 ml) was added slowly followed by 30% hydrogen peroxide (1.4 ml) and the mixture stirred at room temperature for 2 more hr. The reaction mixture was diluted with brine and extracted thoroughly with ether. The ether layer was washed successively with 10% ferrous sulfate solution, 5% sodium carbonate solution and water and then dried over sodium sulfate. Removal of the solvent gave an oil (1.19 g) which was chromatographed over alumina (21 g) with *n*-hexane, benzene and ether as eluent. Fraction 7, eluted with 25% ether–benzene mixture, gave 658 mg (62%) of a solid, mp ~45°, which could not be further purified by crystallization. The analysis by glpc showed **2** to be 93% pure; the impurities were unreacted photoadduct I (**6**, 1.5%) and the epimeric alcohol (**3**, 6%): ir (film) 2.95, 5.81, 8.10, 8.45, 8.65 and 9.33 μ; nmr 226 (b, 1, $W_{1/2}$ = 6.0 cps, equatorial C_7-β proton), 220 (s, 3, CH_3O ester), 186 (s, 3, CH_3O–), 106 (b, 1, exchangeable with D_2O, C_7-α-OH) [in DMSO-d_6 it appeared at 246 (d, 1, J = 3 cps)], 72 (s, C_{16} protons), 65 (s, C_{17} protons), 51 cps (d, J = 6.5 cps, C_{19} and C_{20} protons). Here also we see only one type of C_7 proton and C_7-OH proton corroborating the glpc results.

The alcohol was rechromatographed over alumina to give a solid, mp 44–48°, which could not be purified by recrystallization, and analyzed.

Anal. Calcd for $C_{22}H_{38}O_4$: C, 72.09; H, 10.45. Found: C, 72.27; H, 10.49.

7α,8α-Dihydroxy-13β-isopropyl-13α-methoxypodocarpan-15-oic Acid Methyl Ester (4).—To a solution of the photoadduct I (**6**, 542 mg) in pyridine (AR, 10 ml) and dry ether (10 ml) was added a solution of osmium tetroxide (0.5 g) in dry ether (10 ml). When the solution was left at room temperature for 6 days covered with aluminum foil, dark crystals gradually separated. A solution of sodium bisulfite (1.024 g) in water (15 ml) and pyridine (5 ml) was added with continuous stirring. The complex cleared to give a brown solution which was extracted with 300 ml of chloroform (five times). The extract was washed with water thoroughly (three times) and dried (Na_2SO_4). Evaporation of the solvent gave 590.6 mg of an oil (**4**): ir (film) 2.96, 5.80, 8.02 and 9.38 μ; nmr 363 (b, exchangeable with D_2O, $C_{7,8}$-α-OH), 222 (s, CH_3O ester), 210 (t, 1, J = 3 cps, equatorial C_7-β proton), 190 (s, CH_3O ether), 72 (s, C_{16} protons), 61 (s, C_{17} protons), 52 cps (d, J = 6.5 cps, C_{19} and C_{20} protons); in DMSO-d_6, C_7-α-OH appeared at 288 (d, J = 5 cps) and C_8-OH at 339 cps (s).

Oxidation of Diol 4, to Ketoaldehyde 5.—The crude diol **4** (0.55 g) was dissolved in glacial acetic acid (50 ml) and the lead tetraacetate (511 mg) was added to it slowly. The mixture was left at room temperature overnight (21 hr) and then the excess lead tetraacetate was decomposed by stirring at room temperature for 30 min with ethylene glycol (0.2 ml). The mixture was diluted with aqueous sodium chloride solution and then extracted with ether, washed with aqueous $NaHCO_3$ solution, water and dried (Na_2SO_4). Evaporation of the solvent gave an oil (459.5 mg). The crude ketoaldehyde was chromatographed twice over alumina (1.5 g) and eluted with *n*-hexane, and ether. *n*-Hexane fraction gave the ketoaldehyde **5** (258 mg) as an oil: ir (film) 5.80, 5.83, 8.08 and 9.35 μ; nmr 582 (t, 1, J = 1.8 cps, CH_2CHO) 218 (s, 3, CH_3O ester), 180 (s, 3, CH_3O ether), 145 (s, 2, C_{14} protons), 74 (s, C_{16} protons), 63 (s, C_{17} protons), 56 cps (d, J = 6.5 cps, C_{19} and C_{20} protons).

Product **5** (258 mg) was rechromatographed over alumina (2.5 g) and eluted with *n*-pentane and analyzed.

Anal. Calcd for $C_{22}H_{36}O_5$: C, 69.59; H, 9.47. Found: C, 69.41; H, 9.54.

Treatment of Photoadduct I (6) with Methanolic Perchloric Acid.—Photoadduct I (**6**, 25 mg) was dissolved in methanolic perchloric acid (2.5 ml, containing about 1 mg of 72% $HClO_4$) and its decomposition was followed by glpc. The decomposition was complete in 1 hr, giving methyl abietate, palustrate and dehydroabietate.

Registry No.—**1**, 18508-94-6; *p*-nitrobenzoate of **1**, 18508-95-7; **2**, 18508-96-8; **4**, 18508-97-9; **5**, 18508-98-0; **6**, 18508-99-1; **6a**, 18509-00-7; **7**, 18509-01-8.

Acknowledgment.—The authors wish to thank Mr. G. Boudreaux, of Southern Utilization Research and Development Division, New Orleans, La., for taking the nmr spectra; Dr. G. Sengupta, Chemistry Department, Harvard University, for the mass spectra; and Dr. H. Takeda, of this laboratory, for some helpful discussions.

The Oxidation of Steroid 9(11)-Olefins in Nitrosyl Fluoride Solutions[1]

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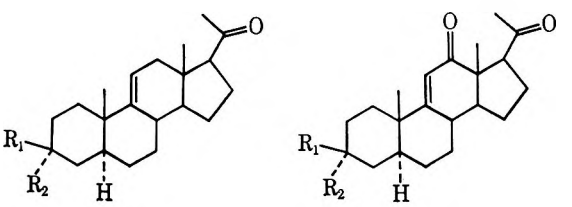
Steroid 9(11)-olefins, when reacted at 50° in a solution of nitrosyl fluoride in ethyl acetate, form the corresponding α,β-unsaturated 12-ketones. The structure of the products was proven by partial synthesis from a known sapogenin. The reaction is not due to the presence of the impurity nitrogen dioxide, since under the same conditions this reagent forms 17-nitro derivatives.

Although nitrosyl fluoride (NOF), the most reactive halide of nitrous acid, has been known for over 60 years,[2] its use as a reagent in organic chemistry has been limited to relatively few types of compounds. In the older literature the only report of its reaction with an organic substance is that of treatment of NOF with benzene under unspecified conditions. The product, nitrosobenzene, was identified only by odor and color.[3] More recently, a number of investigators have reported the reaction of NOF with fluoroolefins,[4] fluoro ketones,[5] and Δ^5-steroids.[6] These reactions were carried out either with neat reagents or in the presence of nonpolar solvents such as carbon tetrachloride or freons. In all the cases reported, the reactions could be explained as involving an initial addition of elements of NOF to the carbon–carbon or carbon–oxygen double bond. Either the addition products or derivatives resulting from hydrolysis or further reaction with NOF were isolated.

We wish to report that the reaction of NOF with some relatively hindered 9(11)-steroid olefins in a polar medium gives rise to a different type of reaction.

When nitrosyl fluoride was added to a solution of 3β-hydroxy-5α-pregn-9(11)-en-20-one acetate (**1a**) in ethyl acetate and the reaction was maintained at 50° for 18 hr, the starting material was completely consumed and was transformed into an unstable intermediate which was not characterized. When the crude reaction product was chromatographed on neutral alumina, a 20% yield of a new product was obtained which analyzed for $C_{23}H_{32}O_4$ and showed a uv maximum at 238 mμ (ϵ 12,700). The nmr and ir spectra were consistent with the formulation of the product as the diketone derived from the oxidation of the starting material at position 12. This compound, 3β-hydroxy-5α-pregn-9(11)-ene-12,20-dione acetate (**2a**), had not been reported in the literature; however, the closely related 3-ketone, 5α-pregn-9(11)-ene-3,12-20-trione (**2b**), had been previously characterized.[7]

The nitrosyl fluoride reaction was therefore carried out on the corresponding ketone (**1b**) and a product was obtained in 30% yield which was suspected to be compound **2b**. Comparison of the infrared spectrum of



1 **2**

a, R_1 = OAc; R_2 = H
b, R_1; R_2 = =O
c, R_1; R_2 = O, 5β-H

our oxidation product with that of an authentic sample[8] showed them to be similar but not identical. We therefore felt that this contradiction could best be clarified by an independent synthesis of ketone **2b**. This was accomplished according to Scheme I. Hecogenin acetate (**3**) was converted into 9(11)-dehydrohecogenin acetate (**4**) by oxidation with selenium dioxide.[9] The product was then degraded by a modification of the standard method[10] to 3β-hydroxy-5α-pregna-9(11),16-diene-12,20-dione acetate (**5**). This bis-α,β-unsaturated ketone possessed certain unusual properties which will be mentioned later. When subjected to catalytic hydrogenation in the presence of pyridine and ethyl acetate until 1 mol of hydrogen was taken up, the dienedione was converted into its 16,17-dihydro derivative **6**. Saponification and oxidation with chromium trioxide–acetone gave authentic compound **2b**. This sample was identical in all respects with our nitrosyl fluoride oxidation product but different from the "authentic sample."

This apparent anomaly was clarified when 5β-pregn-9(11)-ene-3,20-dione (**1c**) was allowed to react with nitrosyl fluoride in ethyl acetate. 12-Ketone **2c** was formed which was in fact identical with the sample

(1) This work was supported by contract with the Schering Corp., Bloomfield, N. J.

(2) O. Ruff and K. Stäuber, *Z. Anorg. Chem.*, **47**, 190 (1905).

(3) O. Ruff, W. Meuzel, and W. Neumann, *Z. Anorg. Allg. Chem.*, **208**, 293 (1932).

(4) I. L. Knunyants, E. G. Bykhovskaya, V. N. Frosin, and Ya. M. Kisel, *Dokl. Akad. Nauk SSSR*, **132**, 123 (1960), *Chem. Abstr.*, **54**, 20840i (1960); D. A. Barr and R. N. Haszeldine, *J. Chem. Soc.*, 1151 (1960); S. Andreades, *J. Org. Chem.*, **27**, 4163 (1962).

(5) S. Andreades, *ibid.*, **27**, 4157 (1962).

(6) G. A. Boswell, Jr., *ibid.*, **31**, 991 (1966); G. A. Boswell, Jr., *Chem. Ind.* (London), 1929 (1965).

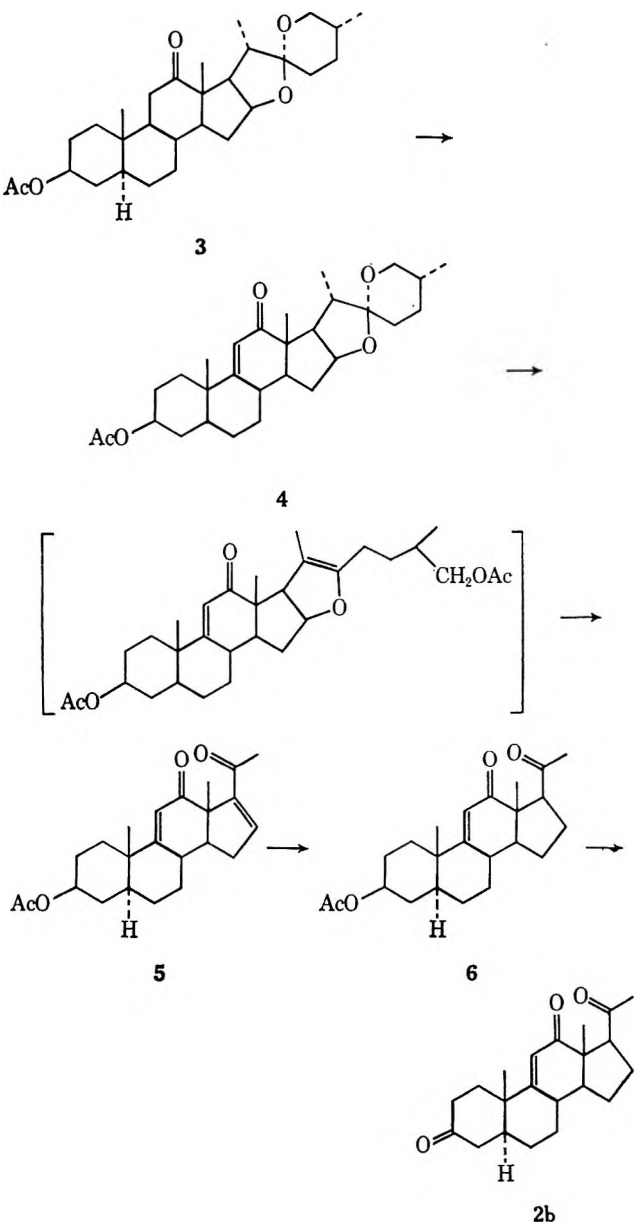
(7) R. N. Jones, P. Humphries, and K. Dobriner, *J. Amer. Chem. Soc.*, **72**, 956 (1950).

(8) We wish to thank Dr. T. F. Gallagher, custodian of the late Dr. Dobriner's collection, for his help in the characterization of these compounds.

(9) A. Bowers, E. Denot, M. B. Sanchez, F. Neumann, and C. Djerassi, *J. Chem. Soc.*, 1859 (1961).

(10) M. E. Wall and S. Serota, *Tetrahedron*, **10**, 238 (1960).

SCHEME I



procured from Dr. Gallagher, and which had been mistakenly reported to be the 5α compound.[11]

The hydrogenation of either dienedione **5** or ketone **6** under ordinary conditions in the absence of pyridine gave a 3:2 mixture of the saturated dione acetate and the previously reported[12] 12β-hydroxy-3β-acetoxypregnan-20-one. Since the saturated dione acetate was not reduced at all under these conditions, the reduction of the 12 carbonyl group in the unsaturated ketone must be especially enhanced by the presence of the 9(11) double bond, presumably due to complexing with the catalyst. Therefore, although the rates of hydrogenation of the 16 and the 9(11) double bonds are significantly different as expected, the existence of a third competing site precludes the possibility of a cleanly selective hydrogenation of the 16 double bond under ordinary conditions. However, the addition of pyridine to the reaction mixture completely inhibited the reduction of the 12 carbonyl group and further enhanced the difference between the rates of hydrogenation of the 16 double bond and the hindered 9(11) double bond, so that ketone **6** was readily obtained from dienedione **5**.

The ultraviolet spectrum of dienedione **5** is unusual, showing λ_{max} at 229 mμ (ε 17,000). This is in contrast to other $\Delta^{9(11)}$-12 ketones and Δ^{16}-20 ketones which normally absorb at 237 and 240 mμ, respectively. The hypsochromic shift caused by a 12 carbonyl group on the Δ^{16}-20 ketone system has been observed previously[13] and has been explained by assuming that the Δ^{16}-20 ketone exists in a *s-trans* orientation which causes the two carbonyl oxygen atoms attached to C-12 and C-20 to approach one another very closely. The resulting dipole–dipole interaction increases the energy required to excite the chromophore resulting in a hypsochromic shift. The effect evidently does not involve twisting about the 17–20 single bond, since the other conjugated ketone at C-12 also undergoes a hypsochromic shift, and in this case twisting about the single bond between the double bond and the carbonyl group is severely restricted because of ring strain.

The dienedione is also unusual in its extreme reactivity toward nucleophiles,[14] reacting with methoxide ion in methanol even faster at C-16 than 3β-hydroxy-16-pregnene-12,20-diene acetate.

The exact nature of the oxidizing species which is present when NOF is dissolved in ethyl acetate at room temperature and reacted with a steroid at 50° is as yet unknown. It was suggested by a referee that NOF is not present at all in the solution but is transformed into oxides of nitrogen which are the true oxidizing species. To clarify this point several additional experiments were undertaken.

First we attempted to investigate the constitution of the nitrosyl fluoride employed.[15] The mass spectrum of the gaseous reagent obtained directly from the cylinder showed the presence of silicon tetrafluoride, nitric oxide and hydrogen fluoride, normal reaction products of NOF with the glass inlet line of the mass spectrometer. In addition, it was possible to detect the presence of some nitrogen dioxide present as an impurity in the reagent. Nitrogen dioxide adds to unhindered olefins to form primarily nitrite esters of nitro alcohols.[16] In the case of a hindered steroid olefin, however, we were not aware that this reaction had been previously attempted. We therefore treated steroid **1a** in ethyl acetate with nitrogen dioxide to see if this was the agent responsible for the formation of the conjugated ketone (Scheme II).

(11) The 5β ketone has been synthesized earlier by another route [P. Hegner and T. Reichstein, *Helv. Chim. Acta*, **26**, 721 (1943)] and its properties are in agreement with our preparation.

(12) W. J. Adams, D. N. Kirk, D. K. Patel, V. Petrow, and I. A. Stuart-Webb, *J. Chem. Soc.*, 870 (1955).

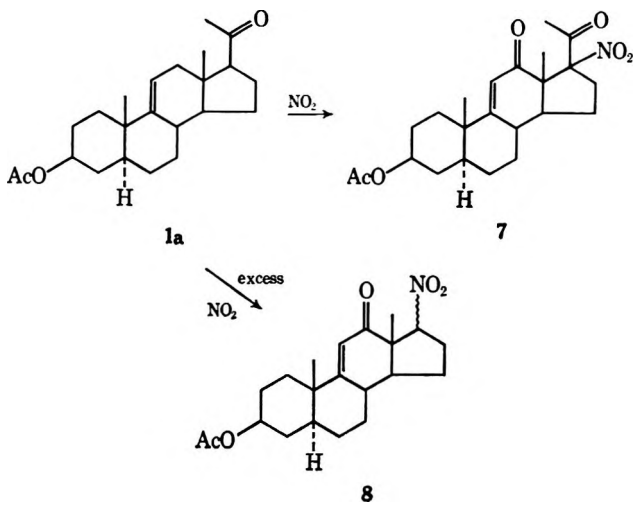
(13) G. P. Mueller, R. E. Stobaugh, and R. S. Winniford, *J. Amer. Chem. Soc.*, **75**, 4888 (1953).

(14) G. S. Abernethy and M. E. Wall, *J. Org. Chem.*, **34**, in press.

(15) The nitrosyl fluoride used for all of the experiments described in this paper was the commercial product purchased from the Ozark-Mahoning Co., Tulsa, Okla. 74119.

(16) H. Shechter, *Rec. Chem. Progr.*, **25**, 55 (1964).

SCHEME II



In the presence of excess NO_2 the reaction mixture was very complex. However a small amount of a crystalline product was obtained whose structure can be inferred from the structure of the starting material and from spectral data to be compound **8**. In the presence of a very limited quantity of nitrogen dioxide, the nitro ketone **7** was obtained along with substantial amounts of starting material. In neither reaction mixture was the presence of any of the product **2a** detectable.

We therefore conclude that the conversion of compounds **1** to **2** is brought about by the combined presence of the reagent nitrosyl fluoride in the solvent ethyl acetate. This behavior can be likened to the reaction of hindered olefins with other oxidizing agents to form conjugated ketones.[17]

Experimental Section[18]

3β-Hydroxy-5α-pregn-9(11)-ene-12,20-dione Acetate (2a).—3β-Hydroxy-5α-pregn-9(11)-en-20-one acetate[19] (1.0 g, 2.79 mmol) was dissolved in 40 ml of ethyl acetate in an all-polyethylene system. Nitrogen was bubbled through the reaction mixture which was cooled in an ice bath. Nitrosyl fluoride was then bubbled into the reaction mixture which on saturation turned a brilliant green-blue. The solution was transferred under nitrogen pressure into a monel flask, which was then sealed and maintained at about 50° overnight. The reaction mixture was washed with water and saturated sodium chloride solution and the aqueous layers were back-washed with ethyl acetate. The combined organic solutions were dried over sodium sulfate and evaporated to give 1.26 g of a chartreuse oil. The oil was dissolved in a minimum amount of 1:1 benzene–hexane and chromatographed on 120 g of alumina. The column was eluted with 1500 ml of 1:1 benzene–hexane, and 750 ml of 1% methanol in 1:1 benzene–hexane in a three-flask gradient. Compound **2a** (206 mg, 2070), obtained from the chromatography in crystalline form, was recrystallized from methylene chloride–hexane and melted at 138–139°: ir (KBr) λ_{max} 1735, 1704, 1678, 1809, 1248 cm^{-1}; nmr C_{11} τ 4.28 (d, J = 2), C_{17} 6.80 (t, J = 8), C_{21} 7.60, –OAc, 7.98, C_{19} 8.89, C_{18} 9.16; uv ϵ_{238}^{max} 12,660.

Anal. Calcd for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 74.41; H, 8.82, and no F or N.

5α-Pregn-9(11)-ene-3,12,20-trione (2b).—5α-Pregn-9(11)-ene-3,20-dione (0.913 g, 2.9 mmol) in 170–180 ml of ethyl acetate, was treated as in the previous reaction to yield 1.14 g of a crude gum. The gum was absorbed from chloroform onto 20 g of alumina which was then added atop a column of 125 g of alumina as a slurry in 1:1 benzene–hexane. The column was eluted with 1800 ml of 1:1 benzene–hexane, and 900 ml of 2% methanol in 1:1 hexane–benzene in a three-flask gradient system. From the column was obtained 290 mg of crude product (30%) which, after florisil cleanup and recrystallization, melted at 246.5–248.5°: ir (KBr) λ_{max} 1708, 1670, 1600 cm^{-1}; nmr C_{11} τ 4.23 (d, J = 2), C_{17} 6.78 (t, J = 8), C_{21} 7.60, C_{19} 8.69, C_{18} 913; uv ϵ_{236}^{max} 12,800.

Anal. Calcd for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.75; H, 8.43.

5β-Pregn-9(11)-ene-3,12,20-trione (2c).—5β-Pregn-9(11)-ene-3,20-dione (500 mg, 1.59 mmol) in 50 cc of ethyl acetate was allowed to react as in the previous example to give 750 mg of a crude oil. The oil was chromatographed on 5 g of alumina and added, in a slurry with 50% benzene–hexane, to a 13:1 column of 100 g of alumina. The column was eluted with 1000 cc of 50% benzene–hexane and 500 cc of 2% methanol in 50% benzene–hexane in a three-flask gradient. The 160 mg which was eluted was rechromatographed on a 20 × 40 cm × 1 mm plate of silica gel HF, developing with 1:3 acetone–carbon tetrachloride. The major band was fluorescent and yielded 43 mg of yellow crystals upon elution with chloroform. Florisil cleanup, sublimation and recrystallization from methylene chloride–hexane afforded 17.8 mg, mp 181.5–183°. The infrared spectrum was identical with that of an authentic sample: ir (KBr) λ_{max} 1705, 1668, 1600 cm^{-1}; nmr C_{11} τ 4.04 (d, J = 2.5), C_{17} 6.76 (t, J = 8), C_{21} 7.57, C_{19} 8.70, C_{18} 9.12; uv ϵ_{237}^{max} 12,800.

9(11)-Dehydrohecogenin acetate was prepared by the selenium dioxide oxidation of hecogenin acetate as described by Bowers, *et al.*[9] Its nmr spectrum showed the characteristic vinyl proton absorption at 342 cps.

3β-Hydroxy-5α-pregna-9(11),16-diene-16,20-dione Acetate (5).—9(11)-Dehydrohecogenin acetate (10.2 g) was refluxed in 20 ml of acetic anhydride containing 10 ml of pyridine and 3.4 g of methylammonium chloride for 4 hr. The reaction mixture was cooled and poured into ice water. The mixture was extracted with two portions of ethyl acetate. The combined extracts were washed with water and saturated sodium chloride solution, then dried over sodium sulfate and evaporated to give 14 g of an oil.

The oil was dissolved in 20 ml of 1,2-dichloroethane and 20 ml of glacial acetic acid and the mixture cooled to −15° in a Dry Ice–acetone bath. A solution of 2.6 g of chromium trioxide in 20 ml of 90% acetic acid was added over a 15-min period. The reaction mixture was stirred at −5° for 45 min. Ethanol (10 ml) was added and the reaction mixture refluxed for 5 hr. The mixture was washed twice with water and once with saturated sodium chloride solution. The aqueous washes were backwashed with four portions of methylene chloride. The combined organic extracts were dried over magnesium sulfate, filtered and evaporated to give 11.6 g of a black oil. Chromatography on 1 kg of silica gel, eluting with 4 l. each of 5, 10 and 25% acetone in carbon tetrachloride, provided 4.1 g of crude product. This was passed through a cleanup column of *ca.* 10 g of alumina in ether and recrystallized from acetone–hexane to give 2.85 g of compound **5** melting at 150–154°, containing no more than 5% of its 16-dehydro derivative by nmr and mass spectral estimation: ir (mull) λ_{max} 3075, 1737, 1696, 1680, 1602, 1250 cm^{-1}; nmr C_{16} τ 3.33 (m), C_{11} 4.32 (d, J = 2), C_2 7.63, –OAc 7.95, C_{19} 8.73, C_{18} 8.85; uv ϵ_{239}^{max} 17,000.

Anal. Calcd for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 74.56; H, 8.12.

3β-Hydroxy-5α-pregn-9(11)-ene-12,20-dione Acetate (6).—To

(17) H. R. Bentley, J. A. Henry, D. S. Irvine, and F. S. Spring, *J. Chem. Soc.*, 3673 (1953).

(18) Unless otherwise indicated, chromatography was carried out on Woelm neutral, activity III alumina. Ultraviolet spectra were determined in absolute ethanol. Nmr spectra were determined in deuteriochloroform at 60 Mc, with a tetramethylsilane internal standard. Unless otherwise indicated, all nmr peaks were singlets; J values are in cycles per second.

(19) The $\Delta^{9,11}$ steroids used in this study were kindly given to us by Dr. H. Herzog, Schering Corp., Bloomfield, N.J.

30 ml of ethyl acetate was added 3 ml of pyridine and 60 mg of 5% palladium on charcoal catalyst. The mixture was hydrogenated to saturation, then 300 mg of compound 5 in 30 ml of ethyl acetate was added. The approximate rate of hydrogen uptake was 0.12 mequiv/min for the first mole, abruptly decreasing to 0.012 mequiv/min. Approximately half of the reaction mixture was removed after the uptake of 1 mequiv. It was filtered and evaporated to give the expected product contaminated with less than 5% of the 9(11) dihydro derivative (by nmr estimation) and no discernible 12β-hydroxypregnane. One crystallization from methanol afforded material melting at 134–137°.

The hydrogenation of the remaining half of the reaction mixture was permitted to proceed to completion. Filtration and evaporation gave 3β-hydroxy-5α-pregnane-12,20-dione acetate uncontaminated by any other steroid, by nmr analysis.

Treatment of 3β-Hydroxy-5α-pregn-9(11)-en-20-one Acetate (1a) with Excess Nitrogen Dioxide in Ethyl Acetate at 50°.—The steroid (1.08 g) was dissolved in 40 ml of dry ethyl acetate in a monel flask and the solution chilled in an ice bath. Gaseous nitrogen dioxide was passed into the reaction mixture for 1 hr. The reaction vessel was sealed and incubated at 53° for 18 hr. The reaction mixture was concentrated under vacuum. Ethyl acetate was added to the residue. The solution was washed with water and saturated sodium chloride solution. Both aqueous washes were extracted with a portion of ethyl acetate. The combined organic solutions were dried over sodium sulfate and evaporated to give a brown oil which appeared to be a complex mixture containing no starting material by tlc. The oil was adsorbed onto 10 g of alumina and placed atop a column of 110 g of alumina in 1:1 benzene–hexane. The column was eluted with a three-flask gradient of 1800 ml of 1:1 benzene–hexane and 900 ml of 2% methanol in 1:1 benzene–hexane, then with 1000 ml of 2% methanol in 1:1 benzene–hexane. Only one compound (60 mg) was obtained in crystalline form. Upon recrystallization from methylene chloride–hexane, it melted at 202–206° with profuse sweating. Nmr, ir and mass spectra confirmed the structure to be 3β-hydroxy-17ξ-nitroandrost-9(11)-en-12-one acetate **8**: ir (mull) 3062, 1730, 1670, 1595, 1545, 1306, 1245, 1158, 1032, 783 cm^{-1}; nmr ($CDCl_3$) C_{11} τ 4.22, C_{17} 4.96 (t, J = 9), C_3 5.32 (m), –OAc 7.97, C_{19} 8.89, C_{18} 8.95; uv ϵ_{237}^{max} 14,600; mass spectrum, 375.2062 (calcd for $C_{21}HN_{29}O_5$, 375.2046).

Reaction of 3β-Hydroxy-5α-pregn-9(11)-en-20-one Acetate (1a) with a Limited Amount of Nitrogen Dioxide.—In 60 ml of dry ethyl acetate was dissolved 0.58 g of nitrogen dioxide. The solution was added to the steroid (1.0 g) in a monel flask. The vessel was sealed and incubated at 50° for 18 hr. The reaction mixture was washed with saturated sodium bicarbonate solution and saturated sodium chloride solution, then dried over sodium sulfate and evaporated to give 0.95 g of brown oil which, by tlc, contained mostly starting material in combination with many other products. The oil was dissolved in 1:1 ethyl acetate–benzene and passed through 120 g of alumina. A yellow oil (550 mg) was eluted, which consisted of at least seven components by tlc with two spots predominating. This oil was chromatographed on 75 g of silica gel, eluting with 3 l. of 2–3% acetone in carbon tetrachloride. Eluted first was 290 mg of a yellow oil estimated to be 80% starting material by its nmr spectrum and by tlc. About 50 mg of a crystalline product was then obtained, which upon recrystallization from methylene chloride–hexane formed colorless needles of 3β-hydroxy-17ξ-nitro-5α-pregn-9(11)-ene-12,20-dione acetate (**7**): mp 199–210°; ir (mull) 3062, 1745, 1722, 1680, 1602, 1550, 1278, 1252, 1145, 1030 cm^{-1}; nmr C_{11} τ 4.12, C_{21} 7.44, –OAc 7.96, C_{19} 8.90, C_{18} 9.19; uv ϵ_{237}^{max} 11,500; mass spectrum, 417.2172 (calcd for $C_{23}H_{31}NO_6$, 417.2151).

Registry No.—2a, 18266-99-4; 2b, 18267-00-0; 2c, 18267-01-1; 5, 18267-02-2; 7, 18267-03-3; 8, 18267-04-4; nitrosyl fluoride, 7,789-25-5.

The Alkaloids of *Peschiera lundii* (D.C.) Miers.[1] Isolation and Structure Elucidation of Voacristine Pseudoindoxyl and Iboxygaine Hydroxyindolenine

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Voacristine pseudoindoxyl ($C_{22}H_{28}N_2O_5$) and iboxygaine hydroxyindolenine ($C_{20}H_{26}N_2O_3$) were isolated from *Peschiera lundii* (D.C.) Miers. Their structures were determined on the basis of spectral data and confirmed by partial synthesis from related alkaloids. In addition, voacangine, coronaridine, voacristine, 20-epivoacristine, iboxygaine, ibogaine, olivacine, and vobasine were found in the same plant. Most of the iboga alkaloids isolated were oxidized to the corresponding hydroxyindolenines and rearranged to pseudoindoxyls, several of which were chemically characterized for the first time.

As part of a continuing study of the chemotaxonomy and biological activities of selected portions of the *Apocynaceae*,[2] we became interested in a Brazilian representative of the *Tabernaemontaneae*, identified as *Peschiera lundii* (D. C.) Miers.[3] The close botanical relationship between *Peschiera* and *Tabernaemontana* species has often led to confusion and either name has been assigned to a species, according to a botanist's individual preference. The detailed isolation and characterization of several alkaloids from *P. lundii* is now reported. In the course of determining the structure of two new alkaloids from this plant, and because of the recent isolation[4,5] of a number of hydroxyindolenines and pseudoindoxyls of iboga alkaloids, several known

(1) Problems in Chemotaxonomy. V.

(2) For example, see J. A. Weisbach, R. F. Raffauf, O. Ribeiro, E. Macko, and B. Douglas, *J. Pharm. Sci.*, **52**, 350 (1963); M. P. Cava, S. S. Tjoa, Q. A. Ahmed, and A. I. daRocha, *J. Org. Chem.*, **33**, 1055 (1968).

(3) The plant material used in this study was collected by Dr. Aparicio Duarte near Porto Seguro in the state of Bahia, Brazil. His assistance in the collection and identification of the material is gratefully acknowledged. A voucher specimen, no. 6828, has been deposited in the Herbarium Bradeanum, Rio de Janeiro, Brazil.

(4) C. Hootele, R. Levy, M. Kaisin, J. Pecher, and R. H. Martin, *Bull. Soc. Chim. Belges*, **76**, 300 (1967).

(5) B. C. Das, E. Fellion, and M. Plat, *C. R. Acad. Sci. Paris*, **C264**, 1765 (1967).

iboga alkaloids were oxidized to the corresponding hydroxyindolenines and subsequently rearranged to pseudoindoxyls.

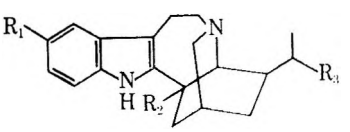
An alcohol extract of the leaves, stems, and bark of plants collected in the state of Bahia, Brazil, was treated in the usual manner to provide a crude alkaloid mixture. This mixture was selectively divided into five fractions by pH extraction.

From the pH 1 ether extract and pH 7 precipitate, the previously characterized alkaloids, coronaridine (**1**), voacangine (**2**), voacristine (**3**), and 20-epivoacristine (**4**) were isolated by repeated column chromatography. These compounds were identified by comparing their ultraviolet and infrared spectra and melting points with those of authentic samples.[6] After voacristine (**3**) and 20-eipvoacristine (**4**) were isolated from the pH 7 precipitate, the residue was rechromatographed. A fraction eluting from neutral alumina immediately after 20-epivoacristine (**4**) provided a light yellow amorphous material, which could not be crystallized as the free base. Upon treatment with methanolic hydrogen chloride, the solution turned dark and a yellow crystalline hydrochloride designated as hydrochloride A, mp 261°, was obtained after work-up. Its ultraviolet (uv) absorption [λ_{max}^{EtOH} 228 mμ (ε 24,500), shoulder near 253, with long-wavelength absorption at 412] suggested a pseudoindoxyl structure. The infrared (ir) spectrum exhibited intense bands at 5.73 (nonconjugated ester) and 5.95 μ (conjugated carbonyl); the latter peak corresponds to ones in the spectra of iboluteine, desmethoxyiboluteine, and voaluteine. The elemental analysis and molecular weight of 400 (mass spectra) are in agreement with a formulation of $C_{22}H_{28}N_2O_5$; this composition corresponds to that of the pseudoindoxyl of either voacristine or 20-epivoacristine. After our characterization of the hydrochloride A had been carried out, the isolation of "montanine" from *Tabernaemontana rupicola* Benth was reported.[7] The compound was formulated as the pseudoindoxyl of voacristine, although evidence concerning the stereochemistry of the 20-hydroxyl group was not provided. A comparison of nmr and ir spectra, melting points, and optical rotations of compound A with the published data for "montanine" showed that the two compounds were identical. As described below, we have been able to effect a direct conversion of voacristine into hydrochloride A, thus establishing the configuration of the 20-hydroxyl group of compound A. We suggest that the name "montanine" for this alkaloid be abandoned in favor of voacristine pseudoindoxyl, as the name "montanine" has been in use since 1955[8,9] for an *Amaryllidaceae* alkaloid of entirely different structure.

Several procedures for the mild oxidation of iboga alkaloids have been reported.[10-12] We chose to examine the air oxidation of voacristine (**3**). A solution of pure voacristine in chloroform was aerated at room temperature for several days; the gradual transformation of the voacristine into a new product was shown by tlc monitoring of the solution. The reaction mixture afforded a crystalline product, mp 175–177°. Its ir spectrum displayed no peak ascribable to NH near 2.7 μ; nmr data also showing an absence of NH proton, uv spectrum [λ_{max}^{EtOH} 229 mμ (ε 13,400), 264 (5600), 292 (6150), 316 (5150)], and elemental analyses were in accord with its formulation as the hydroxyindolenine[13] (**5**) of voacristine. The latter compound was rearranged in hot methanolic hydrogen chloride to the yellow crystalline voacristine pseudoindoxyl hydrochloride (**6**), mp 261°, which was identical with the isolated hydrochloride A in all respects (ir, uv, and nmr spectra and melting point). For further comparison, 20-epivoacristine pseudoindoxyl was prepared by similar oxidation of 20-epivoacristine to the corresponding hydroxyindolenine (**7**), mp 209–210°, which was rearranged to the pseudoindoxyl hydrochloride (**8**), mp 315°. Both compounds were characterized for the first time.

After voacristine pseudoindoxyl (**6**) was isolated, the residue from the pH 7 precipitate was rechromatographed. A very small amount of vobasine[14] (**9**), mp 228° (from chloroform), mp 267° (from acetone), was isolated from the alumina column (identified by comparison of melting point and ir, uv, and mass spectra with those of an authentic sample).

The pH 7 ether extracts of the total alkaloids were complex fractions which showed several close running spots on tlc. A new base B, mp 223°, was isolated from this fraction, in addition to the known alkaloids, voacristine (**3**), its pseudoindoxyl (**6**), iboxygaine (**10**), ibogaine (**11**), and olivacine (**12**). The latter is the



1, R_1 = H; R_2 = $COOCH_3$; R_3 = H
2, R_1 = OCH_3; R_2 = $COOCH_3$; R_3 = H
3, R_1 = OCH_3; R_2 = $COOCH_3$; R_3 = OH
4, R_1 = OCH_3; R_2 = $COOCH_3$; R_3 = ~~OH epi
10, R_1 = OCH_3; R_2 = H; R_3 = OH
11, R_1 = OCH_3; R_2 = H; R_3 = H

only alkaloid found in this plant which does not belong to either the iboga or the 2-acylindol alkaloid groups. The new base B was assigned the $C_{20}H_{26}N_2O_3$ (elementary analysis and high resolution mass spectra). Its nmr and ir spectra (Figure 1) showed the absence of NH; its uv spectrum, which is very similar to those of voacristine hydroxyindolenine and 20-epivoacristine hydroxyindolenine, suggested the presence of a hydroxyindolenine chromophore.[10,15,16] Furthermore, these

(6) An authentic sample of 20-epivoacristine was kindly supplied by Dr. J. Poisson, Laboratoire de Pharmacie Galenique, Faculte de Pharmacie de Paris, Paris VI, France. F. Puisieux, M. B. Patel, J. M. Rowson, and J. Poisson, *Ann. Pharm. Fr.*, **23**, 33 (1965).

(7) C. Niemann and J. W. Kessel, *J. Org. Chem.*, **31**, 2265 (1966).

(8) W. C. Wildman and C. J. Kaufman, *J. Amer. Chem. Soc.*, **77**, 1248 (1955).

(9) Y. Inubushi, H. M. Fales, E. W. Warnhoff, and W. C. Wildman, *J. Org. Chem.*, **25**, 2153 (1960).

(10) M. F. Bartlett, D. F. Dickel, and W. I. Taylor, *J. Amer. Chem. Soc.*, **80**, 126 (1958).

(11) U. Renner, D. A. Prins, and W. G. Stoll, *Helv. Chim. Acta*, **42**, 1572 (1959).

(12) F. Percheron, *Ann. Chim.*, **4**, 303 (1959).

(13) After this manuscript had been prepared, isolation and synthesis of this compound appeared in H. K. Schnoes, D. W. Thomas, R. Aksornvitaya, W. R. Schleigh, and S. M. Kupchan, *J. Org. Chem.*, **33**, 1225 (1968).

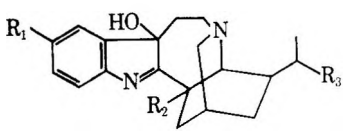
(14) J. A. Weisbach, and B. Douglas, *Chem. Ind.* (London), 623 (1965).

(15) G. B. Guise, M. Rasmussen, E. Ritchie, and W. C. Taylor, *Aust. J. Chem.*, **18**, 927 (1965).

(16) G. B. Guise E. Ritchie, and W. C. Taylor, *ibid.*, **18**, 1279 (1965). An authentic sample of voaluteine was kindly supplied by Dr. E. Ritchie.

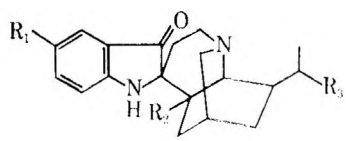
compounds have in common a high intensity uv absorption around 225–230 mμ with three low intensity uv bands around 265, 290, and 315 mμ, instead of one (or with a shoulder) low intensity band near 280–295 mμ found in the parent indoles. These facts led us to believe that the base B is the hydroxyindolenine (**13**) of iboxygaine. This was confirmed by air oxidation of iboxygaine (**10**) and direct comparison of the product with the isolated base B.

Two of the major alkaloids, coronaridine (**1**) and voacangine (**2**), were also oxidized. These alkaloids, which have no 20-hydroxy group, seemed significantly more stable to air oxidation than the corresponding hydroxy bases. In these instances, the best results were obtained when the compounds were oxidized *via* Grignard derivatives. In this procedure,[16] Grignard derivatives of coronaridine and voacangine were converted into the corresponding hydroxyindolenines (**14** and **15**)



5, R_1 = OCH_3; R_2 = $COOCH_3$; R_3 = OH
7, R_1 = OCH_3; R_2 = $COOCH_3$; R_3 = ~~OH epi
13, R_1 = OCH_3; R_2 = H; R_3 = OH
14, R_1 = H; R_2 = $COOCH_3$; R_3 = H
15, R_1 = OCH_3; R_2 = $COOCH_3$; R_3 = H

and rearranged with acid to the pseudoindoxyls (**16**) and (**17**). Neither the synthesis of coronaridine hydroxyindolenine (14) and coronaridine pseudoindoxyl (**16**) nor their isolation from a plant source has been previously reported. In view of the isolation of voacangine pseudoindoxyl from other sources (voaluteine[15,16] and rupicoline[7]), one can anticipate the "natural" occurrence of compounds **14** and **16**.



6, R_1 = OCH_3; R_2 = $COOCH_3$; R_3 = OH
8, R_1 = OCH_3; R_2 = $COOCH_3$; R_3 = ~~OH epi
16, R_1 = H; R_2 = $COOCH_3$; R_3 = H
17, R_1 = OCH_3; R_2 = $COOCH_3$; R_3 = H
18, R_1 = OCH_3; R_2 = H; R_3 = OH

Peschiera lundii, in contrast to P. affinis,[17] contains substantial amounts of iboga alkaloids, as well as olivacine (**12**), usually associated with the genera *Tabernaemontana*, *Tabernanthe*, and *Voacanga*;[18,19] only trace amounts of vobasine (**9**) and no sarpagine-type alkaloids (*e.g.*, affinisine[17]) were isolated. Thus, if these

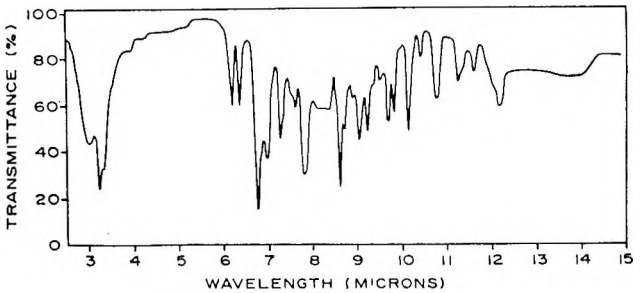
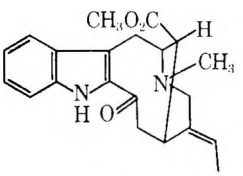


Figure 1.—The infrared spectrum of iboxygaine hydroxyindolenine in chloroform.

chemical differences are of chemotaxonomic significance, *P. lundii* might be better viewed as a *Tabernaemontana* species than as a species of *Peschiera*.



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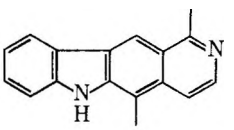

12

Experimental Section[20]

Extraction.—An alcoholic extract of 16 kg of leaves, stems, and bark[3] was extracted with 2% tartaric acid (16 l.), which was then washed three times with 2-l. portions of ether. The ether layer was extracted with dilute hydrochloric acid, which was combined with the tartaric acid extracts. The aqueous extract was made alkaline with ammonia (pH 8–9) and extracted with chloroform (23 l.). This was washed, dried, and evaporated to dryness. The total alkaloids were redissolved in 0.2 *M* H_3PO_4 (5 l.), and extracted with ether at pH 1. Concentration of the ether gave fraction A (18.9 g). The aqueous layer was neutralized (pH 7). A precipitate which formed was filtered and dried; it gave fraction B (*ca.* 50 g). The neutral, aqueous solution was continuously extracted with ether into the following fractions: C, 3-hr ether extract (3.5 g); D, 1-week ether extract (55 g); and E, 5-week ether extract (9 g). The fractions B and D are identical with C and E, respectively, on silica gel tlc (8% methanol in chloroform).

Fraction A [Coronaridine (1) and Voacangine (2)].—One gram of fraction A was dissolved in 30 ml of boiling benzene and filtered from insoluble material (110 mg). The benzene solution was washed with pH 4 buffer, which was discarded. The dried organic layer was then chromatographed over 40 g of neutral alumina II. Elution with benzene gave 15 mg of coronaridine and 55 mg of voacangine. Both compounds were identified by comparison with authentic samples.

Fractions B and C [Voacristine (3), 20-Epivoacristine (4), Voacristine Pseudoindoxyl (6), Iboxygaine (10), and Vobasine (9)].—The combined fraction (23 g) was dissolved in benzene (50 ml) and filtered. The filtrate was concentrated and chromatographed over a Florisil column. Amorphous material (6.2 g) was obtained from the chloroform eluate (2 l), and an additional 5 g was obtained from the methanol–chloroform wash. Repeated chromatography of the chloroform fraction over neutral alumina III eluted with chloroform gave voacristine (2 g, free base): mp 90° (benzene solvated), 163–164° (from ether); $[\alpha]^{25}D$ −25° (*c* 1.035, $CHCl_3$); hydrochloride, mp 177–178° (chloroform solvated).

The column was further eluted with chloroform to give crystalline 20-epivoacristine (2.5 g): mp 115°; $[\alpha]^{25}D$ −44.5° (*c* 1.25, $CHCl_3$). The column was finally washed with chloroform–

(17) M. P. Cava, S. K. Talapatra, O. Ribeiro, R. F. Raffauf, J. A. Weisbach, and B. Douglas, *Chem. Ind.* (London), 1193 (1964).

(18) M. Gorman, N. Neuss, N. J. Cone, and J. A. Deyrup, *J. Amer. Chem. Soc.*, **82**, 1142 (1960).

(19) W. I. Taylor in "The Alkaloids," Vol. 8, R. H. F. Manske, Ed., Academic Press, New York, N. Y., 1965, p 203.

(20) All previously reported alkaloids isolated were analyzed and compared with authentic samples.

methanol. The recovered residue was rechromatographed over neutral alumina III. After some additional voacristine was isolated, 0.9 g of amorphous material was obtained; it failed to crystallize as the free base. The amorphous base melted at 135–140°. Upon treatment with methanolic hydrogen chloride, yellow crystalline voacristine pseudoindoxyl hydrochloride was obtained (420 mg): mp 261°; $[\alpha]^{25}D$ −223.5 (c 0.47, EtOH), uv λ_{max}^{EtOH} 228 mμ (ε 24,500), shoulder at 253.

Anal. Calcd for $C_{22}H_{28}N_2O_5 \cdot HCl$: C, 60.30; H, 6.47; N, 6.42. Found: C, 60.15; H, 6.78; N, 6.80.

Rechromatography of all combined residues and other fractions over Florisil gave a small amount of iboxygaine.

In another large-scale isolation (from a separate plant collection), a small amount of vobasine was isolated after the 20-epivoacristine fraction.

Fraction D or E [Voacristine (3), Voacristine Pseudoindoxyl (6), Ibogaine (11), Iboxygaine (10), Iboxygaine Hydroxyindolenine (13)].—Fraction D (30 g) was washed with pH 4.5–5.5 buffer until the benzene layer showed only one spot on tlc (silica gel–8% methanol–chloroform); it was then concentrated and chromatographed over alumina. Voacristine (3) and its pseudoindoxyl (6) were isolated. The combined buffer was made basic with ammonia, extracted with chloroform, and concentrated. Chromatography of the residue over Florisil (280 g) with chloroform elution first gave a small amount of ibogaine (11, 400 mg), mp 149–150z, and then iboxygaine (10, 1.3 g), mp 232z. Rechromatography of the combined mother liquor over neutral alumina III with chloroform gave more iboxygaine (1.5 g) and a new base iboxygaine hydroxyindolenine (13): mp 223; $[\alpha]^{25}D$ 111° (c 0.026, $CHCl_3$); uv λ_{max}^{EtOH} 227 mμ (ε 13,300), 265 (5400), 285 (6150), 313 (4750).

Anal. Calcd for $C_{20}H_{26}N_2O_3$: C, 70.15; H, 7.65; N, 8.15. Found: C, 69.66; H, 7.84; N, 7.90.

Hydroxyindolenine and Pseudoindoxyl of Coronaridine (14 and 16).—Coronaridine hydrochloride (2.8 g) was dissolved in chloroform (30 ml) and treated with a few drops of concentrated ammonia. After the solution was dried over magnesium sulfate, it was concentrated to dryness. The oily residue was dissolved in ether (40 ml) and treated with ethyl magnesium bromide (3 *M*, 5 ml). The mixture was heated on a steam bath for 15 min and cooled; then methylene chloride (60 ml) was added. Air was bubbled through the solution for 25 hr and it was then hydrolyzed with 5% hydrochloric acid.

After the aqueous layer was washed with methylene chloride, it was made alkaline with ammonia, and extracted with chloroform. The concentrated chloroform extract was chromatographed over neutral alumina III eluted with benzene. Some coronaridine (200 mg) was recovered, followed by its crystalline hydroxyindolenine (55 mg), which was recrystallized from ether–petroleum ether (bp 30–60°), mp 95–105° dec.

Anal. Calcd for $C_{21}H_{26}N_2O_3$: C, 71.16; H, 7.39; N, 7.90. Found: C, 70.89; H, 7.62; N, 7.87.

The hydroxyindolenine (380 mg) was dissolved in methanolic hydrogen chloride (10 ml) and heated on a steam bath for 1 hr. The solvent was then removed, and the residue was crystallized from a methanol–acetone mixture to give 310 mg of coronaridine pseudoindoxyl hydrochloride, mp 278–279° dec.

Anal. Calcd for $C_{21}H_{26}N_2O_3 \cdot HCl$: C, 64.53; H, 6.96; N, 7.17; Cl, 9.07. Found: C, 64.58; H, 7.03; N, 7.06; Cl, 8.80.

Hydroxyindolenine and Pseudoindoxyl of Voacristine (5 and 6).—Voacristine (solution of 1.5 g of 25 ml of chloroform) was kept at room temperature for 5 days, until tlc showed that most voacristine had disappeared. The solution was then chromatographed over neutral alumina II (300 g) eluted with chloroform. Voacristine (100 mg) was recovered, followed by amorphous fractions. The amorphous powder was dissolved in benzene (50 ml) and washed with pH 4.0–4.5 buffer (five 15-ml portions). The combined aqueous extracts were made alkaline with ammonia and extracted with chloroform. After the chloroform extract was chromatographed over Florisil with 5% methanol–chloroform, it gave 650 mg of voacristine hydroxyindolenine: mp 175–177°; $[\alpha]^{25}D$ 47.2° (c 0.67, $CHCl_3$).

Anal. Calcd for $C_{22}H_{28}N_2O_5$: C, 65.98; H, 7.05; N, 7.00. Found: C, 65.89; H, 7.14; N, 6.82.

The hydroxyindolenine (50 mg) was dissolved in saturated methanolic hydrogen chloride (2 ml) and heated on a steam bath for 50 min. Methanol was removed *in vacuo*, and the residue was crystallized from chloroform. The yellow hydrochloride, mp 261°, was identical with the isolated voacristine pseudoindoxyl hydrochloride (ir and uv spectra and melting point). The hydrochloride was converted into the corresponding hydrobromide, mp 272°, whose ir spectrum was identical with the published spectrum of "montanine" hydrobromide.

Hydroxyindolenine and Pseudoindoxyl of 20-Epivoacristine (7 and 8).—20-Epivoacristine (1.5 g) in chloroform (50 ml) was kept at room temperature for 2 weeks. After chromatography over neutral alumina III (300 g) with chloroform, the hydroxyindolenine obtained (800 mg) was recrystallized from methanol–ether: mp 209–210°; $[\alpha]^{25}D$ −48.3° (c 0.69, $CHCl_3$).

Anal. Calcd for $C_{22}H_{28}N_2O_5$: C, 65.98; H, 7.05; N, 7.00. Found: C, 66.00; H, 7.15; N, 6.90.

The hydroxyindolenine was rearranged in methanolic hydrogen chloride as before and recrystallized from chloroform–acetone. The corresponding pseudoindoxyl hydrochloride (220 mg) was obtained: mp 315° dec (decolorized at 280°); $[\alpha]^{25}D$ 251.1° (c 0.68, EtOH).

Anal. Calcd for $C_{22}H_{28}N_2O_5 \cdot HCl$: C, 60.30; H, 6.47; N, 6.42: Cl, 8.11. Found: C, 59.86; H, 6.75; N, 6.50; Cl, 8.03.

Hydroxyindolenine and Pseudoindoxyl of Iboxygaine (13 and 18).—Iboxygaine (200 mg) in chloroform (50 ml) was kept overnight at room temperature and chromatographed over Florisil (50 g). From the 3% methanol–chloroform eluate, 10 mg of iboxygaine was recovered. The 10% methanol–chloroform fraction gave a hydroxyindolenine (25 mg), identical with the iboxygaine hydroxyindolenine isolated from the plant. Attempted acid rearrangement of the hydroxyindolenine to pseudoindoxyl did not yield a crystalline product.

Registry No.—**5**, 15215-86-8; **6**, 18646-15-6; **6** hydrochloride, 18646-16-7; **7**, 18646-17-8; **8** hydrochloride, 18646-18-9; **13**, 18646-19-0; **14**, 16671-16-2; **16** hydrochloride, 18646-21-4.

6-Mercapto and Other Substituted Derivatives of 9-D-Arabino- and 9-D-Xylopyranosylpurine.[1,2] Synthesis and Spectral Properties

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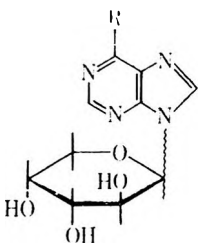
Received July 8, 1968

The 6-mercaptopurine nucleosides of α- and β-D-arabinopyranose and β-D-xylopyranose (**3a**, **3b**, and **10b**, respectively) and 9-(β-D-xylopyranosyl)thioguanine (**18**), together with some intermediates and derivatives, have been synthesized and their properties have been studied. The nmr evidence support the *1C* conformation for all nucleosides of α-arabinopyranose and the *C1* conformation for those of β-xylopyranose. A pronounced shielding effect upon the nmr signals of the acetyl protons is noted in those purine pentopyranosides where both the C-2′ acetoxy group and the C-1′ purine ring are equatorial. This effect is absent from the corresponding anomers where the purine ring is axial. Some of these pentopyranosyl purines disobeyed Hudson's isorotation rules.

Interest in the nucleosides of 6-mercaptopurine (6-MP) and thioguanine (TG) stems from their antitumor activity and other biological activity. Among these nucleosides are the ribosides of 6-MP[3] and TG,[4] the arabinofuranoside of 6-MP,[5] and the α- and β-deoxyribofuranosides of TG.[6] We have recently prepared other nucleosides[7] of these bases and now report the synthesis and properties of the β-D-xylopyranosides of 6-MP and TG (**10b** and **18**, respectively) and the α- and β-D-arabinopyranosides of 6-MP (**3a** and **3b**). The spectral properties of these compounds and their derivatives are of considerable interest. The present results extend our recent observations on the conformations and optical rotations of the anomeric pairs of D-arabinopyranosyl- and D-xylopyranosyladenines.[2a]

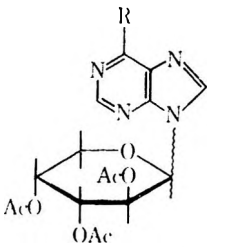
The 6-MP nucleosides were readily prepared in good yields by the usual reactions.[7] Nitrous acid converted 9-(α-D-arabinopyranosyl)adenine[2a] (**1a**) into the corresponding hypoxanthine nucleoside **2a**. Acetylation (to **6a**), thiation with phosphorus pentasulfide (to **7a**), and deacetylation afforded the desired **3a**. The β anomer **3b** and the β-D-xyloside **10b** were similarly prepared from **1b**[2a] and 9-(β-D-xylopyranosyl)adenine,[2a,8] respectively.

The acetylated arabinosides **4a** and **4b** were needed for an examination of their physical properties. Acetylation of **1b** in pyridine with acetic anhydride at room temperature afforded a mixture of tri- and tetraacetates, **4b** and **5b**, according to the nmr spectrum. However, the triacetate **4b** could be isolated and purified by crystallization. The same acetylation conditions afforded an even more highly acetylated mixture from **1a**. Heating this mixture in refluxing 80% acetic acid afforded the homogeneous tetraacetate **5a**. Pure **4a** was obtained by acetylation of **1a** in a limited amount of acetic anhydride.



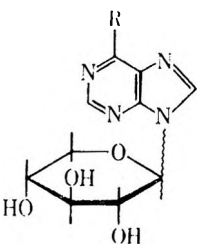
1, R = NH_2
2, R = OH[9]
3, R = SH[9]

a series = α anomer
b series = β anomer



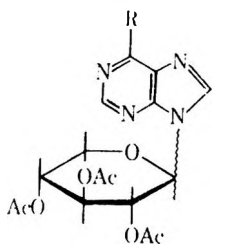
4, = NH_2
5, R = NHAc
6, R = OH
7, R = SH

a series = α anomer
b series = β anomer

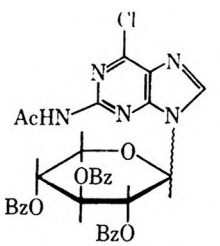


8, R = NH_2
9, R = OH[9]
10, R = SH[9]

a series = α anomer
b series = β anomer



11, R = OH (α)
12, R = OH (β)
13, R = SH (β)



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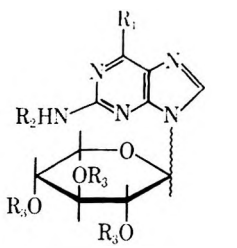

15, R_1 = OH;[9] R_2 = R_3 = H
16, R_1 = OH; R_2 = H; R_3 = Ac
17, R_1 = OH; R_2 = R_3 = Ac
18, R_1 = SH;[9] R_2 = R_3 = H
19, R_1 = SH; R_2 = H; R_3 = Ac

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(2) (a) This is paper II on pentopyranosyl nucleosides. For paper I, see A. P. Martinez, W. W. Lee, and L. Goodman, *J. Org. Chem.*, **34**, 92 (1969). (b) A portion of this material was presented at the 155th National Meeting of the American Chemical Society, San Francisco, Calif., April 1968.

(3) (a) L. R. Duvall, *Cancer Chemotherapy Rept.*, **11**, 195 (1961); (b) R. M. Whittington, S. L. Rivers, and M. E. Patno, *ibid.*, **34**, 47 (1964).

(4) F. R. White, *ibid.*, **11**, 202 (1961).

(5) (a) See A. P. Kimball, G. A. LePage, and B. Bowman, *Can. J. Biochem.*, **42**, 1753 (1964), for antitumor activity; (b) see A. P. Kimball, G. A. LePage, B. Bowman, and S. J. Herriot, *Proc. Soc. Exptl. Biol. Med.*, **119**, 248 (1965), for suppression of homograft response.

(6) See G. A. LePage and I. G. Junga, *Mol. Pharmacol.*, **3**, 37 (1967), for utilization by murine tumor cells.

(7) (a) G. L. Tong, K. J. Ryan, W. W. Lee, E. M. Acton, and L. Goodman, *J. Org. Chem.*, **32**, 859 (1967); (b) G. L. Tong, W. W. Lee, and L. Goodman, *ibid.*, **32**, 1984 (1967).

(8) G. W. Kenner, B. Lythgoe, and A. R. Todd, *J. Chem. Soc.*, 652 (1944).

(9) The purine rings are all written in the completely aromatic form for convenience, although the 6-hydroxy and 6-thiol derivatives exist as the *keto* tautomers.

The reaction of bromo-2,3,4-tri-*O*-benzoyl-D-xylose[10] with the mercury derivative[11] of 2-acetamido-6-chloropurine afforded the nucleoside **14**, which could be isolated and characterized although the reaction was not complete under any of the conditions studied. Reaction of crude **14** with sodium hydroxyethylmercaptide[7] afforded the guanine nucleoside **15**. Because of its tendency to gel, **15** was best isolated as its crystalline sodium salt. Subsequent acidification gave **15** as a more tractable solid.

Compound **15** was very insoluble in any acetylation medium. Consequently, after 80 hr in acetic anhydride and pyridine, a trace of insoluble **15** remained along with some triacetate **16** and tetracetate **17**. However, the crude mixture was thiated satisfactorily with phosphorus pentasulfide in pyridine. Deacylation in methanolic sodium methoxide afforded the desired thioguanine nucleoside **18**. Attempts to prepare **18** by the reaction of sodium hydrogen sulfide with either crude or crystalline chloropurine nucleoside **14** afforded mixtures of products from which crystalline **18** could not be isolated. The properties of these compounds are given in Tables I–VI.

We previously reported[2a] that the anomers of D-arabinopyranosyladenine, **1a** and **1b**, disobeyed Hudson's isorotation rules[12] while the corresponding D-xylopyranosides, **8a** and **8b**, obeyed the rules. Compounds **1a** and **1b** were the first exceptions[2a] to the generalization that purine nucleosides[13a] obey Hudson's rules while pyrimidine nucleosides[13b] disobeyed them. Since the generalizations were based on furanosyl nucleosides, it is of interest to obtain more information on pentopyranosyl nucleosides. Table I records the results obtained in this study. It is apparent that the arabinopyranosides of hypoxanthine (**2a** and **2b**) and 6-MP (**3a** and **3b**) also disobey Hudson's rules in the solvents used. When these nucleosides are acetylated, to afford **4**, **6**, and **7**, a variety of optical rotatory behavior resulted. Thus, depending on the solvent, these anomeric pairs may or may not obey Hudson's rules. This was true also of the one available pair of xylopyranosides, **11** and **12**.

It is well known[14] that the solvent influences both the magnitude *and* sign of the optical rotations of the solute in various ways. These include (1) the degree of solvation with the solute[14] and (2) the change in population of various dissymmetric conformations.[14] The second includes changes in conformation of the sugar ring, in rotamer distribution of the sugar substituents, and in freedom of rotation of the base about the glycosyl bond. Whether one or more of these factors are responsible for the variety of behavior recorded in Table I is not obvious. However, the nmr data in Table II suggest little or no conformational change in the sugar moiety of the arabino- and the xylopyranosyl nucleosides upon acetylation.

TABLE I

OPTICAL ROTATIONS ($[\alpha]$D, DEGREE)[a] OF SOME PENTOPYRANOSYL NUCLEOSIDES

	Solvent			
	H_2O[b]		DMF[c]	
Compd	α	β	α	β
1[d]	−35	+35	−48	+50
2	−45	+32	−64	+71
3	*e*	*e*	−35	0
4	0	*e*	−18	−5
6	+10[f]	−5[f]	−28	+8
7	+39[f,g]	−37[f,g]	+27[f]	−16[f]
11, 12	−11[f]	−29[f]	−36	−33
8[d]	−7[f]	−30[f]	−30[f]	−46[f]
9b		−23		
10b				−31
15				+9
18				−28
13				−83
16				−11
17				−25
19				−58

[a] Optical rotations were measured at ambient temperature (21–24°) with a Perkin-Elmer Model 141 automatic polarimeter. [b] Concentrations were 0.15–0.18%. [c] Concentrations in *N*,*N*-dimethylformamide were 0.5% except **2** and **16** at 0.25% and **6**, **11**, and **12** at 0.35%. [d] From ref 2a. [e] Not determined because of low solubility. [f] Obeys Hudson's isorotation rules. [g] Run in methanol at 0.25% concentration.

The signals of the H-1′ protons of all of the α-arabinosides (**2a**, **3a**, **4a**, **5a**, **6a**, and **7a**) and all of the β-xylosides (**9b**, **10b**, **12**, **13**, **15**, **16**, **17**, **18**, and **19**), whether acetylated or not, have the large coupling constants that show that H-1′ and H-2′ are *trans* diaxial.[15a] This is only possible for the α-arabinosides in the *1C* conformation and the β-xylosides in the *C1* conformation.

The signals of the H-1′ protons of all of the β-arabinosides (**2b**, **3b**, **4b**, **6b**, and **7b**) and the one α-xyloside (**11**), whether acetylated or not, have small values for $J_{1',2'}$ and are downfield from the H-1′ protons of their corresponding anomers. On conformational grounds it had been previously stated that the α-xyloside **8a**, should, like the β anomer **8b** be in the *C1* conformation.[2a] Since the H-1′ equatorial proton of **8a** was downfield from the axial H-1′ proton of **8b**, it appeared to obey the generalization that equatorial protons signals are downfield from those of axial protons in the same chemical and steric environment.[2a,15] If this generalization is valid for other nucleoside pairs, then the H-1′ protons of the α-xyloside **11** and the β-arabinosides are equatorial, so that the conformation of **11** is *C1* and that of the β-arabinosides (**2b**, **3b**, **4b**, **6b**, and **7b**) is *1C*. Since there are exceptions to the above generalization,[15] other evidence for the assignment of conformation was examined.

A complete assignment of the nmr signals to the pyranose protons would definitely establish the conformations of the nucleosides. This was not possible

(10) H. G. Fletcher, Jr., and C. S. Hudson, *J. Amer. Chem. Soc.*, **69**, 921 (1947).

(11) R. H. Iwamoto, E. M. Acton, and L. Goodman, *J. Med. Chem.*, **6**, 684 (1963).

(12) C. S. Hudson, *Advan. Carbohyd. Chem.*, **3**, 15 (1948). The α and β anomers of the 2′-deoxyribopyranosyl derivatives of theophylline also reverse the relative signs of their rotation upon acetylation. See J. Davoll and B. Lythgoe, *J. Chem. Soc.*, 2526 (1949).

(13) T. R. Emerson, R. J. Swan, and T. L. V. Ulbricht: (a) *Biochem. Biophys. Res. Commun.*, **22**, 505 (1966); (b) *Biochem.*, **6**, 843 (1967).

(14) K. Mislow, "Introduction to Stereochemistry," W. A. Benjamin, Inc., New York, N. Y., 1965, p 58.

(15) (a) L. D. Hall, *Advan. Carbohyd. Chem.*, **19**, 51 (1964). (b) R. U. Lemieux and J. D. Stevens, *Can. J. Chem.*, **43**, 2059 (1965). (c) The latter authors point out that axial acetoxy signals are generally at lower field than equatorial ones, but there are exceptions. Assigning conformations on the basis of acetoxy signals alone is not always unequivocal. In the present work the acetoxy signal results and the H-1′ signal results agree and mutually support the conformational assignments.

TABLE II

NMR DATA FOR PENTOPYRANOSYL NUCLEOSIDES[a]

Compd	H-1′,[b] δ	$J_{1',2'}$, cps	Acetyl H,[b] δ			Purine H[b] δ		Δδ	Solvent
			Shielded	Equational	Axial				
1a[c]	5.48	9				8.29	8.43	0.16	A + C
1b[c]	6.13	1.5				8.28	8.41	0.13	A + C
2a	5.30	9				8.04	8.19	0.15	A
2b	6.03	<1				8.11	8.19	0.08	A
3a	5.25	9				8.18	8.36	0.18	A
3b	5.97	<1				8.20	8.29	0.09	A
2a	5.51	9				8.18	8.33	0.15	C
2b	6.13	1				8.19	8.35	0.16	C
8a[c]	6.11	2				8.27	8.47	0.20	A + C
8b[c]	5.43	9				8.23	8.34	0.11	A + C
9b	5.26	9				7.98	8.16	0.18	A
10b	5.36	9				8.10	8.33	0.23	A
15	5.10	9				7.82			A + C
18	5.01	9				7.92			A
4a	5.90	8	1.61 (3)	1.88 (3)	2.09 (3)	8.10	8.16	0.06	A
4b	6.28	2		2.03 (6)	2.18 (3)	8.19 (2)		0	A
5a	5.87	8	1.61 (3)	1.87 (6)[e]	2.10 (3)	8.11	8.18	0.07	A
6a	5.83	8	1.68 (3)	1.87 (3)	2.09 (3)	8.00	8.11	0.11	A
6b	6.15	2.5		1.92, 1.95 (6)	2.11 (3)	8.02 (2)		0	A
7a	5.86	8	1.69 (3)	1.88 (3)	2.10 (3)	8.14	8.33	0.19	A
7b	6.16	2		1.93, 1.96 (6)	2.10 (3)	8.15	8.22	0.06	A
4a	5.91	9	1.81 (3)	2.07 (3)	2.26 (3)	8.12	8.40	0.28	B
4b	6.34	2		2.05 (6)	2.33 (3)	8.05	8.38	0.35	B
5a	5.85	~8	1.78 (3)	2.04 (6)[e]	2.23 (3)	8.15	8.35	0.20	B
6b	6.28	<1		2.06 (6)	2.23 (3)	8.08	8.38	0.30	B
11	6.09	2		1.96, 2.05, 2.10 (9)		8.02 (2)		0	A
12	*d*	*d*	1.74 (3)	2.00, 2.02 (6)		8.08	8.32	0.24	A
13	*d*	*d*	1.74 (3)	1.99, 2.01 (6)		8.21	8.51	0.30	A
16	*d*	*d*	1.72 (3)	2.04, 2.07 (6)		7.93	...	...	A + C
17	*d*	*d*	1.79 (3)	2.01, 2.04 (6)	2.23 (3)[e]	8.19	...	...	A + C
19	*d*	*d*	1.70 (3)	1.90, 1.93 (6)		8.00	...	...	A

[a] Nmr data were obtained on Varian A-60 with TMS external reference for DMSO-d_6 (A) and A + C (C is D_2O); TMS was internal reference for $DCCl_3$ (B). [b] All H-1′ signals are doublets and purine H signals are singlets. All acetyl H's are singlets. Where necessary the number of protons are shown in parenthesis. All signal intensities indicated the proper number of protons. [c] From ref 2a. [d] The H-1′ signals are hidden in a group of protons between δ 5.5 and 6.0. Only one of these, **12**, has been run at higher resolution (see Tables III and IV) and shows the expected large $J_{1',2'}$. [e] Protons of N-Ac here.

TABLE III

CHEMICAL SHIFTS OF PYRANOSE PROTONS IN SOME NUCLEOSIDES[a]

Compd	δ				
	H-1′	H-2′	H-3′	H-4′	H-5′
7a	5.96 d[b]	5.69 t	5.44 q	5.28 m	4.01 d
					4.22 d
7b	6.22 d	5.10 q	5.46 q	5.2 m	4.06 m
12	5.97 d	5.72 t	5.49 t	5.11 s	4.10 q, 3.81 t

[a] Chemical shift values were obtained on Varian HA-100 with TMS internal reference. [b] Symbols are d, doublet; t, triplet; q, quartet; m, multiplet; s, sextet.

TABLE IV

PYRANOSE PROTON COUPLING CONSTANTS OF SOME NUCLEOSIDES[a]

Compd	J, cps					
	1′,2′	2′,3′	3′,4′	4′,5′a	4′,5′e	5′a,5′e
7a	9.0[b]	9.5	3.5	<1	1.5	13.0
7b	2.0	5.0	3.0	*c*	*c*	*c*
12	8.5	9.0	9.5	10.5	5.5	11.0

[a] Coupling constants were obtained on Varian HA-100 with TMS internal reference. [b] Values are given to the nearest 0.5 cps. [c] Not determined.

for the unblocked nucleosides because all of the pyranose proton signals fell too close together at 100 Mc as well as 60 Mc. However, the protons of the acetylated nucleosides showed improved resolution in the 100-Mc spectra. Three acetylated nucleosides were examined and the results are given in Tables III and IV. Spin decoupling experiments were used to confirm the proton assignments. The 60-Mc spectra of these three are like those of the other corresponding nucleoside anomers where only the base is changed. Hence the 100-Mc spectra of these three are representative of the other nucleosides also.

The β-xyloside **12** showed H-1′ as a doublet, H-2′ and H-3′ as triplets, H-4′ as a sextet, H-5′e as two pairs of doublets at δ 4.10, and H 5′a as a triplet (because $J_{4',5'a}$ and $J_{5'a,5'e}$ are nearly equal) at δ 3.81. All of the signals are well separated and clearly resolved. The large coupling constants for all the neighboring protons (except H-5′e) clearly established their *trans*-diaxial relationships and the conformation of **12** as *C1*.

The α-arabinoside **7a** showed H-1′ as a doublet, H-2′ as a triplet, and H-3′ as two pairs of doublets. The large coupling constants between these protons showed that H-1′, H-2′, and H-3′ have a *trans*-diaxial relationship to each other as required by the *1C* conformation. The signals of H-4′ appeared as a narrow multiplet; those of H-5′e and H-5′a appear as two pairs of doublets; the doublets of one of these pairs were barely resolved. The *trans*-diaxial relationships of H-1′, H-2′, and H-3′ establish the conformation of **7a** as *1C*.

The β-arabinoside **7b** showed H-1′, a doublet, at lowest field and H-3′, two pairs of doublets, at next lowest field. The signals of H-2′ are shifted considerably upfield (compared with those of **12** and **7a**) and overlapped those of H-4′. Spin decoupling was used to establish H-2′ as a pair of doublets with $J_{2',3'}$ of 5 cps. This value was smaller than those observed for the *trans*-diaxial protons in **7a** and **12**. The signals for H-4′ and those for the H-5′ protons were not sufficiently resolved for interpretation. The H-5′ protons signals of **7b** were definitely not like those of **12**, but were more similar to those of **7a**. These H-5′ signals of **7b** should be (1) like those of **12** (in which H-4′ and H-5′a were *trans* diaxial) if **7b** were in the *C1* conformation or (2) like those of **7a** if **7b** were in the *1C* conformation. The data for H-2′ and H-5′ suggest that **7b** may not be in the ideal *1C* chair form or that it may exist in conformational equilibrium with the *1C* form being favored.[16] This same conformational situation may hold for the other β-D-arabinopyranosyl nucleosides, whether acetylated or not.

The location of the acetoxy signals of the arabinosides (see Table II) also support the *1C* conformations which require one axial acetoxy group and two equatorial ones, with the signals of the former being downfield[15a,b] from the latter two. This is the case with **4b**, **6b**, and **7b**. For the α anomers, **4a**, **5a**, **6a**, and **7a**, the axial group signal is located at the same place as for the β anomers (δ 2.09–2.18). However, one of the two equatorial group signals is shifted upfield (δ 1.61–1.69). This shift suggests that for these α anomers the purine moiety is spatially located so that ring current anisotropy[17] can effectively shield the C-2′ acetoxy protons. Examination of Dreiding models show that statistically there is greater opportunity for the C-2′ acetoxy protons to be above the plane of the equatorial purine ring in the α anomers than when the purine ring is axial as in the β anomers.

If shielding can occur when both C-1′ purine and C-2′ acetoxy are equatorial, then the same effect should be seen for the β anomers of the D-xylopyranosyl nucleosides, but not the α anomers. This is indeed the case for the β anomers **12**, **13**, **16**, **17**, and **19** where the shielded equatorial acetoxy signals fall between δ 1.70 and 1.79 and are well separated from the other two equatorial acetoxy signals (1.90–2.07). See Table II. The single acetylated α anomer in the xylose series, **11**, appears to retain the *C1* conformation. Its H-1′ proton is at δ 6.09 like the equatorial H-1′ proton of **8a** (6.11). None of the signals of its acetoxy groups is shifted by ring-current shielding to δ 1.70–1.79. However, the three equatorial acetoxy group signals are spread apart more than those in any other example in Table II, suggesting some differences in magnetic environment for these three groups.

A few nmr spectra were run in deuteriochloroform ($DCCl_3$). The results for **4a**, **4b**, **5a**, and **6b** show the same relationship between acetoxy groups that are axial, equatorial, and equatorially shielded as in deuterated dimethyl sulfoxide (DMSO-d_6). All of the proton signals are shifted downfield relative to those in DMSO-d_6.[18,19] Of interest is the fact that the difference in chemical shifts between the two purine protons H-2 and H-8, Δδ, is considerably greater in $DCCl_3$ than in DMSO-d_6.[20] In the latter solvent, the value of Δδ becomes 0 for three acetylated nucleosides (**4b**, **6b**, and **11**) where the purine is axial but not for the corresponding unacetylated nucleosides (**1b** and **2b**) nor for the acetylated anomers (**4a**, **6a**, and **12**) where the purine is equatorial.

Two nmr spectra were obtained in D_2O. These also show that the H-1′ and H-2′ of the α-arabinopyranoside **2a** are *trans* diaxial and that H-1′ is upfield from H-1′ of the β-arabinopyranoside **2b** which is equatorial. Thus, changing the solvent from D_2O to DMSO-d_6 to $DCCl_3$ does not result in any sugar conformation change.

In the previous communication,[2a] the shielding effect of the benzene ring of a C-2′ benzyloxy group upon one of the purine protons was noted when both groups were equatorial. Reported here is the ring-current shielding effect of the purine upon a C-2′ group when both are equatorial. An earlier example of this is 9-(3-acetamido-tri-*O*-acetyl-3-deoxy-β-D-glucopyranosyl)hypoxanthine.[19] The upfield shift of its equatorial C-2′ acetoxy protons (to δ 1.76) relative to the other acetoxy signals is ascribed to the difference in shielding caused by an adjacent bulky substituent at C-1′ [19] (which is equatorial). No shielding effect of the phenyl ring upon the C-2′ acetoxy protons is observed for benzyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside[21] and 2,3,4,6-tetra-*O*-acetyl-1-*S*-benzoyl-1-thio-β-D-glucopyranose[21] where the C-1 and C-2 groups are both equatorial. This may be due to the extra two atoms of S and C moving the phenyl ring to a less favorable position away from the C-2 acetoxy group For the acetylated pyrimidine nucleo-

TABLE V

ULTRAVIOLET SPECTRA OF SOME PYRANOSYLPURINES

Compd	Maxima, λ, mμ (ε × 10⁻³) pH 1[a]	pH 7[a]	pH 13[a]
2a	247 (11.0)	247 (11.3)	253 (11.9)
2b	248 (13.0)	248 (12.7)	253 (13.7)
3a	322 (24.2)	317 (23.4)	310 (22.7)
3b	321 (23.2)	317 (23.7)	309 (23.2)
4a	255 (15.1)	258 (15.1)	258 (15.1)
6a	247 (12.5)	247 (12.7)	252 (14.0)
7a	322 (24.8)	317 (21.9)	312 (22.8)
7b	322 (24.6)	318 (21.8)	310 (22.8)
9	247 (11.8)	247 (12.3)	253 (12.8)
10	322 (25.0)	318 (23.9)	310 (26.1)
12	248 sh[b]	243 sh	253 (14.7)
	247 (14.2)	247 (14.2)	
13	322 (25.0)	318 (21.5)	311 (22.8)
15	250 (11.9)	252 (13.1)	262 (10.8)
16	255 (13.3)	252 (14.7)	252–265 (12.2)
	275 sh		
17	262 (8.7)	265 sh	251 (14.8)
	345 (22.9)	342 (24.2)	272 (7.1)

[a] Solvents were 0.1 *N* HCl for pH 1, Beckman 3581 buffer for pH 7, and 0.1 *N* NaOH for pH 13. [b] sh, shoulder.

(16) As a comparison, β-L-arabinopyranose tetraacetate is reported to exist in conformational equilibrium containing about 80% of the favored conformation (*C1* for the L series or *1C* for the D series). See ref 15b.

(17) A. D. Broom, M. P. Schweizer, and P. O. P. Ts'o [*J. Amer. Chem. Soc.*, **89**, 3612 (1967)] have observed that ring-current diamagnetic anisotropy of one purine ring can effectively shield the protons of another purine ring in nucleosides that stack together in solution.

(18) See Table I in ref 17a.

(19) F. W. Lichtenthaler and H. P. Albrecht, *Chem. Ber.*, **99**, 575 (1966).

(20) One referee has suggested that this is due to the hydrogen bonding between the DMSO solvent and the "acidic" H-8 proton, first detected by L. Katz and S. Penman, *J. Mol. Biol.*, **15**, 220 (1966).

(21) C. V. Holland, D. Horton, and M. J. Miller, *J. Org. Chem.*, **32**, 3077 (1967).

TABLE VI

PURINE NUCLEOSIDES OF D-ARABINOPYRANOSE AND D-XYLOPYRANOSE

Compd	Yield,[a] %	Mp, °C	Solvent[b]	Chromatography[c] Solvent	R_f	Formula	Calcd, % C	H	N	S	Found, % C	H	N	S
2a	95[d]	219–220	M	ME-20	0.07	$C_{10}H_{12}N_4O_5 \cdot CH_3OH$	44.0	5.37	18.7		43.9	5.21	18.9	
2b	63	260–261	W	ME-30	0.30	$C_{10}H_{12}N_4O_5$	44.8	4.51	20.9		44.7	4.60	21.1	
3a	98	260–262	M			$C_{10}H_{12}N_4O_4S$	42.2	4.22		11.25	42.3	4.29		11.22
3b	73	212.5–215.5	M			$C_{10}H_{12}N_4O_4S \cdot {}^1/_3CH_3OH$	42.1	4.56		10.88	42.1	4.73		10.90
4a	59	228–229	D[e]	ME-0	0.18	$C_{16}H_{19}N_5O_7$	48.9	4.87	17.8		48.5	4.87	17.6	
5a		105–110	D–H	ME-4	0.29	$C_{16}H_{21}N_5O_8 \cdot {}^1/_4HOAc$	49.3	4.92	15.6		49.0	5.17	15.4	
6a	65	268–269	F[e]	ME-5	0.19	$C_{16}H_{18}N_4O_8$	48.7	4.60	14.2		48.8	4.82	14.2	
6b	(76)	216–217	D–F	ME-30	0.67	$C_{16}H_{18}N_4O_8 \cdot {}^1/_4H_2O$	48.1	4.67	14.0		48.1	4.53	14.2	
7a	(100)	282–283	M	ME-5	0.67	$C_{16}H_{18}N_4O_7S$	46.8	4.43	13.7	7.80	46.7	4.63	13.8	7.92
7b	(59)	243–245[f]	M	E	0.69	$C_{16}H_{18}N_4O_7S$	46.8	4.43	13.7		46.5	4.66	13.7	
9b	(71)	221–222[g]	W	ME-20	0.10	$C_{10}H_{12}N_4O_5 \cdot H_2O$	42.0	4.93	19.6		42.2	5.03	19.2	
10b	(76)	218–226	W			$C_{10}H_{12}N_4O_4S \cdot {}^1/_2H_2O$	40.9	4.46	19.1	10.9	40.9	4.15	19.1	10.5
11	89	262–263	F			$C_{16}H_{18}N_4O_8 \cdot H_2O$	46.6	4.89	13.6		46.7	4.71	13.7	
12	69	283–284	F	ME-20	0.53	$C_{16}H_{18}N_4O_8$	48.7	4.60	14.2		48.9	4.72	14.2	
13	100	190–200	C–M			$C_{16}H_{18}N_4O_7S$	46.8	4.42		7.80	46.7	4.63		7.86
14	(7)	184.5–185.5	B–D	EC-20	0.29	$C_{33}H_{26}ClN_5O_8$	60.5	4.00	10.7	5.40[h]	60.4	3.96	10.7	5.35[h]
15	28	287–288	D[e]	ME-30	0.21	$C_{10}H_{13}N_5O_5 \cdot H_2O$	39.9	5.02	23.3		40.3	5.27	23.6	
16	(65)	291–292	A	H	1.37	$C_{16}H_{19}N_5O_8$	46.9	4.67	17.1		46.7	4.63	16.7	
17	13	294.5–295.0	C–T	EC[i]	0.20	$C_{18}H_{21}N_5O_9 \cdot 0.9CCl_4$	38.5	3.59	11.87	21.7	38.6	3.72	11.95	21.7
18	(73)	235–237[j]	M	ME-30	0.54	$C_{10}H_{13}N_5O_4S \cdot CH_3OH$	39.8	5.17	21.1	9.67	39.8	5.15	20.8	9.56
19	(67)	305–306	E[e]	H	1.32	$C_{16}H_{19}N_5O_7S$	45.1	4.50		7.52	44.8	4.58		7.67
15 Na salt	24	...	M[e]			$C_{10}H_{12}N_5O_5Na \cdot CH_3OH$	39.2	4.79	20.8		39.6	4.81	20.4	

[a] Yields are for analytical sample except values in parenthesis which are for homogeneous product suitable for use in the next reaction. [b] Solvents for crystallization are A, acetone; B, benzene; D, diethyl ether; C, chloroform; E, ethanol; F, ethyl acetate; H, *n*-hexane; M, methanol; T, carbon tetrachloride; W, water. [c] Solvents for tlc on silica gel HF plates are denoted by ME-20, etc., where M = methanol, E = ethyl acetate, and 20 = per cent of first solvent; likewise, C = chloroform. The spots are located relative to the front with R_f = 1.00. For paper chromatography, the solvent systems are E, 5% aqueous Na_2HPO_4, pH 8.9; H, *n*-butanol–acetic acid–water (5:2:3). Spots are referred to adenine with R_{Ad} = 1.00. [d] From **4a**. [e] Triturated with this solvent. All attempts to recrystallize **19** resulted in darkening and decomposition. [f] Tan color. [g] G. W. Kenner, B. Lythgoe, and A. R. Todd [*J. Chem. Soc.*, 652 (1944)] reported mp 220° from methanol. [h] Chlorine analysis. [i] Developed twice. [j] Decomposition temperature.

sides, some shielding effects have been noted. Cushley, *et al.*,[22] observed an anisotropic effect of the pyrimidine 5,6 double bond on the acetoxy groups which resulted in shielding or deshielding of these proton signals, depending on their spatial relationship to the 5,6 double bond.

Acetylation may affect the sugar–purine conformations even though the pyranose ring conformations are unchanged. The pronounced shielding effect upon the C-2′ acetoxy group that is found in one but not the other anomer suggest differences in restriction of rotation about the glycosidic bond between these anomers. These differences may change when no acetyl groups are on the hydroxyl groups, and hydrogen bonding is possible. In addition, the spatial relationship of base to sugar is changed as the base changes from an equatorial to an axial position. All of these differences may contribute to the factors that determine if these nucleosides obey Hudson's isorotation rules.

Table V lists the ultraviolet (uv) spectra of some pyranosylpurines.

Experimental Section[23]

Hypoxanthine Nucleosides.—By the usual procedure[7b] the reaction of 2.0 g (7.5 mmol) of **1b** with 3.8 g (55 mmol) of sodium nitrite in 100 ml of water and 12.5 ml of acetic acid at room temperature for 3 days, during which a second portion of 0.5 g of sodium nitrite was added after 24 hr, afforded the hypoxanthine nucleoside **2b**. The completeness of reaction was monitored by tlc with solvent ME-30. With some of the other adenine nucleosides, a reaction time of 20 hr was sufficient.

All of the acetylations (*e.g.*, **2b** → **6b**) were performed at room temperature, generally overnight, using acetic anhydride and pyridine.[7b] Completeness of reaction was monitored by tlc, with ME-30 or other solvent systems.

6-Mercaptopurine Nucleosides.—The hypoxanthine nucleoside, *e.g.*, **6a**, was refluxed with about 6 mol ratios of phosphorus pentasulfide in pyridine under nitrogen[7b] for about 4 hr and worked up to afford **7a**, or the appropriate mercaptopurine nucleosides. In the case of **7a** the initial crude product (100%) yield), mp 232–234°, was reddish rather than white, was homogeneous by tlc, and analyzed correctly for sulfur. One recrystallization with a charcoal treatment removed the color.

The deacetylation of **7a** and the other acetylated derivatives was carried out in hot methanolic sodium methoxide.[7b]

2-Acetamido-6-chloro-9-(2,3,4-tri-*O*-benzoyl-β-D-xylopyranosyl)-9*H*-purine (14).—A mixture containing 5.20 g (8.18 mmol) of 2-acetamido-6-chloropurine mercuric oxide complex[11] on 30% Celite and 200 ml of xylene was heated at reflux temperature with 4.2 g (8.6 mmol) of 2,3,4-tri-*O*-benzoyl-α-D-xylopyranosyl bromide[10] for 3.5 hr by the usual procedure[7a] to afford 5.00 g (93%) of a solid foam which contained mainly **14** (R_f 0.20 in EC-20) and about three other components (R_f 0, 0.7, and 1.0 in EC-20). This crude product was suitable for the next step.

For the analytical sample, a 6.64-g portion of crude product of the above purity was chromatographed on a column 20 cm long containing 40 g of alumina (neutral, Bio Rad AG 7, 100–200 mesh), eluting successively with benzene (400 ml) and benzene–ethyl acetate (6:4), 800 ml. Evaporation of the last 500 ml of benzene–ethyl acetate afforded a residue which was crystallized from toluene–ether (2:25) to afford 0.58 g (7.2%) of **14**, mp 178.5–180.0°. Another crystallization from benzene–ether (1:10) afforded the analytical sample of **14**.

9-(β-D-Xylopyranosyl)guanine (15).—Crude **14** (from 65.4 mmol of 2-acetamido-6-chloropurine–mercuric oxide complex), 20 ml (0.28 mol) of 2-mercaptoethanol, 175 ml of methanol, and 250 ml of 1 *N* methanolic sodium methoxide was heated at reflux under a nitrogen atmosphere for 4 hr. The hot reaction mixture was treated with 2.0 g (0.37 mol) of sodium methoxide and refrigerated for 18 hr at 0°. The crystalline sodium salt of **15** was collected, washed with 100 ml of cold methanol, then 200 ml of anhydrous ether, and dried to afford 5.31 g (24%). See Table VI for analysis. Treatment of an aqueous solution of the sodium salt with acetic acid afforded **15**, still gellike, but

(22) R. J. Cushley, K. A. Watanabe, and J. J. Fox, *J. Amer. Chem. Soc.*, **89**, 394 (1967).

(23) Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Paper chromatograms were run by the descending technique on Whatman No. 1 paper. Tlc was run on silica gel HF (E. Merck AG Darmstadt) in the appropriate solvent. All spots on chromatograms were detected by uv light. Solutions were dried with magnesium sulfate, anhydrous. All solutions were concentrated *in vacuo* with a bath temperature of less than 50° unless noted otherwise. *N,N*-Dimethylformamide is designated as DMF. Skellysolve B is a petroleum fraction, essentially *n*-hexane, bp 62–70°. Celite is a diatomateous earth product of Johns-Manville.

easily filterable. This crystallized when stirred in acetone; see Table VI.

9-(β-D-**Xylopyranosyl**)**thioguanine** (**18**).—A mixture of 2.00 g (6.64 mmol) of **15**, 70 ml of pyridine, and 13 ml of acetic anhydride was stirred at room temperature for 88 hr, then worked up to afford a tan foam (M), R_f 0.06 (major spot) and 0.20 (**16** and **17**, respectively) in solvent EC-100, when developed thrice. This foam was suitable for thiation. For analysis, the tan foam was stirred for several hours in ether, collected, and dried to afford 1.78 g (65%) of the triacetate **16**. This was recrystallized for analysis. The pure tetraacetate **17** was obtained from M which was partially freed of **16** by fractional precipitation from methylene chloride. The methylene chloride soluble material was then recrystallized from chloroform–carbon tetrachloride (1:1) to give **17**.

A 2.40-g portion (*ca.* 5.86 mmol) of the mixture of **16** and **17**, of purity equivalent to M, was heated with 10.0 g (45 mol) of phosphorus pentasulfide in 200 ml of pyridine[7] at reflux for 4.5 hr under a nitrogen atmosphere and worked up to afford 1.65 g (67%) of white, crystalline **19**. For analysis, see Table VI.

A solution of 1.20 g of **19**, 2.0 ml of 2-mercaptoethanol, and 0.20 g of sodium methoxide in 250 ml of methanol was heated at reflux for 3 hr under a nitrogen atmosphere. The solution was cooled to about 40°, treated with 20 g of IRC-50 (H^+) resin (prewashed with methanol), and stirred until pH 5–6 was attained (about 20 min). The mixture was filtered, treated with charcoal, filtered again, and evaporated. The residue was triturated with methanol–acetone (1:19) and the solid was collected to afford 0.68 g (73%) of **18**, homgeneous in solvent ME-30 with R_f 0.50. This was recrystallized once for analysis; see Table VI.

Registry No.—**2a**, 18520-77-9; **2b**, 18520-78-0; **3a**, 18520-79-1; **3b**, 18520-80-4; **4a**, 18520-81-5; **4b**, 18520-82-6; **5a**, 18520-83-7; **6a**, 18520-85-9; **6b**, 18520-84-8; **7a**, 18520-86-0; **7b**, 18520-87-1; **9b**, 18520-88-2; **10b**, 18520-89-3; **11**, 18520-90-6; **12**, 18520-91-7; **13**, 18520-92-8; **14**, 18520-93-9; **15**, 18520-94-0; **15** Na salt, 18520-95-1; **16**, 18520-96-2; **17**, 18598-35-1; **18**, 18598-36-2; **19**, 18530-32-0.

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Oligonucleotide Syntheses on Insoluble Polymer Supports. II. Pentathymidine Tetraphosphate

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The linear oligonucleotide pentathymidine tetraphosphate (TpTpTpTpT) has been synthesized stepwise on an insoluble polymer support containing thymidine bound *via* 5′ ether linkage to a styrene–divinylbenzene copolymer containing methoxytrityl functional groups. Condensation of the bound thymidine with 3′-O-acetylthymidine 5′-phosphate activated by 2,4,6-triisopropylbenzenesulfonyl chloride or picryl chloride followed by 3′-O-deacetylation gave polymer-supported thymidylyl-(3′→5′)-thymidine in 70–80% conversions based on thymidine, corresponding to about 350–380 μmol of dinucleoside phosphate per gram of polymer. Repetition of the condensation and deacetylation steps gave the higher oligomers each in approximately 35–80% conversion based on the next lowest member. The over-all conversion into pentamer was about 10% based on initial polymer-bound thymidine.

The procedural advantages which accrue from stepwise synthesis of complex oligomeric substances on inert polymer supports have been discussed by Merrifield, particularly with respect to polypeptide synthesis;[1] more recently the application of this concept to oligonucleotides has been investigated in several other laboratories.[2–6] We have continued our work on oligonucleotides using an insoluble polymer bearing methoxytrityl chloride functional groups to which the nucleoside is attached by 5′-ether formation. The oligonucleotide chain is then extended by condensation of appropriately protected 5′-nucleotides with the free 3′-hydroxyl group of the polymer-bound nucleoside. Our system thus incorporates the characteristics of insolubility found in the polymers of Letsinger, *et al.*,[2] and the functionality of the soluble polymers described by Hayatsu and Khorana[3] and Cramer, *et al.*[4] The Letsinger system utilizes polymer-bound carbonyl chloride functional groups as nucleoside attachment sites through amide[2a,b] or ester[2c,d] formation. In other recent work Blackburn and coworkers have explored a system in which the polymer-bound oligonucleotide terminus is a nucleotide attached to an insoluble polymer by a phosphoramidate linkage.[6]

This paper will describe the synthesis of thymidine homooligonucleotides up to the pentanucleoside tetraphosphate stage. Several features different from our previous procedure[5] have led to increased per cent conversions. The effect of altering reaction variables will be discussed for each step of the synthesis outlined in Scheme I.[7]

(1) R. B. Merrifield, *Science*, **150**, 178 (1965).

(2) (a) R. L. Letsinger and V. Mahadevan, *J. Amer. Chem. Soc.*, **87**, 3526 (1965); (b) *ibid.*, **88**, 5319 (1966); (c) R. L. Letsinger, M. H. Caruthers, and D. M. Jerina, *Biochemistry*, **6**, 1379 (1967); (d) R. L. Letsinger, M. H. Carothers, P. S. Miller, and K. K. Ogilvie, *J. Amer. Chem. Soc.*, **89**, 7146 (1967).

(3) (a) H. Hayatsu and H. G. Khorana, *ibid.*, **88**, 3182 (1966); (b) *ibid.*, **89**, 3880 (1967).

(4) F. Cramer, R. Helbig, H. Hettler, K. H. Scheit, and H. Seliger, *Angew. Chem. Intern. Ed. Engl.*, **5**, 601 (1966).

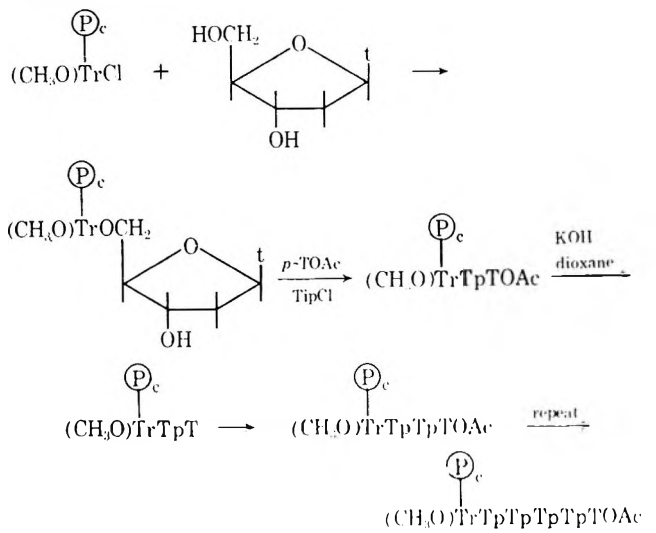
(5) L. R. Melby and D. R. Strobach, *J. Amer. Chem. Soc.*, **89**, 450 (1967).

(6) G. M. Blackburn, M. J. Brown, and M. R. Harris, *J. Chem. Soc., C*, 2438 (1967).

(7) The symbol —Ⓟc denotes the cross-linked polystyrene backbone and $(CH_3O)TrT$ the pendant methoxytrityl group with thymidine (T) attached *via* 5′-ether linkage; TpT and TpTOAc, respectively, refer to thymidylyl-(3′→5′)-thymidine and its 3′-O-acetate. The higher oligomers are abbreviated in the conventional way.

SCHEME I

INSOLUBLE POLYMER-SUPPORTED OLIGONUCLEOTIDE SYNTHESIS[a]



[a] T = thymidine; t = thymine; TipCl = 2,4,6-triisopropylbenzenesulfonyl chloride. *p*-TOAc should read pTOAc.

Methoxytrityl Chloride Polymers and Condensation with Thymidine.—The synthesis of the cross-linked methoxytrityl chloride support polymer from the appropriate styrene–iodostyrene–divinylbenzene copolymer was described previously;[5] the same procedure was used to prepare polymers with 0.75, 1, 2, and 20% cross-linking by varying the amount of divinylbenzene in the monomer mixture. These variations in cross-linking imparted marked differences in the degree of solvent-induced swelling of the polymers but had little or no effect on the efficiency of conversion to supported thymidine polymers except at very high levels of cross-linking (Table I). However 0.75 or 1% cross-linked supports were preferred since they have higher thymidine loadings and allowed more facile acid-induced cleavage of products from the polymer.

Assay for Polymer-Supported Thymidine.—Previously we analyzed for polymer-bound thymidine by spectrophotometric determination of thymine released by exhaustive hydrolysis of the polymer in refluxing hydrochloric acid–acetic acid mixture.[5] We now find it more convenient to hydrolyze the polymer with 1% trifluoroacetic acid in benzene at room temperature. Under these conditions intact thymidine is released quantitatively in 24 hr. However, this reagent was not satisfactory for release of polymer-bound oligonucleotides (see below).[8]

Nucleotide Condensation with Polymer-Supported Thymidine.—In our previous paper we described the formation of polymer-bound dimer, thymidylyl-(3′→5′)-thymidine, in about 50% conversion, based on thymidine, using dicyclohexylcarbodiimide (DCC) as the condensing agent.[5] However, because of the long reaction times required and the low conversions obtained with DCC we turned to the arenesulfonyl chlorides which Khorana and coworkers had introduced as condensing agents for oligonucleotide synthesis.[9,10] We also investigated the use of picryl chloride.[11]

(8) Trifluoroacetic acid in chloroform or dioxane was used for product release in the soluble polymer work of Hayatsu and Khorana[3] and Cramer, *et al.*[4]

TABLE I

CONVERSION OF METHOXYTRITYL CHLORIDE POLYMER TO THYMIDINE DERIVATIVES[a]

Polymer degree of cross-linking, %[b]	Chloride polymer: % Cl found	Chloride polymer: Equiv μmol of Cl/g	Thymidine polymer, μmol of T/g: Theory[c]	Thymidine polymer, μmol of T/g: Found	Thymidine polymer, μmol of T/g: Convn, %
0.75	2.8	790	679	637	94
1.0	2.6	734	636	610	96
2.0	2.4	676	594	553	93
20.0[d]	1.9	535	482	382	79

[a] Reaction time, 48 hr; solvent, pyridine–benzene mixture. For details see ref 5. [b] Per cent by weight of divinylbenzene. [c] Calculated from per cent Cl found. These figures reflect the weight gain of the polymer resulting from substitution of Cl by thymidine. [d] This polymer was prepared using a monomer charge in which the iodostyrene content was increased to maintain potential functionality at about the same level as the less cross-linked polymers.

Table II summarizes synthesis conditions for a series of TpTOAc polymers. Maximum conversions (70–80%)[12] to TpTOAc were achieved using 2,4,6-triisopropylbenzenesulfonyl chloride in anhydrous pyridine as represented in expt 1, 6, and 7. The optimized conditions used therein form the basis for comparison of several reaction variables as follows.

A. Degree of Polymer Cross-Linking.—At low levels of polymer cross-linking (0.75–2%) variation in the degree of cross-linking had little or no effect on per cent conversion of bound thymidine to the dimer TpTOAc despite large differences in solvent-induced polymer swellage (Table II, expt 1, 6, and 8). Absolute amounts of dimer formed differed because of variations in thymidine content of the polymers. However, on highly cross-linked polymer (20%), percentage conversion was reduced from 70–80% to about 60% (Table II, expt 11). This change probably reflects decreased accessibility of polymer-bound functional groups.

B. Nucleotide Salt Form and Mole Ratio Relative to Nucleoside.—Lohrmann and Khorana have shown that whereas DCC is an effective condensing agent only with pyridinium salts of nucleotides the arenesulfonyl chlorides are effective also with nucleotide salts of strongly basic amines.[10] We found bis(triethylammonium) 3′-O-acetylthymidine 5′-phosphate (pTOAc) to be preferable to the pyridinium salt (70–80% *vs.* 55% conversion, Table II, expt 9 and 10) and, furthermore, that the mono(triethylammonium) salt was less suitable than the bis salt (59% *vs.* 73% conversion, expt 1 and 3).

We usually used a three- to fivefold molar excess of nucleotide relative to polymer-bound nucleoside and observed no significant differences in conversion within these limits; no advantage was found in higher nucleotide ratios. At the nucleotide concentration used (~0.1 *M*), lower nucleotide/nucleoside ratios imposed solvent volumes so small that all of the solvent was

(9) R. Lohrmann and H. G. Khorana, *J. Amer. Chem. Soc.*, **88**, 829 (1967).
(10) T. M. Jacob and H. G. Khorana, *ibid.*, **86**, 1630 (1964).
(11) F. Cramer, R. Wittmann, K. Danek, and G. Weimann, *Angew. Chem.*, **75**, 92 (1963).
(12) As in our previous paper,[5] we distinguish between conversion and yield, the former being determined by the ratio moles of product/total moles of starting material and the latter by the ratio moles of product/moles of unrecovered starting material.

TABLE II

CONVERSION OF METHOXYTRITYLTHYMIDINE POLYMERS TO THYMIDYLYL-(3′→5)-THYMIDINE 3′-O-ACETATE DERIVATIVES

Expt no.	Precursor thymidine polymer: μmol of T/g	Precursor thymidine polymer: % cross-link	pTOAc,[a] mol/mol of T	Condensing agent,[b] mol/mol of pTOAc	Reaction time, hr	Product TpTOAc polymer: μmol of TpTOAc/g: Found	Product TpTOAc polymer: μmol of TpTOAc/g: Cor[c]	Convn, %
1	637	0.75	4.7	2	4	383	462	73
2	637	0.75	4.7	2	16	369	440	69
3	637	0.75	4.7	2	4	319	372	59
4	637	0.75	4.7	1	4	266	302	48
5	637	0.75	4.7	1	4	252	284	45
6	546	1.0	3.0	2	4	365	436	80
7	546	1.0	3.0	3	4	337	396	72
8	553	2.0	3.0	2	4	331	388	71
9	565	1.0	5.0	2	20	334	392	70
10	565	1.0	5.0	2	20	273	309	55
11	382	20.0	4.7	2	4	216	240	63
12	565	1.0	*d*		48	314	366	65
13	565	1.0	4.5	2	18	356	423	75

[a] The bis(triethylammonium) salt throughout excepting expt 3, and 5 for which the mono(triethylammonium) salt was used and expt 10 which utilized the pyridinium salt. The solvent was anhydrous pyridine. [b] 2,4,6-Triisopropylbenzenesulfonyl chloride in all cases excepting expt 13 for which picryl chloride was used. [c] The corrected figures take into account the polymer weight gain resulting from addition of the elements of pTOAc; see Experimental Section. [d] The phosphorylating solution from expt 1 was filtered under anhydrous conditions and added to the fresh batch of thymidine polymer.

imbibed by the polymer forming a nonfluid gel which could not be adequately mixed.

C. Condensing Agent/pTOAc Ratio.—Consistent with the conclusions of Khorana and coworkers we found a ratio of 2–3 mol of triisopropylbenzenesulfonyl chloride per mole of nucleotide to be optimum.

Such solutions retained phosphorylating capacity after having been used in an initial phosphorylating reaction. For example, when the solution from expt 1, Table II, was filtered onto a new batch of thymidine polymer, a further 65% conversion to dimer acetate, TpTOAc, was obtained (expt 12, Table II).

D. Reaction Time.—The mononucleotide and condensing agent in pyridine were allowed to react for 30 min prior to adding polymer. A subsequent reaction time of 4 hr was sufficient to achieve maximum yields.

E. Other Condensing Agents and Solvents.—Picryl chloride[11] proved to be an effective condensing agent although it gave a dark brown polymer; this color persisted as a contaminant in the isolated products but was readily separated by chromatography. Methanesulfonyl chloride proved to be unsatisfacory.

Anhydrous pyridine was used as solvent in all experiments of Table II. Other experiments showed that dichloromethane and dioxane were unsuitable solvents and that dimethylformamide diminished conversions particularly when present during the nucleotide activation period.

Acidic Release of Products from Oligonucleotide Polymer.—For polymer-supported oligonucleotide synthesis to be practical the product must be removed from the support under conditions sufficiently mild that the oligonucleotide is not degraded. With trityl-bound systems an acidic reagent must be used, and in our previous work the reagent of choice was 80% aqueous acetic acid saturated with benzene (HOAc–H_2O–C_6H_6, 16:4:5 v/v), the benzene assisting to swell the polymer; this remains the preferred reagent. With thymidine homooligonucleotides release times of about 18 hr allowed quantitative removal of the TpTOAc from all of the polymers investigated. In Table III are summarized the results of product cleavage with respect to reaction time and degree of cross-linking using several acidic reagents.

TABLE III

ACIDIC CLEAVAGE OF THYMIDYLYL-(3′→5′)-THYMIDINE 3′-O-ACETATE FROM METHOXYTRITYL SUPPORT POLYMERS

Expt no.	Acidic reagent[a]	Polymer source[b]	Polymer cross-link, %	Reaction time, hr	TpTOAc liberated: Polymer,[c] μmol/g	TpTOAc liberated: % of total
1	A	1	0.75	18	383	100
2	A	1	0.75	0.25	373	97
3	A	3	0.75	18	319	100
4	B	3	0.75	18	270	84
5	C	3	0.75	18	136	43
5	A	6	1.0	18	365	100
6	A	6	1.0	0.25	276	76
8	A	13	1.0	18	356	100
9	A	13	1.0	86	356	100

[a] Reagent A is HOAc–H_2O–C_6H_6 (16:4:5 v/v); B trifluoroacetic acid–$CHCl_3$ (1:99 v/v); and C trifluoroacetic acid–C_6H_6 (1:99 v/v). For detailed work-up see Experimental Section. [b] The numbers refer to the first column of Table II. [c] Each value represents an average of at least two analyses reproducible to within ±2% of the value shown.

In previous sections of this paper it has been shown that in various condensation reactions with polymer-bound reactants the per cent conversions are relatively insensitive to the degree of polymer cross-linking. However, the latter property markedly affects the rate of the acidic cleavage reaction; thus oligonucleotide was nearly quantitatively released from 0.75% cross-linked polymer in 15 min while in the same period of time only about 75% of the product was released from 1% cross-linked polymer (Table III, expt 2 and 7).

In our previous paper[5] we remarked on the increased acid lability of the polymer–oligonucleotide trityl ether bond relative to the equivalent bond in the nucleoside polymer. Although that work was carried out with DCC condensing agent, the same increased lability is manifested in sulfonyl chloride condensed derivatives. For example, in expt 2, Table III, a reaction time of 15 min released 373 μmol of TpTOAc/g of polymer. This was the only product isolated (although with longer release times a small amount of unreacted thymidine was also released, *e.g.*, 30 μmol of T/g for expt 1). On the other hand, the thymidine

TABLE IV

DEACETYLATION OF POLYMER-SUPPORTED THYMIDYLYL-(3′→5′)-THYMIDINE 3′-O-ACETATE WITH 0.2 *M* KOH IN METHANOL–DIOXANE[a]

Expt no.	TpTOAc polymer source[b]	Polymer cross-linking, %	Hydrolysis time, hr	TpTOAc, μmol/g of polymer	Product TpT, μmol/g[c]
1	1[d]	0.75	0.25	385	295
2	9[d]	1.0	0.25	327	351
3	9[d]	1.0	24.0	327	343
4	6	1.0	0.5	365	297
5	13	1.0	0.25		356
6	8[d]	2.0	0.5	319	318
7	8	2.0	0.5	331	296
8	11	20.0	0.5	216	184

[a] For general conditions see Experimental Section. [b] Refers to the first column in Table II. [c] Homogeneous by paper chromatography in solvents A and C. [d] New preparations, prepared similarly to corresponding preparations of Table II.

polymer afforded only 44 μmol of T/g under identical conditions, less than 12% of that expected on the basis of the TpTOAc released.

The results in Table III also focus a peculiar characteristic of the trifluoroacetic acid–benzene reagent. This reagent was effective for quantiative assay of thymidine polymers, and yet under essentially identical conditions it released less than half of the TpTOAc from the derivative polymer. Thus the behavior of trifluoroacetic acid–benzene was qualitatively the converse of that of the acetic acid–water–benzene reagent.

Deacetylation of Polymer-Bound Thymidylyl-(3′→5′)-thymidine 3′-O-Acetate.—Prior to oligonucleotide chain extension to higher oligomers it is necessary to deacetylate the polymer-bound 3′-O-acetate. This hydrolysis was accomplished quantitatively by treating the polymer with 0.2 *M* potassium hydroxide in methanol–dioxane (1:9 v/v) for 15–30 min at room temperature.[13] Several other alkaline reagents were examined but none was as effective as the above combination. For analytical purposes with small amounts of polymer and large volumes of reagent, a hydrolysis time of 15 min was shown to be adequate, but for preparative purposes 30 min was allowed. Results are summarized in Table IV. In these experiments alkaline hydrolysis of the polymer was followed by an extensive washing procedure and isolation of dry polymer from which products were released by acetic acid treatment. Recoveries of the dimer TpT were erratic but several of the experiments clearly show a 10–25% loss of polymer dimer. These results suggest that the normally acid-labile trityl ether bond, when incorporated in the polymeric structure, is somehow further labilized so that cleavage occurs even in basic media.[14] Several different washing procedures were employed subsequent to the deacetylation step, but no correlation could be made between the extent of product loss and composition of the wash solvents (see below).

Conversion of Polymer-Supported Thymidylyl-(3′→5′)-thymidine into Thymidylyl-(3′→5′)-thymidylyl-(3′→5′)-thymidine 3′-O-Acetate.—Since the nature of the activated pTOAc intermediate is unknown, the form of the phosphate group in the TpTOAc polymer immediately after condensation is uncertain. However, it is no doubt converted into the pyridinium or triethylammonium salt during the wash cycle (moist pyridine or dilute aqueous triethylamine in pyridine). Subsequent to deacetylation with potassium hydroxide the TpT exists as the potassium salt (KTpT), and in this form the polymer swelled markedly less in organic solvents than the onium salt forms. Assuming that swelling might affect subsequent reactions we examined the effect of converting the KTpT polymer into the pyridinium or triethylammonium salts by washing with the corresponding acetates in pyridine. Although this procedure restored the swelling characterisics of the polymer, it did not improve percentage conversion to trimer acetate. For example, the Et_3NH^+ form of a 1% cross-linked dimer polymer containing 297 μmol of TpT/g gave a product containing 211 μmol of TpTpTOAc/g while the K^+ form of a 2% cross-linked polymer gave an identical result corresponding to 78% conversion after correction for polymer weight gain.

The paper chromatographic mobility of the trimers from those polymers merit some special attention. TpTpT, deacetylated with potassium hydroxide while bound to polymer or derived from polymer-bound KTpT and deacetylated with ammonia *after* release from the polymer, moved as a single band with mobility very similar to reference pT in the ammoniacal solvent system A.[15] On the other hand, when trimer derived from KTpT was ion exchanged with triethylammonium acetate while bound to the polymer, and was released and deacetylated with ammonia, it moved as a multiple band with a major component of low mobility as above and a diffuse minor component with $R_f \sim 0.25$. Both forms were shown to be authentic TpTpT by specific enzymic hydrolysis. We ascribe the mobility differences to different salt forms of TpTpT of which three are possible. When potassium salt polymer was agitated for 4 hr with 1 *M* triethylammonium acetate in pyridine, 78% of the isolated TpTpT retained low mobility while 22% had been converted into the more mobile species. Further equilibration of the polymer with 1 *M* tetraethylammonium acetate in moist pyridine for 20 hr converted virtually all the trimer into the high-mobility form.

Conversion of Polymer-Bound Trimers into Higher Oligomers.—Repetition of the deacetylation and nucleotide condensation reactions gave the tetramer and pentamer derivatives (Tables V and VI). Conversions to these higher members were in the range 35–65% based on next lowest oligomer. Table V shows results only for the highest oligomer isolated at each stage but in each case it was accompanied by the lower oligomers. Complete assay at each step is illustrated in Table VI which shows satisfactory materials balance.[16]

Although the chromatographic mobility of TpTpT was significantly affected by its salt form, such effects

(13) N-Acyl groups apparently survive these conditions intact.

(14) In experiments with dimethoxytrityl analogs of the polymers described here we encountered severe loss of dimer as a result of extensive washing of the TpTOAc derivative with anhydrous pyridine.

(15) See Experimental Section; the R_f of reference sodium pT was 0.15 ± 0.01.

(16) Nucleoside is ignored in the materials balance since the acidic release times were insufficient to liberate all the thymidine.

TABLE V
PENTATHYMIDINE TETRAPHOSPHATE SYNTHESES

Polymer stage	Product[a]	% convn[b]	Product[a]	% convn[b]	Product[a]	% convn[b]
T	637[c,d]		565[d,e]		546[e]	
TpT	295	53	356	75	332	71
TpTpT	161	58	185	56	236	79
TpTpTpT	74	47	112	63	114	51
TpTpTpTpT	40	55			41	37

[a] μmoles per gram of polymer, uncorrected for weight gain. [b] After correction for weight gain. [c] 0.75% cross-linked. [d] Et_3NH^+-exchanged intermediates. [e] 1% cross-linked. [f] K salt forms throughout.

TABLE VI
TETRATHYMIDINE TRIPHOSPHATE SYNTHESIS
2% CROSS-LINKED POLYMER

Stage	Products, μmol/g of polymer T	TpT	TpTpT	TpTpTpT	Highest oligomer Amt, μmol/g cor	% convn
T	553					
TpTOAc	47	319			372	67
TpT	95	318			371	67
TpTpTOAc	38	109	212		232	73
TpTpT	35	108	216		236	74
TpTpTpTOAc		65	153	70	72	34

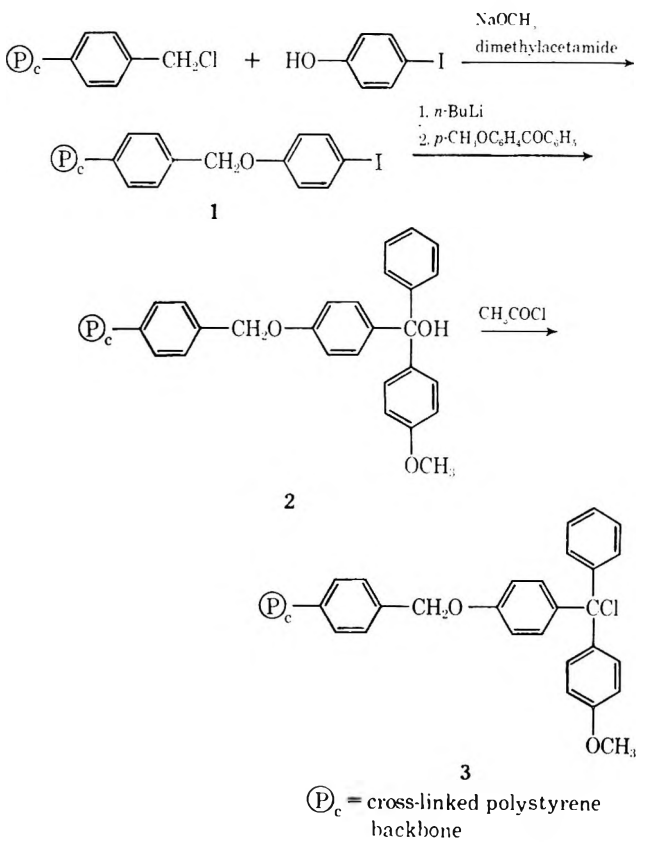
were virtually insignificant with the tetramer TpTpTpT and pentamer TpTpTpTpT.

Other Support Polymers.—With the exception of the aminophenoxymethylpolystyrene of Blackburn, *et al.*, all other oligonucleotide support polymers previously described[2-5] have, as nucleoside attachment sites, functional groups bound to phenyl rings which are directly attached to the polyalkylene backbone of the polymer. We reasoned that the contiguity of the functional group and backbone might sterically hinder phosphorylation of the 3′-hydroxyl group of a polymer-supported nucleoside and that a more favorable environment might be provided by separating the trityl group from the polymer backbone by an extended bridge of several atoms. The preparation of one such "extended" polymer is outline in Scheme II and its use in synthesis of the pentanucleoside tetraphosphate TpTpTpTpT will be discussed below.

Reaction of chloromethylated 1% or 2% divinylbenzene–styrene copolymer[17] containing 1.7–2.0 mmol of Cl/g with sodium 4-iodophenoxide in dimethylacetamide proceeded in essentially quantitative conversion to give the iodo polymer **1**. When a limited amount of the phenoxide was used, remaining chloromethyl groups were capped by reaction with excess sodium methoxide. In this way, polymers with a wide range (up to 1380 μmol/g) of iodine content were conveniently prepared. Conversion of **1** into **3** was carried out essentially as described for the *p*-iodostyrene–styrene copolymer[5] to obtain polymers containing 300–1100 μmol of Cl/g. Condensation of extended polymer of type **3** containing 400–500 μmol of Cl/g with thymidine in pyridine–benzene[3] gave thymidine polymers in 90–94% conversion, but polymers of higher chloride content (>1 mmol/g) gave lower conversions (85%) into thymidine polymer in-

(17) R. B. Merrifield, *J. Amer. Chem. Soc.*, **86**, 2149 (1963).

SCHEME II
SYNTHESIS OF EXTENDED SUPPORT POLYMER



1 2 3

$Ⓟ_c$ = cross-linked polystyrene backbone

dicating inaccessibility of an increasing proportion of chloride groups.

Optimum nucleoside loading for the formation of polymer-supported TpTOAc was determined by reaction of 3′-O-acetylthymidine 5′-phosphate with thymidine polymers having 150–700 μmol of T/g. Polymers containing 400–700 μmol of T/g gave TpTOAc in amounts of 200 ± 15 μmol/g; thus the percentage conversion decreased as the initial nucleoside content of the polymer increased. On the other hand, polymers containing thymidine in the range of about 150–400 μmol of T/g gave fairly constant (60 ± 5%) conversions into TpTOAc. These data are for 2% cross-linked polymers which gave slightly higher conversions than did the 1% cross-linked polymer support. These observations imply that at loadings up to about 400 μmol of T/g about 40% of the supported thymidine is inaccessible to phosphorylation, but any thymidine in excess of 400 μmol/g is totally inaccessible.

Stepwise synthesis of thymidine oligomers up to the pentamer, TpTpTpTpT, was carried out to compare the results with those obtained using copolymer supports. Accordingly, an "extended" polymer containing 410 μmol of T/g was phosphorylated under the optimum conditions described above, to give a product containing 216 μmol of TpTOAc/g (59% conversion). Successive steps of deacetylation and phosphorylation gave polymers containing 108 μmol of TpTpTOAc/g, 41 μmol of TpTpTpTOAc/g and 20 μmol of TpTpTpTpTOAc/g which represent 52, 39, and 49% conversions, respectively, based on the next lower member in the series. The over-all conversion into the pentanucleoside tetraphosphate based on initially bound

thymidine was 6%.[18] These data show that use of the copolymer support[5] gives somewhat higher over-all conversions for the synthesis of thymidine oligomers than does the "extended" support and emphasize that the method of introduction of the functional group into the polymer support may have significant effects in solid phase oligonucleotide synthesis.

Product Characterization.—The thymidine oligonucleotides were completely hydrolyzed by spleen and venom phosphodiesterase. The nucleotide/nucleoside ratios were determined and shown to be satisfactory. Paper chromatographic mobilities of the oligomers are listed in Table VII.

Summary.—The efficiency of any polymer-supported synthesis scheme must be evaluated in terms of several characteristics, *e.g.*, high yields and conversions into products, absolute amounts of products carried by the polymer, rapidity of synthesis, ease of handling, polymer and product recoveries, and availability of intermediates. Compared to other systems the scheme described here meets reasonable requirements in all aspects including yields, but at rather low conversions in steps leading to the higher oligomers. Moreover, the conditions established are suitable for the polymer-supported synthesis of deoxycytidine and purine-containing oligonucleotides which are the subject of the succeeding paper in this series.

Experimental Section

General Methods and Materials.—Paper chromatography was carried out by the descending technique using Whatman No. 40 paper. Solvent systems used A, 2-propanol-concentrated ammonium hydroxide-water (7:1:2, v/v); B, ethanol–1 *M* ammonium acetate (pH 7.5) (7:3); and C, 1-butanol–acetic acid–water (5:2:3).

Ultraviolet spectra were determined with a Cary Model 15 recording spectrophotometer. The expression OD_{267} unit is defined as that amount of substance in 1 ml of solution which gives an optical density of 1.00 through a 1-cm path length at the indicated wavelength. The following molar extinction coefficients (267 mμ) were used: TpT, 18,500;[19] TpTpT, 25,400;[2c] TpTpTpT, 34,000;[20] and TpTpTpTpT, 42,500.[20]

Pyridinium 3′-O-acetylthymidine 5′-phosphate (pTOAc) (0.1 *M* in anhydrous pyridine), prepared as previously described,[5] was converted into the mono- or bis(triethylammonium) salt by addition of 1 or 2 equiv of anhydrous triethylamine which had been distilled from potassium hydroxide. 2,4,6-Triisopropylbenzenesulfonyl chloride[21] was recrystallized from hexane. Methoxytrityl chloride support polymer was prepared and condensed with thymidine as previously described.[5]

Small-scale reactions (3-ml volume or less) were carried out in screw-cap vials. Larger scale reactions (5 ml or larger) were carried out in reactors made by fusing a Teflon fluorocarbon resin stopcock to the outlet of a coarse-frit cylindrical funnel and a screw-cap top to the input. The outlet tube below the stopcock was equipped with a one-hole rubber stopper for insertion into a filter flask for removal of liquid components. The screw-cap tops were obtained from commercially available screw-cap erlenmeyer flasks and allow the use of polyethylene-lined caps which provide liquid and air-tight seals and permit easy access to the reactor contents. Moisture-sensitive reactants were mixed and transferred in a drybox.

(18) These values are for the same polymer carried continuously from T to TpTpTpTpT. Highest percentage conversions observed with similarly prepared polymers for the isolated reactions T → TpT, TpT → TpTpT, etc., were 66, 64, 40, and 49%, respectively, or an over-all 8% conversion into pentamer.

(19) P. T. Gilham and H. G. Khorana, *J. Amer. Chem. Soc.*, **80**, 6212 (1958).

(20) T. M. Jacob and H. G. Khorana, *ibid.*, **87**, 368 (1965).

(21) Aldrich Chemical Co., Milwaukee, Wis.

TABLE VII

PAPER CHROMATOGRAPHY OF THYMIDINE OLIGONUCLEOTIDES

	Mobility (R_f)		
	Solvent A		
Compound	Onium salt	Potassium salt	Solvent C[a]
TpT	0.47	0.47	0.36
TpTpT	0.26	0.16	0.19
TpTpTpT	0.14	0.13	0.12
TpTpTpTpT	0.09	0.08	0.08

[a] No distinguishable difference conferred by salt form.

Iodo Polymer 1. Scheme II.—A mixture of 21.7 g of chloromethylpolystyrene[17] containing 1.96 mmol of Cl/g, 9.5 g (43.1 mmol) of 4-iodophenol, 2.75 g (51 mmol) of sodium methoxide, and 125 ml of freshly distilled dimethylacetamide was stirred at 85° for 18 hr with exclusion of moisture. After cooling the mixture, solids were collected by filtration, and the polymer was washed on the filter with a large volume of dimethylformamide (DMF), water, DMF, and methanol. The composition of wash solvents was changed gradually during all washing operations. After being dried at 100° *in vacuo*, the polymer weighed 28.4 g. *Anal.* Calcd: I, 18.3. Found: I, 17.0.

Methoxytrityl Alcohol Polymer 2. Scheme II.—Into a resin kettle, which had a 9-cm coarse fritted disk base and a stopcock beneath for removal of liquids, was placed 20 g of 1 and 400 ml of reagent grade benzene. The suspension was stirred under nitrogen during and after the addition of 100 ml of 1.6 *M* *n*-butyllithium in *n*-hexane.[22] After 24 hr, liquid reagents were removed and the lithio polymer was washed by suspension in 400 ml of benzene for 15 min. The wash liquid was removed and replaced with a solution of 25 g (0.12 mol) of 4-methoxybenzophenone in 400 ml of benzene. The reaction mixture was stirred for 24 hr under nitrogen. Excess reagents were removed, and the polymer was washed with benzene, 50% acetic acid, water, DMF, and methanol. The vacuum-dried product weighed 21.8 g. *Anal.* Found: I, 0.13. The polymer was converted into the chloride derivative with acetyl chloride in benzene as previously described.[5]

Thymidine Polymer Assay.—To 10–20 mg of thymidine polymer in a small vial was added 3 ml of 1% trifluoroacetic acid in benzene (v/v), the vial was sealed and agitated at room temperature for 18–24 hr. The mixture was filtered, the vial was rinsed, and the polymer was washed with five 1-ml portions of 80% aqueous acetic acid on the filter. The filtrate was evaporated to dryness on a rotary evaporator at a temperature not exceeding 25°. The residue was taken up in a precisely measured volume of water (50–100 ml) and the amount of thymidine determined spectrophotometrically.

Condensation of Polymer-Supported Thymidine with pTOAc.—In a typical experiment a solution of 600 μmol of $(Et_3NH^+)_2$-pTOAc in 6 ml of anhydrous pyridine was treated with 360 mg (1200 μmol) of 2,4,6-triisopropylbenzenesulfonyl chloride, and the mixture was allowed to stand at room temperature for 30 min during which time triethylammonium chloride separated. This "activated" mixture was added to 400–500 mg of thymidine-containing polymer using about 2 ml of dry pyridine as rinse. The reactor was capped and agitated continuously at room temperature for the appropriate period of time (usually 4 hr). The mixture was filtered and the polymer washed by shaking for 1 min or so with each of five 8-ml portions of reagent grade pyridine then by mechanical agitation for 15 min with each of four 8-ml portions of pyridine and four 8-ml portions of aqueous pyridine (1:99 v/v) (total wash time about 2 hr). The polymer was then washed by agitation with several portions of ethanol and vacuum dried over phosphorus pentoxide for a minimum of 6 hr.

In those instances where solvent and/or condensing agents were varied, the calculated amount of pTOAc in pyridine was evaporated to dryness under anhydrous conditions and the appropriate solvent was added to the residue. Condensing agent was added and the reaction continued as described above.

Oligonucleotide Removal from Polymer.—A 10–20-mg portion of oligonucleotide polymer (*e.g.*, the TpTOAc derivative above) was continuously agitated with 3 ml of acetic acid–benzene reagent (HOAc–H_2O–C_6H_6, 16:4:5 v/v) for the appropriate

(22) Foote Mineral Co., Exton, Pa.

period of time, and the mixture was then filtered and washed as described under the thymidine assay procedure. The filtrate was evaporated to dryness, and the residue was treated for 1 hr with 1 ml of concentrated ammonium hydroxide. The hydrolysate was concentrated to a small volume and chromatographed on Whatman No. 40 filter paper. The uv-absorbing bands were cut out and eluted with water, and the solution was analyzed spectrophotometrically.

Deacetylation of Polymer-Supported 3-O-Acetate Derivatives.—The hydrolyzing medium was prepared by dilution of 2 *M* potassium hydroxide in methanol with nine volumes of dioxane. In a typical hydrolysis reaction 8 ml of this solution was added to 300 mg of dry TpTOAc polymer, and the mixture was continuously agitated at room tempeature for 30 min. The mixture was filtered and the polymer washed with eight 8-ml portions of methanol–dioxane (1:9, v/v), 15 min for each portion, then with methanol, and vacuum dried as before.

In those instances where ion exchange was desired, the polymer was washed with four or five portions of methanol–dioxane mixture, 5 min each, then with eight portions of 10% triethylammonium acetate in pyridine (or 10% pyridinium acetate in pyridine) for 30 min each, then twice with dimethylformamide to remove a trace of unidentified flocculent white solid, and finally with several changes of reagent grade pyridine, then with methanol, and dried.

Higher Oligomers.—Further condensation to higher oligomers was conducted as described for the initial supported thymidine–pTOAc condensation.

Enzymic Hydrolyses.—Spleen phosphodiesterase solution was prepared by dissolving 10–15 units of lyophilized enzyme[23] in 2 ml of 0.2 *M* aqueous ammonium acetate (pH 5.7). To ten OD_{267} units of oligonucleotide in 10 μl of water was added 40 μl of enzyme solution and the mixture was incubated at 37° for 5–6 hr. The hydrolysis mixture was spotted on Whatman No. 40 paper and chromatographed.

Venom phosphodiesterase solution was prepared by dissolving 5–7 mg of lyophilized enzyme[23] in 1 ml of 0.1 *M* Tris HCl buffer (pH 8.9). Samples of 20 μl solution per ten OD units of oligonucleotide were used in the hydrolysis with subsequent treatment as above. Nucleotide/nucleoside mole ratios found were within ±8% of theory.

Calculation of Corrected Values of Polymer-Bound Products.—If it is assumed that the weight increase of the polymer during the reaction

$$\text{Ⓟ}_c\text{Tr}(\text{OCH}_3)\text{T}(\text{pT})_n\text{OAc} \longrightarrow \text{Ⓟ}_c\text{Tr}(\text{OCH}_3)\text{T}(\text{pT})_{n+1}\text{OAc}$$

is due only to the added protected nucleotide, then the polymer weight increase is kA, where k is the molecular weight of the protected nucleotide[24] times 10^{-6} and A is the number of μmoles of $\text{T}(\text{pT})_{n+1}\text{OAc}$ oligomer formed. If B is the number of μmoles of $\text{T}(\text{pT})_{n+1}\text{OAc}$ oligomer *found* per gram of product polymer, then for 1.000 g of starting polymer

$$B = \frac{A}{1.000 + kA} \quad \text{or} \quad A = \frac{B}{1.000 + kB}$$

When $n = 0$, $k = 447 \times 10^{-6}$; $k = 405 \times 10^{-6}$ for all other values of n. The value of A thus determined was used to calculate the percentage conversion for all reactions described herein.

Registry No.—Pentathymidine tetraphosphate, 17853-36-0.

Acknowledgments.—We wish to thank Dr. R. E. Benson for helpful discussions and Miss Eleanor Applegate for invaluable technical assistance.

(23) Worthington Biochemical Corp., Freehold, N. J.

(24) The weight increase included 1 mol of triethylamine.

Oligonucleotide Syntheses on Insoluble Polymer Supports. III. Fifteen Di(deoxyribonucleoside) Monophosphates and Several Trinucleoside Diphosphates

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The previously described insoluble styrene–divinylbenzene copolymer containing methoxytrityl functional groups has been condensed with the N-acylated deoxyribonucleosides N-benzoyldeoxyadenosine, N-anisoyldeoxycytidine, and N-acetyldeoxyguanosine to give the corresponding supported nucleosides in amounts corresponding to 325–360 μmol/g of polymer. Condensation of these products, and a similar thymidine-containing polymer, with the protected nucleotides N-3′-O-diacetyldeoxyadenosine 5′-phosphate, N-anisoyl-3′-O-acetyldeoxycytidine 5′-phosphate, N-3′-O-diacetyldeoxyguanosine 5′-phosphate, and 3′-O-acetylthymidine 5′-phosphate in the presence of 2,4,6-triisopropylbenzenesulfonyl chloride gave 15 dinucleoside phosphates in isolated conversions of 10–60% based on polymer-bound nucleoside. Several dinucleoside monophosphate-containing polymers were 3′-O-deacetylated and further condensed to trinucleoside diphosphate derivatives from which were isolated deoxyadenylyl-(3′→5′)-thymidylyl-(3′→5′)-thymidine (dApTpT), deoxyguanylyl-(3′→5′)-thymidylyl-(3′→5′)-thymidine (dGTpT), deoxycytidylyl-(3′→5′)-deoxycytidylyl-(3′→5′)-thymidine (dCpCpT), deoxycytidylyl-(3′→5′)-thymidylyl-(3′→5′)-thymidine (dCpTpT), and thymidylyl-(3′→5′)-deoxycytidylyl-(3′→5′)-thymidine (dTpCpT) in conversions of 10–75% based on dinucleoside phosphate. Specific enzymic hydrolysis showed the products to contain exclusively 3′→5′ phospho diester linkages.

A large proportion of previously reported work on polymer-supported oligonucleotide syntheses has dealt with thymidine-containing homooligonucleotides[1-5] while only limited studies on polymer-supported heterooligonucleotides have been described. These include the synthesis of thymidylyl-(3′→5′)-deoxyadenosine (dTpA), thymidylyl-(3′→5′)-deoxycytidine (dTpC), and thymidylyl-(3′→5′)-deoxyguanosine (dTpG)[6] on a soluble support as reported by Khorana and coworkers,[1] the deoxycytidine-containing products deoxycytidylyl-(3′→5′)-thymidine (dCpT), deoxycytid-

(1) (a) H. Hayatsu and H. G. Khorana, *J. Amer. Chem. Soc.*, **88**, 3182 (1966); (b) *ibid.*, **89**, 3880 (1967).

(2) F. Cramer, R. Helbig, H. Hettler, K. H. Scheit, and H. Seliger, *Angew. Chem. Intern. Ed. Engl.*, **5**, 601 (1966).

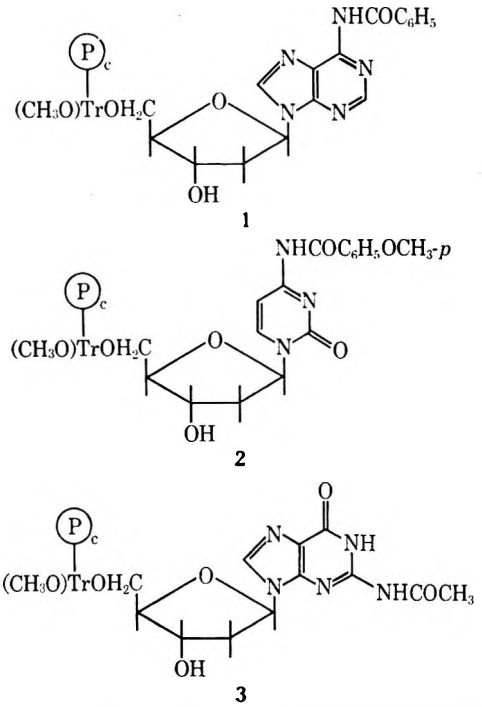
(3) (a) L. R. Melby and D. R. Strobach, *J. Amer. Chem. Soc.*, **89**, 450 (1967); (b) *J. Org. Chem.*, **34**, 421 (1969).

(4) (a) R. L. Letsinger, M. H. Caruthers, and D. M. Jerina, *Biochemistry*, **6**, 1379 (1967); (b) R. L. Letsinger, M. H. Caruthers, P. S. Miller, and K. K. Ogilvie, *J. Amer. Chem. Soc.*, **89**, 7146, (1967).

(5) G. M. Blackburn, M. J. Brown, and M. R. Harris, *J. Chem. Soc., C*, 2438 (1967).

(6) Conventional oligonucleotide symbolism and abbreviations are used throughout this paper; see previously cited references. For simplicity, dinucleoside phosphates will sometimes be referred to as dimers and trinucleoside diphosphates as trimers.

CHART I
NUCLEOSIDE POLYMERS[a]



[a] —Ⓟc = cross-linked polystyrene backbone and $(CH_3O)Tr$ = pendant 4-methoxytrityl group. These formulations will be further abbreviated as Ⓟo $(CH_3O)TrdA^{Bz}$, etc., indicating 5′ attachment of nucleoside to the polymer.

ylyl-(3′→5′)-thymidylyl-(3′→5′)-thymidine (dCpTpT) and deoxycytidylyl-(3′→5′)-thymidylyl-(3′→5′)-thymidylyl-(3′→5′)-thymidine (dCpTpTpT),[7] and, more recently, the guanine-containing dimer deoxyguanylyl-(3′→5′)-deoxyguanosine[8] prepared on an *insoluble* support by Letsinger and coworkers.

This paper will present the results of our initial studies on the synthesis of 15 of the possible 16 di(deoxyribonucleoside) monophosphates derived from the four major natural deoxynucleosides deoxyadenosine (dA), deoxycytidine (dC), deoxyguanosine (dG), and thymidine (T) using the *insoluble* methoxytrityl-containing styrene–divinylbenzene (DVB) copolymer support described in our previous work[3]; the latter dealt exclusively with TpT and its oligomers which will not be considered here. In addition, the transformation of several polymer-supported dinucleoside monophosphates to trinucleoside diphosphates containing dA, dC, and dG will be discussed.

Polymer-Supported Nucleosides and Their Assay.—N-Benzoyldeoxyadenosine[9] (dA^{Bz}), N-anisoyldeoxycytidine[9] (dC^{An}), and N-acetyldeoxyguanosine[10] (dG^{Ac}) were condensed, in anhydrous pyridine, with 1% cross-linked divinylbenzene (DVB)–styrene copolymer bearing methoxytrityl chloride functional groups[3] to give the supported nucleoside derivatives **1**, **2**, and **3** (Chart I) containing, respectively, 360, 325, and 350 μmol of protected nucleoside per gram of polymer.[11] These

(7) (a) R. L. Letsinger and V. Mahadevan, *J. Amer. Chem. Soc.*, **87**, 3526 (1965); (b) *ibid.*, **88**, 5319 (1966).

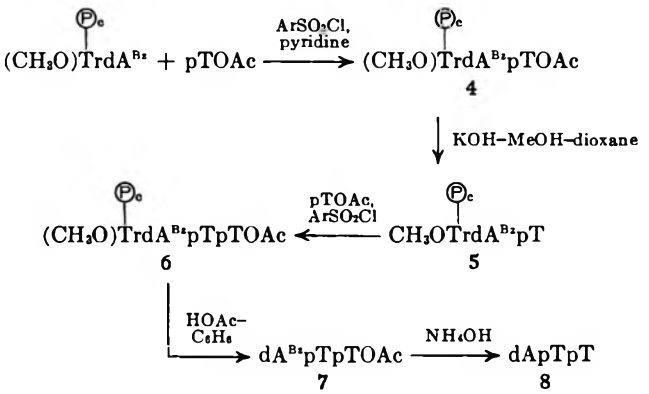
(8) T. Shimidzu and R. L. Letsinger, *J. Org. Chem.*, **33**, 708 (1968).

(9) H. Schaller, G. Weimann, B. Lerch, and H. G. Khorana, *J. Amer. Chem. Soc.*, **85**, 3821 (1963).

(10) S. A. Narang, T. M. Jacob, and H. G. Khorana, *ibid.*, **87**, 2988 (1965).

(11) In previous publications we have cited loadings to the nearest whole number, but here we cite values to the nearest multiple of five to conform more realistically to the limits of accuracy of the assay procedures.

SCHEME I



values correspond to about 55–60% conversions based on active chloride in the starting polymer. We had achieved much higher conversions in the thymidine series using a mixed benzene–pyridine solvent, but this mixture was unsuitable for the present work because of the relatively low solubility of these acylated nucleosides.

Infrared spectra of the three nucleoside polymers exhibit strong bands in the 5.9–6.1-μ region characteristic of the acylated nucleosides. Quantitative assay was carried out by hydrolysis of the polymers with 1% trifluoroacetic acid in benzene at room temperature for 24 hr. In this way intact N-anisoyldeoxycytidine was released quantitatively and was directly estimated spectrophotometrically. N-Benzoyldeoxyadenosine was quantitatively released and degraded to N-benzoyladenine. This was hydrolyzed with aqueous ammonia to free adenine which was isolated by paper chro-

TABLE I
DI(DEOXYRIBONUCLEOSIDE) MONOPHOSPHATE SYNTHESES

Product	Chromatographic mobility, solvent A[a] R_f	R_{pT}[d]	λ_{max}, mμ H_2O	pH 2	ε max[b] (H_2O)	Polymer, μmol/g	% convn[c]
dApA	0.37	2.8	258	256	30,800	35	10
dApC	0.35	2.7	262	265	22,200	90	26
dApG	0.19	1.5	253	256	27,300	65	17
dApT	0.34	3.5	261	261	20,500	130	39
dCpA	0.36	2.7	262	267	22,200	30	9
dCpC	0.33	3.0	270	279	27,000	95	24
dCpG	0.16	1.2	254	277	19,700	85	24
dCpT	0.32	3.0	268	273	18,800	180	60
dGpA	0.16	1.3	255	257	27,300	35	10
dGpC	0.15	1.4	256		19,700	95	25
dGpG[e]	0.06	0.5	252	255	27,400	135	40
dGpT	0.17	1.5	256	256	20,800	190	59
dTpA	0.36	4.0	260	260	20,500	110	21
dTpC	0.35	3.9	268	273	18,800	205	42
dTpG	0.17	1.9	255	257	20,800	90	17

[a] 2-Propanol–concentrated NH_4OH–water (7:1:2, v/v). [b] Several of these molar extinction coefficients were taken from ref 14b, the remainder were calculated by summing the extinctions of the constituent nucleotides and nucleosides at the appropriate wavelengths and ignoring hypochromicity. The number of μmoles of material were determined using these molar extinctions. [c] Conversions based on nucleoside polymers having, respectively, 360 μmol of dA^{Bz}, 325 μmol of dC^{An}, 350 μmol of dG^{Ac}, and 550 μmol of T/g of polymer, respectively. The per cent values were corrected for polymer weight gain (see ref 3b). [d] Mobility relative to pT. [e] Because of its very low mobility dGpG does not form a well-resolved band in solvent A; thus its per cent conversion figure may be considerably more in error than the ±2% limits for the others.

TABLE II

DEOXYADENYLYL-(3′→5′)-THYMIDYLYL-(3′→5′)-THYMIDINE

Polymer stage	Component	Chromatographic mobility, solvent A		λ_{max}, mμ (H_2O)	ϵ[a] (H_2O)	Polymer, μmol/g	% convn
		R_f	R_{pT}				
Nucleoside	dA^{Bz}					360	
Dinucleoside phosphate	dApT	0.34	3.5	261	20,500	70	19
Trinucleoside diphosphate	dApT					100	
	dApTpT	0.14	1.0	263	28,900	55	79[b]

[a] A. M. Duffield and A L. Nussbaum [*J. Amer. Chem. Soc.*, 86, 111 (1964)] report ϵ 20,500 for dpTpA. For the trimer we added 8400, the extinction of pT at 260 mμ. [b] Conversion based on dinucleoside phosphate of precursor, not corrected for weight gain.

TABLE III

DEOXYGUANYLYL-(3′→5′)-THYMIDYLYL-(3′→5′)-THYMIDINE

Stage	Component	Chromatographic mobility, solvent A		λ_{max}, mμ (H_2O)	ϵ[a] (H_2O)	Polymer, μmol/g	% convn[b]
		R_f	R_{pT}				
Nucleoside	dG^{Ac}					350	
Dinucleoside phosphate	dGpT	0.17	1.5	257	20,800	105	30
Trinucleoside diphosphate	dGpT					115	
	dGpTpT	0.06	0.45	256	29,000	65	62

[a] Reference 14b reports ϵ 20,800 for dGpT. For the trinucleoside diphosphate we added 8200, the extinction of pT at 256 mμ. [b] Not corrected for weight gain.

TABLE IV

DEOXYCYTIDINE–THYMIDINE OLIGOMERS[a]

Dinucleoside phosphate polymer	Derived trimer polymer products	Chromatographic mobility, solvent A		Spectral data, pH 2		Polymer, μmol/g	% convn
		R_f	R_{pT}	λ_{max}, mμ	ϵ		
dCpC						95	
	dCpC	0.32	2.0	279	27,000[b]	50	
	dCpT	0.38	2.4	273	21,200[c]	20	
	dCpCpT	0.12	0.8	276	31,500[d]	15	16
dCpT						100	
	dCpT	0.40	2.4	273	21,200	75	
	dCpTpT	0.15	0.9	270	30,100[e]	10	10
dTpC						120	
	dTpC	0.36		273	21,200[c]	30	
	TpT	0.45		267	18,500	30	
	dTpCpT	0.10		271	30,100[e]	25	21

[a] In contrast to the polymers of Tables I–III which were prepared by nucleotide condensation with triisopropylbenzenesulfonyl chloride and 3′-O-deacetylated with KOH–MeOH–dioxane, the dinucleoside phosphate precursors of Table IV were prepared by dicyclohexylcarbodiimide condensation (see ref 3a) and deacetylated with the crown ether–KOH complex of ref 18. [b] Sum of dpC and dC extinctions. [c] Value taken from that reported for dTpC, P. T. Gilham and H. G. Khorana, *J. Amer. Chem. Soc.*, 80, 6212 (1958). [d] Value taken from dTpCpC, A. L. Nussbaum, G. Scheuerbrandt, and A. M. Duffield, *ibid.*, 86, 102 (1964). [e] Sum of dCpT and pT at 270 mμ.

matography and determined spectrophotometrically.[12] Acid treatment of the N-acetyldeoxyguanosine polymer quantitatively liberated the guanine-containing constituents as a mixture of N-acetylguanine and undegraded N-acetyldeoxyguanosine. The mixture was hydrolyzed with ammonia; the two constituents (guanine and deoxyguanosine) were isolated by paper chromatography and separately assayed spectrophotometrically, the molar sum of the products being equivalent to the amount of initially bound N-acetyldeoxyguanosine.

(12) One should be able to estimate the amount of N-benzoyladenine by direct spectrophotometric analysis, but at this point we had to be assured that the hydrolysate did not contain a mixture of N-benzoyladenine and undegraded N-benzoyldeoxyadenosine.

Condensation of Polymer-Supported Derivatives with Protected Nucleotides.—The nucleoside polymers **1**, **2** and **3**, as well as the thymidine analog,[3] were condensed with the acylated 5′ nucleotides N-3′-O-diacetyldeoxyadenosine 5′-phosphate[13] ($dpA^{Ac}OAc$), N-anisoyl-3′-O-acetyldeoxycytidine 5′-phosphate[14] ($dpC^{An}OAc$), N-3′-O-diacetyldeoxyguanosine 5′-phosphate[15] ($dpG^{Ac}OAc$), and 3′-O-acetylthymidine 5′-phosphate[16] (pTOAc), as their bis(triethylammonium) salts in the presence of 2,4,6-triisopropylbenzenesulfonyl chloride[17,3b] to obtain the polymer-supported acylated dinucleoside phosphates (*e.g.*, **4**) (Scheme I). In those instances where the dimer polymer was carried to the trinucleoside diphosphate stage (*e.g.*, **6**), the 3′-O-acetyl group of the acylated dimer was most conveniently removed by treatment with 0.2 *M* potassium hydroxide in methanol–dioxane.[3b,18] Subsequent nucleotide condensation with polymer of type **5** gave the acylated derivative (**6**) from which the trinucleoside diphosphate was isolated by acidic release (see below), ammoniacal deacylation, and paper chromatography. Per cent conversions, chromatographic mobilities, and ultraviolet spectral data for 15 dinucleoside monophosphates (excluding TpT) are listed in Table I while data for the trinucleoside diphosphates are included in Tables II–IV.

Acidic Removal of Products from Oligonucleotide Polymer.—In previous publications[3] we described the preferred use of acetic acid–water–benzene mixture (16:4:5, v/v) for cleavage of products from the sup-

(13) R. K. Ralph and H. G. Khorana, *J. Amer. Chem. Soc.*, 83, 2926 (1961).

(14) (a) H. G. Khorana, A. F. Turner, and J. P. Vizsolyi, *ibid.*, 83, 686 (1961); (b) H. Schaller and H. G. Khorana, *ibid.*, 85, 3828 (1963).

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(18) In some experiments (Table IV) 3′-O-deacetylation was accomplished with the dicyclohexyl-18-crown-6-ether–potassium hydroxide complex in benzene developed by C. J. Pedersen, *J. Amer. Chem. Soc.*, 89, 7017 (1967). Our results with this reagent were somewhat variable, and we have since preferred to use the KOH–MeOH–dioxane medium.

TABLE V
ENZYMIC HYDROLYSIS[a]

Substrate	Enzyme	Products Identity	Ratio Theory	Ratio Found
dCpC	S	dCp/C	1	0.9
dCpT	S	dCp/T	1	1.0
dCpCpT	S	dCp/T	2	2.3
dApT	S	dAp/T	1	1.2
dApTpT	V	pT/dA	2	2.2
dGpTpT	V	pT/dG	2	2.2

[a] These represent experiments which were quantitated. Other products were hydrolyzed by spleen phosphodiesterase (S) and purified venom phosphodiesterase (V) and found qualitatively to give the expected results based on comparison of paper chromatographic mobilities of products with known reference compounds.

porting methoxytrityl polymer. It was shown that this reagent nearly quantitatively released products from polymer of low cross-linkage (0.5–0.75% DVB) in about 15 min while more highly cross-linked polymer (1–2% DVB) required longer times for maximal product release. Because of its somewhat superior handling properties we have preferred to use 1% cross-linked polymer which imposes the need for longer acid release times. This presents no problem with oligonucleotides containing only pyrimidine bases for which acid exposure times of 5–18 hr were used without deleterious effect. However, since the acid-labile purine nucleosides, deoxyadenosine and deoxyguanosine, cannot tolerate such long exposures to acid, we compromised by using 15-min release times for their derivatives.

Purity of Products.—Since the nucleotide condensation reactions do not proceed quantitatively, the isolated dinucleoside phosphates are accompanied by unchanged nucleoside, although with 15-min acidic release times the amount of nucleoside is negligibly small. Similarly, trinucleoside diphosphate is accompanied by dinucleoside monophosphate and nucleoside. These, of course, can readily be separated by paper or column chromatography. Isolation of the trinucleoside derivatives clearly focus an important aspect of the nucleotide condensation reaction. Thus in the dApT→dApTpT transformation, the amount of dimer (dApT) carried by the trimer polymer exceeds that in the precursor dimer polymer (Table II); the additional dimer was obviously formed by nucleotide condensation with nucleoside which had escaped reaction in the first condensation step. This conclusion is further reflected in the results listed in Tables III and IV for the trinucleoside diphosphates dGpTpT, dCpCpT, and dTpCpT. In the later two the isolation problem is complicated by the presence of not one, but two dimers; *i.e.*, dCpCpT is accompanied by dCpC and dCpT; dTpCpT is accompanied by dTpC and TpT.

The above considerations refer to purity in terms of the gross product comprising a mixture of oligonucleotides of different chain length and/or base sequence. Such mixtures may present separation problems, but, in any event, the products have the desired 3′→5′ phospho diester constitution of natural nucleic acids. This conclusion stems from the results of the specific enzymic hydrolyses outlined in Table V and is further supported by proton nuclear magnetic resonance studies which have been carried out in this laboratory.[19]

A remaining question of purity relates to the presence of "non-natural" by-products derived from undesirable side reactions. Paper chromatograms of many of the gross products (particularly the pyrimidine-only derivatives) exhibited bands comprising only the desired oligonucleotides together with nucleoside and aromatic carboxamide derived from the ammonolysis of N-aroyl derivatives. However, with many of the purine-containing products several contaminants were evident; these were readily resolved and proved to be present in only minor amounts. For example, the dApTpT preparation showed two well-resolved major bands which proved to be the desired trimer and related dimer dApT, minor nucleoside and aromatic carboxamide bands, and two extraneous bands, one with a very low mobility (<dApTpT) and one with intermediate mobility.[20] Since such contaminants were of minor importance they were not further investigated.

Summary.—We have applied our insoluble polymer-supported synthesis technique to the preparation of all 16 di(deoxyribonucleoside) monophosphates derivable from the four major nucleosides and to several trinucleoside diphosphates. Many of the per cent conversions reported here are quite low, but most of the preparations represent a single attempt based on generalized reaction conditions developed for thymidine homooligonucleotide synthesis.[3] Alteration of various reaction conditions to conform with reactivity differences of different reactants and polymer-bound substrates can reasonably be expected to lead to increased percentage conversions and product purity.

Experimental Section

General Method and Materials.—Paper chromatography and solvent systems, spectrophotometry, and general procedures were as described in previous publications.[3]

The acylated nucleosides dA^{Bz}, dC^{An}, and dG^{Ac} were prepared according to published procedures.[9,10] Protected nucleotides $dpA^{Ac}OAc$, $dpC^{An}OAc$, $dpG^{Ac}OAc$, and pTOAc were also prepared as pyridinium salts according to published procedures[13–16]; they were purified by ether precipitation and were converted, as 0.2 *M* solutions in anhydrous pyridine, to bis(triethylammonium) salts by addition of the appropriate amount of purified triethylamine.

Nucleoside Polymer Preparation and Assay.—To a suspension of 1% cross-linked methoxytrityl chloride polymer[3] in anhydrous pyridine (10–15 ml/g) was added the nucleoside (~0.8 mmol/g of polymer) and the mixture was agitated for 48 hr at room temperature and worked up as previously described.[3a]

To assay the polymers, hydrolysis in 1% trifluoroacetic acid in benzene was carried out as previously described.[3b] N-Anisoyldeoxycytidine was determined by direct spectrophotometric examination [dC^{An}, λ_{max} 302 mμ (ε 24,500) in water[9]]. The acid hydrolysate from the dA^{Bz} polymer was evaporated to dryness, taken up in pyridine–concentrated NH_4OH (1:3 v/v), and allowed to stand at room temperature for 48 hr. Paper chromatography on Whatman No. 40 paper in solvent A afforded adenine which was eluted with water and determined spectrophotometrically [λ_{max} 263 mμ (ε 13,100)]. The dG^{Ac} polymer was assayed similarly to the dA^{Bz} analog except that paper chromatography afforded dG [λ_{max} 255 mμ (ε 12,300), pH 2] and guanine [λ_{max} 248 mμ (ε 11,400), pH 2] which were separately determined and the molar amounts summed.

Nucleotide Condensation and Product Isolation.—Nucleoside

(19) C. C. McDonald, W. D. Phillips, L. R. Melby, and D. R. Strobach, unpublished work.

(20) Paper chromatography in solvent system A; see Experimental Section.

polymer was condensed with protected nucleotide bis(triethylammonium) salt in the presence of 2,4,6-triisopropylbenzenesulfonyl chloride as previously described.[3b] Products containing only pyrimidines were released from the polymer by agitation for 5 hr with HOAc–H_2O–C_6H_6 (16:4:5, v/v) while those containing purines were acid treated for only 15 min and immediately freed of acid by rapid evaporation under vacuum in a rotary evaporator at room temperature. The dried crude products were then hydrolyzed for 48 hr in pyridine–concentrated NH_4OH (1:3, v/v) and paper chromatographed.

For the trinucleoside diphosphate preparations of Tables II and III, 3′-O-deacetylation was effected with 0.2 *M* KOH in methanol–dioxane (1:9, v/v) as described previously.[3b] For the preparations in Table IV an equivalent amount of 0.2 *M* crown ether–KOH complex in benzene[18] was used as the hydrolysis medium and the polymer was washed exhaustively with benzene, pyridine, and methanol, then dried prior to the second nucleotide condensation.

Enzymic Hydrolyses.—The purified oligonucleotides were hydrolyzed with spleen and venom phosphodiesterases as previously described;[3b] the results are summarized in Table V.

Registry No.—Deoxyadenylyl-(3′→5′)-thymidylyl-(3′→5′)-thymidine, 17862-43-0; deoxyguanylyl-(3′→5′)-thymidylyl-(3′→5′)-thymidine, 17853-31-5; deoxycytidine–thymidine oligomers, 17853-32-6.

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Pyrimidine Nucleosides. III. Nucleoside Derivatives of Certain 4-Substituted 6-Pyrimidones[1]

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The synthesis of 4,6-disubstituted pyrimidine nucleosides possessing two hydrogen-bonding groups has been achieved for the first time using a modified Hilbert–Johnson procedure. 4-Amino-1-(β-D-ribofuranosyl)-6-pyrimidone (**8**) and 4-amino-1-(2-deoxy-β-D-ribofuranosyl)-6-pyrimidone (**9**) have been prepared by direct utilization of 4-amino-6-pyrimidone (**5**) *via* silylation and subsequent treatment with the appropriate glycosyl halide in acetonitrile. This procedure applied to 4-methylthio-6-pyrimidone gave 4-methylthio-1-(β-D-ribofuranosyl)-6-pyrimidone (**2**). Reductive desulfurization of **2** gave 1-(β-D-ribofuranosyl)-6-pyrimidone (**3**). Oxidation of a blocked derivative of **2** provided the corresponding methyl sulfone **7** which was successfully converted into **8** and also into 4-methoxy-1-(β-D-ribofuranosyl)-6-pyrimidone (**6**).

The success achieved in the preparation of pyrimidine nucleosides *via* the silylation and alkylation procedures[2,3] suggested the possible extension of this work to 4-substituted 6-pyrimidones. Although the Hilbert–Johnson procedure has recently been successfully employed in the case of 4,6-dimethoxypyrimidine[4] to yield 4-methoxy-1-(β-D-ribofuranosyl)-6-pyrimidone (**6**), the methoxy group could not be successfully changed to other substituents. Attempts to prepare the corresponding 2-deoxy-β-D-ribofuranosyl derivative by the Hilbert–Johnson procedure gave only 0.67% of desired product.[4] A recent paper[5] describes the use of the mercuri procedure for ribosylation of 4-substituted 6-pyrimidones. In most cases the *O*-glycosyl derivatives were found to predominate in a mixture of *O*- and *N*-ribosylated products. The use of acetonitrile, however, gave predominately *N*-ribofuranosyl derivatives.

In the present study 4-amino-6-pyrimidone[6] **5** was treated with hexamethyldisilazane to give the trimethylsilyl derivative which was in turn treated directly in acetonitrile with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide. The product obtained after work-up and purification on silica gel was 4-amino-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-6-pyrimidone (**10**) (Scheme I). Deblocking of crude **10** with methanolic ammonia gave 4-amino-1-(β-D-ribofuranosyl)-6-pyrimidone (**8**) in 61% over-all yield. The physical properties of **8** agree with those recorded by Prystas[5] for this compound prepared by the mercuri procedure. Reaction of **12** with 2-deoxy-3,5-di-*O*-*p*-toluyl-D-ribofuranosyl chloride[7] in acetonitrile yielded after purification by alumina column chromatography a 75% yield of a syrupy mixture of blocked anomers (**11** and **11a**). Deblocking of this material with methanolic ammonia gave a 75% yield of a crystalline mixture of anomers **9** and **9a**. 4-Amino-1-(2-deoxy-α-D-ribofuranosyl)-6-pyrimidone (**9a**) was isolated from this mixture by fractional crystallization. 4-Amino-1-(2-deoxy-β-D-ribofuranosyl)-6-pyrimidone (**9**) was isolated from the mother liquors enriched in **9** by preparative tlc with silica gel adsorbent. The assignment of configuration was readily made by a comparison of the pmr of **9** and **9a** measured in deuterium oxide with an internal standard of sodium 2,2-dimethyl-2-silapentane-5-sulfonate. The anomeric proton of **9** exhibited a pseudotriplet centered at 6.27 ppm (width 13.2 cps, $J_{1',2'}$ = 6.6 cps). The anomeric proton of **9a** consisted of a multiplet of four peaks centered at 6.20 ppm (width 9.3 cps, "$J_{H1'}$" = 2.3 and 7.0 cps). These data clearly allow assignment[8-11] of **9** as the β-D anomer and **9a** as the α-D anomer. The ratio of the anomers **9a**:**9** obtained by this silylation and alkylation procedure was approxi-

(1) This work was supported by Research Grants CA-08109-02 and -03 from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service, Bethesda, Md.

(2) Pyrimidine Nucleosides. I: M. W. Winkley and R. K. Robins, *J. Org. Chem.*, **33**, 2822 (1968).

(3) Pyrimidine Nucleosides. II: M. W. Winkley and R. K. Robins, *J. Chem. Soc.*, in press.

(4) M. Prystas, *Collect. Czech. Chem. Commun.*, **32**, 4260 (1967).

(5) M. Prystas, *ibid.*, **33**, 1813 (1968).

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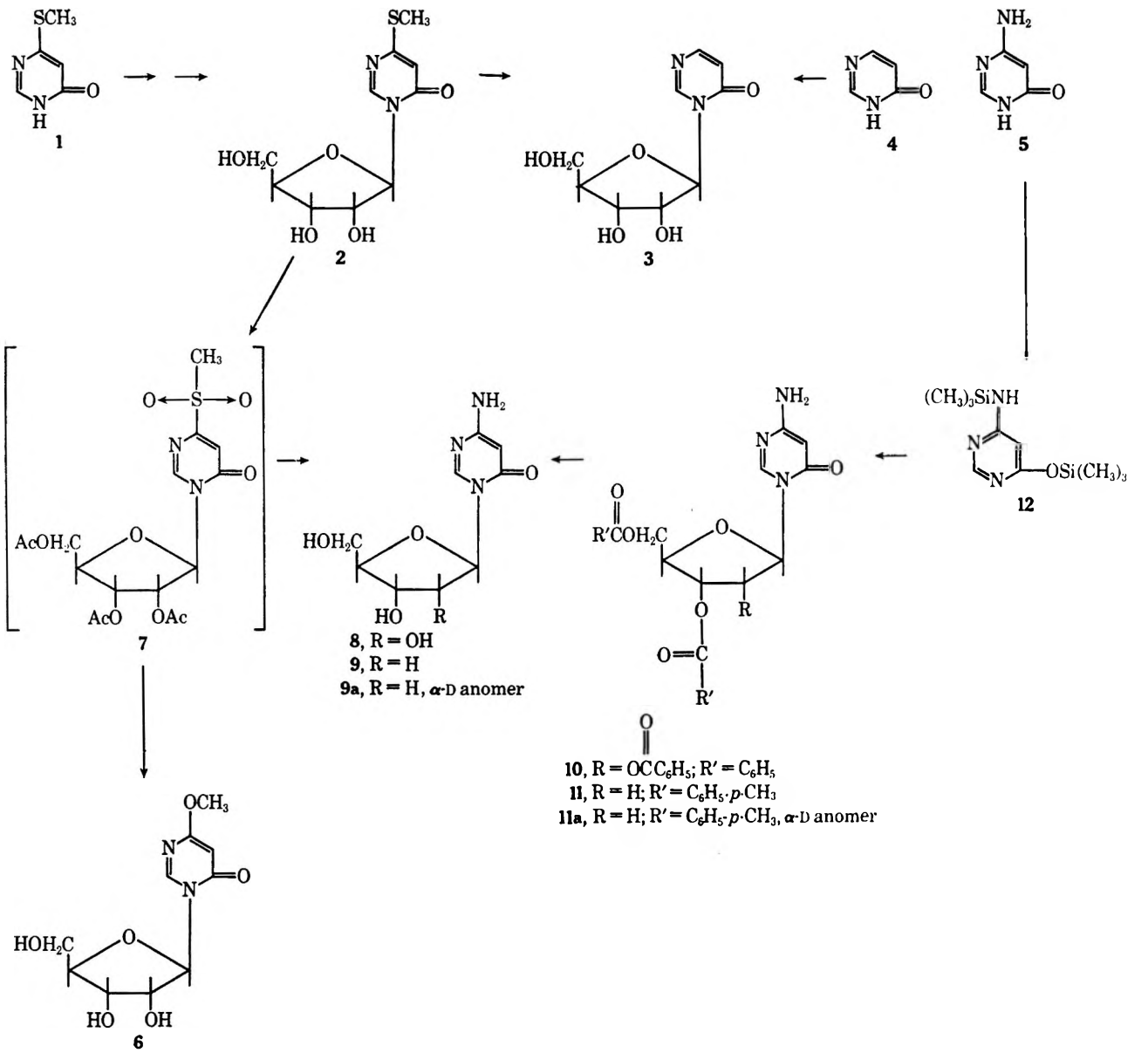
(10) K. J. Ryan, E. M. Acton, and L. Goodman, *J. Org. Chem.*, **31**, 1181 (1966).

(11) M. Prystas, J. Farkas, and F. Sorm, *Collect. Czech. Chem. Commun.*, **30**, 3123 (1965).

SCHEME I



mately 10:1 based on isolated products. This result is in contrast to our earlier findings[12] where the β-D anomer of 6-methyl-2′-deoxycytidine was found to be the predominant anomer using this same procedure. 4-Methylthio-6-pyrimidone[13] **1** was converted into its trimethylsilyl derivative and allowed to react with 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide in acetonitrile. After work-up and purification by alumina column chromatography the syrupy blocked nucleoside was deblocked with methanolic ammonia to give a 15% yield of 4-methylthio-1-(β-D-ribofuranosyl)-6-pyrimidone (**2**). Treatment of **2** with sponge nickel in 2-methoxyethanol produced the known 1-(β-D-ribofuranosyl)-6-pyrimidone[14,15] (**3**) made by the procedure of Pfleiderer and Robins.[15] This conversion established directly the structure assigned to compound **2**.

Compound **2** was acetylated with acetic anhydride–pyridine and the resulting syrupy blocked nucleoside was oxidized with *m*-chloroperbenzoic acid in chloroform to give amorphous 4-methylsulfonyl-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-6-pyrimidone (**7**). Treatment of **7** with liquid ammonia at 80° resulted in a 55% yield of **8**. The sequence **2** → **7** → **8** thus established unequivocally the structure of the nucleoside 4-amino-1-(β-D-ribofuranosyl)-6-pyrimidone (**8**) produced *via* the sequence **5** → **12** → **10** → **8**.

Reaction of **7** with sodium methoxide in methanol at room temperature gave 4-methoxy-1-(β-D-ribofuranosyl)-6-pyrimidone **6** in 48% yield. Prystas[4] reported mp 77–81° for **6** made from 2,4-dimethoxypyrimidine *via* a Hilbert–Johnson procedure. Our product **6** exhibited mp 129–130°. This discrepancy would appear to be due to an ethanol solvation of Prystas' product. It is of interest to note that compound **7** when treated with methanolic ammonia at room temperature or at elevated temperatures gives rise to both compounds **8** and **6** and that **6** is produced in much larger yield than **8**.

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(14) R. Funakoshi, M. Irie, and T. Ukita, *Chem. Pharm. Bull.* (Tokyo), **9**, 406 (1961).
(15) W. Pfleiderer and R. K. Robins, *Chem. Ber.*, **98**, 1511 (1965).

Compounds **8** and **9** are analogs of cytidine and deoxycytidine, respectively, and as such should be of interest in biochemical studies. A very similar analog, 5-azacytidine,[16] has been shown to be incorporated into both RNA and DNA.[17] In effect compound **8** could be viewed as "3-deaza-5-azacytidine."

Experimental Section

Melting points were determined with a Thomas–Hoover capillary melting point apparatus and are uncorrected. Specific rotations were measured in a 1-dm tube with a Perkin-Elmer Model 141 automatic digital readout polarimeter. Proton magnetic resonance (pmr) spectra were measured with appropriate internal standards of tetramethylsilane or sodium 2,2-dimethyl-2-silapentane-5-sulfonate with a Varian A-60 nmr spectrometer. Ultraviolet spectra were determined with a Beckmann DK-2 spectrophotometer. Infrared spectra were determined with a Beckman IR-5 spectrophotometer. Detection of components on SilicAR 7GF (Mallinckrodt) and alumina HF 254 (Brinkmann) was by ultraviolet light. Alumina used in columns was obtained from Merck and Co. (suitable for chromatographic absorption). Silica gel was purchased from J. T. Baker Chemical Co. (suitable for chromatographic use). Solvent proportions were by volume. Evaporations were performed under diminished pressure at 35° with a Buchi Rotovapor.

Trimethylsilyl derivatives of various pyrimidines were prepared using the general procedure of Wittenburg.[18] The pyrimidines were heated under reflux in an excess of hexamethyldisilazane with a catalytic quantity of ammonium sulfate under anhydrous conditions until complete solution was achieved. The time of heating varied from 1 or 2 hr to approximately 3 days. The excess hexamethyldisilazane was removed by distillation under diminished pressure and the residue (oil or crystalline solid) was used directly without further purification.

4-Amino-1-(β-D-ribofuranosyl)-6-pyrimidone (8). Method 1.—To the crystalline bistrimethylsilyl derivative of 4-amino-6-pyrimidone **12** (prepared from 20 g of 4-amino-6-pyrimidone[6]) was added 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (prepared from 50 g of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose) in dry acetonitrile (400 ml). The mixture was sealed and stirred until solution occurred. After 6 days at room temperature the solution was evaporated to a syrup. Excess sodium bicarbonate, water (100 ml), and ethanol (100 ml) were added and the mixture was evaporated to dryness. The remaining traces of water were removed by coevaporation with absolute ethanol. The residue was extracted several times with dichloromethane and the extract evaporated to a syrup. This syrup was extracted once more with dichloromethane and the dichloromethane extract treated with charcoal. The dry syrup obtained upon solvent removal weighed 58.8 g. A portion (48.8 g) of this crude 4-amino-1-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)-6-pyrimidone (**10**) was dissolved in methanol (300 ml) previously saturated at 0° with ammonia and left in a sealed vessel at room temperature for 3 days. Crystals of **8** were deposited. The solution was allowed to evaporate at room temperature. The crystalline residue was triturated with ethanol to yield 14.8 g (61%), mp 233–236° dec (prior browning at 190°). Recrystallization from water provided 12.6 g (52%) of product: mp 237–239° dec (yellowing at 215°); $[\alpha]^{26}D$ −27.6° (*c* 1, dimethylformamide); $\lambda_{max}^{pH\ 1}$ 257 mμ (ε 7300), $\lambda_{min}^{pH\ 1}$ 237 (3800), $\lambda_{max}^{pH\ 4}$ 257 (6100), $\lambda_{min}^{pH\ 4}$ 237 (3800), $\lambda_{max}^{pH\ 11}$ 257 (6400), $\lambda_{min}^{pH\ 11}$ 235 (3700), $\lambda_{max}^{pH\ 14}$ 257 (6300), $\lambda_{min}^{pH\ 14}$ 242 (5400); pmr (DMSO-d_6) δ 5.09 (s, 1, 5-II), 5.88 (d, 1, $J_{1',2'}$ = 3.5 cps, 1′-H), 6.58 (s, 2, 4-NH_2), 8.37 (s, 1, 2-H); pmr (DMSO-d_6–D_2O) δ 3.70 ppm (s, 2, 5′-CH_2OH).

Anal. Calcd for $C_9H_{13}N_3O_5$: C, 44.44; H, 5.39; N, 17.28. Found: C, 44.38; H, 5.33; N, 17.28.

The compound was homogeneous by tlc on SilicAR 7GF with ethyl acetate–methanol (4:1) as developer. The above data for **8** are similar to those recorded for the same nucleoside prepared *via* the mercuri procedure.[5]

Method 2.—4-Methylthio-1-(β-D-ribofuranosyl)-6-pyrimidone (**2**, 0.75 g) was dissolved in acetic anhydride (15 ml) and pyridine (15 ml) and the solution was left overnight at room temperature. The mixture was poured onto ice and extracted with chloroform. The chloroform solution was washed consecutively three times with 1 *N* hydrochloric acid, twice with water, and twice with saturated sodium bicarbonate solution, and three times with water. The dried ($MgSO_4$) chloroform solution was evaporated to dryness to yield 1.64 g of dry syrup.

To this crude 2′,3′,5′-triacetate in chloroform (10 ml) at −15° was added *m*-chloroperbenzoic acid[19] (1.64 g) in chloroform (30 ml) at −15°. The mixture was stirred initially and allowed to stand at room temperature overnight. The solution was diluted with chloroform and washed consecutively with saturated sodium sulfite solution, twice with ice cold 2 *N* sodium carbonate solution, and twice with water. The dried ($MgSO_4$) chloroform solution was evaporated to give a dry syrup (1.59 g). Thin layer chromatography on SilicAR with ethyl acetate as developer showed that this material was homogeneous and different from starting material. An absorption band at 1320 cm^{-1} (KBr) in the infrared spectrum indicated the presence of a methylsulfonyl group.

A portion (0.65 g) of **7** was dissolved in liquid ammonia (100 ml) and the solution was sealed in a steel bomb and heated at 80° for 8 hr. The ammonia was allowed to evaporate and the semi-crystalline residue was triturated with methanol to give 0.20 g (55%) of yellow crystals, mp 231–234° dec. This material was dissolved in hot water and the solution decolorized with charcoal. To the resulting filtrate was added 2-propanol and the solution was cooled to give white crystals, mp 237–239° dec (yellow from 200°). A mixture melting point with **8** prepared by method 1 showed no depression. The infrared spectrum in KBr was also superimposable on that of **8** prepared by method 1.

4-Amino-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-6-pyrimidone (10).—The remaining portion of crude 4-amino-1-(2′,3′,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-6-pyrimidone (**10**, 10 g) was dissolved in benzene (700 ml) and applied to a column (44 × 3.4 cm) of alumina prepacked in benzene. The material was washed on with benzene (2 l.) and 200-ml fractions were collected from the start of the benzene. Elution was effected with benzene–ethyl acetate (2 l.) followed by ethyl acetate. Fractions (100 ml) were collected from fraction 21. Fractions 24–35 were pooled and evaporated to a syrup which was crystallized from methanol to yield 3.98 g (42%), mp 132–134°. Two recrystallizations from methanol afforded pure material: mp 137–138°; λ_{max}^{KBr} 1725 (C=O of benzoate), 1665 cm^{-1} (C=O, NH_2 of pyrimidine).

Anal. Calcd for $C_{30}H_{25}N_3O_8$: C, 64.85; H, 4.54; N, 7.56. Found: C, 64.80; H, 4.45; N, 7.69.

4-Amino-1-(2-deoxy-αβ-D-ribofuranosyl)-6-pyrimidone.—2-Deoxy-3,5-di-*O*-*p*-toluyl-D-ribofuranosyl chloride[7] (35 g) and Type 4A Molecular Sieves (20 g) and **12** (prepared from 20 g of **5**) were stirred in acetonitrile (500 ml) protected from moisture at 15° for several hours. Solution occurred quickly but later a precipitate formed. The mixture was then stirred at room temperature overnight. The mixture was diluted with chloroform and the solution filtered through Celite. The filtrate was evaporated to a syrup and treated with solid sodium bicarbonate, water and ethanol. The mixture was evaporated to dryness and the residue was extracted with 2 l. of chloroform. The chloroform was removed and the residual syrup extracted once more with chloroform. The crude syrupy mixture of anomeric nucleosides obtained on solvent removal weighed 44.37 g. This material was purified by chromatography on a column of alumina. The mixture was dissolved in chloroform (300 ml) and applied to a column (45 × 5.0 cm) of alumina prepacked in benzene. This material was washed on with benzene (1.5 l.). Elution was started with benzene–ethyl acetate (9:1) and 200-ml fractions were collected from the start of this solvent. At fraction 10 the eluting solvent was changed to benzene–ethyl acetate (4:1), at fraction 20 to benzene–ethyl acetate (3:2), at fraction 37 to benzene–ethyl acetate (1:1) and at fraction 64 to ethyl acetate. Fractions 13–80 inclusive were pooled and evaporated to dryness to give 31.6 g (75%) of purified nucleoside material.

This syrupy material (10 g) was dissolved in ammonia saturated (at 0°) methanol (150 ml) in a pressure bottle and allowed to remain at room temperature for 3 days. The solution was filtered and evaporated to dryness. The residue was extracted with a mixture of water and chloroform. The aqueous

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(17) V. Paces, J. Doskocil, and F. Sorm, *Biochem. Biophys. Acta*, **161**, 352 (1968).

(18) E. Wittenburg, *Z. Chem.*, **4**, 303 (1964).

(19) Purchased from Aldrich Chemical Co., Milwaukee, Wis.

solution obtained was washed an additional three times with chloroform. The aqueous solution was evaporated to a syrup which was dissolved in methanol and decolorized with charcoal. After solvent removal the remaining syrup was crystallized (seeding) from methanol–ethyl acetate to yield 3.70 g (75%) (mp 166–170°) of a mixture of anomers consisting largely of the α-D anomer. Thin layer chromatography on SilicAR 7GF with ethyl acetate–methanol (9:1) as developer (several times) revealed two spots with almost identical R_f values—a major slower one and a minor faster one.

Fractionation of the Mixture of Anomers.—The anomeric mixture (3.02 g) was dissolved in methanol and the solution was decolorized with charcoal. The solvent was removed and the residual syrup seeded with pure α anomer. Ethanol was added and the solution warmed. The cooled solution gave crystals, 1.64 g (mp 180–182°), of pure α anomer. The filtrate was evaporated to dryness and the process was repeated to give a further 0.32 g of α anomer plus a trace of β anomer. The fractional crystallization was readily followed by tlc on SilicAR 7GF with ethyl acetate–methanol (9:1) as developer. The β anomer ran a little faster than the α anomer. The remaining mother liquor from the above process was judged to be an approximately 1:1 mixture of the α and β anomers. The mother liquor was evaporated to dryness and the crystalline residue was applied to the edge of 14 plates (2 × 200 ×400 mm) of SilicaAR 7GF and the plates were developed three times using ethyl acetate–methanol (9:1) as solvent. The anomers were clearly separated. The zones were excised and the separated anomers were extracted with methanol. The solvent was removed and the residual individual syrups were coevaporated with absolute ethanol. The two residues were extracted with a mixture of hot absolute methanol and absolute ethanol and the solution concentrated separately to yield 0.22 g (mp 194–196°) of crystalline β anomer 9 and 0.13 g of crystalline α anomer (mp 181–182°).

Recrystallized α anomer exhibited the following characteristics: mp 182–184°; $[\alpha]^{25}D$ −15.4° (*c* 1, water); $\lambda_{max}^{pH\ 1}$ 258 mμ (ε 9000), $\lambda_{min}^{pH\ 1}$ 234 (2700), $\lambda_{max}^{pH\ 4}$ 258 (6100), $\lambda_{min}^{pH\ 4}$ 237 (2700), $\lambda_{max}^{pH\ 11}$ 258 (6100), $\lambda_{min}^{pH\ 11}$ 235 (2500), $\lambda_{max}^{pH\ 14}$ 260 (6100), $\lambda_{min}^{pH\ 14}$ 238 (2700); pmr (D_2O) δ 2.03–3.11 (m, 2, 2′-H's), 3.63–3.82 ("s" centered at 3.66, "s" centered at 3.73, 2, 5′-CH_2OH), 4.35–4.65 (m, 2, 3′- and 4′-H's), 4.73 (solvent), 5.41 (s, 1, 5-H), 6.20 (q, 1, width 9.3, "*J*" = 2.3, "*J*" = 7.0 cps, 1′-H), 8.29 ppm (s, 1, 2-H).

Anal. Calcd for $C_9H_{13}N_3O_4$: C, 47.57; H, 5.77; N, 18.49. Found: C, 47.57; H, 5.73; N, 18.58.

The β anomer 9 was recrystallized from a mixture of methanol, ethanol and ethyl acetate to yield a product: mp 194–196°; $[\alpha]^{23}D$ +57.1° (c 1, water); $\lambda_{max}^{pH\ 1}$ 258 mμ (ε 8700), $\lambda_{min}^{pH\ 1}$ 235 (2500), $\lambda_{max}^{pH\ 4}$ 258 (6100), $\lambda_{min}^{pH\ 4}$ 237 (2500), $\lambda_{max}^{pH\ 11}$ 258 (6100), $\lambda_{min}^{pH\ 11}$ 235 (2700), $\lambda_{max}^{pH\ 14}$ 260 (6100), $\lambda_{min}^{pH\ 14}$ 238 (2500); pmr (D_2O) δ 2.29–2.64 (m, 2, 2-H's), 3.73–3.97 ("d", centered at 3.80, "*J*" = 2.0 cps, "s" at 3.88, 2, 5′-CH_2OH), 4.02–4.25 (m, 1, 4′-H), 4.35–4.72 (m, 3′-H overlapped by solvent at 4.60), 5.42 (s, 1, 5-H), 6.27 (t, 1, width 13.2 cps $J_{1',2'}$ = 6.6 cps, 1′-H), 8.34 ppm (s, 1, 2-H).

Anal. Calcd for $C_9H_{13}N_3O_4$: C, 47.57; H, 5.77; N, 18.49. Found: C, 47.30; H, 5.92; N, 18.57.

1-(β-D-Ribofuranosyl)-4-methylthio-6-pyrimidone (2).—To the trimethylsilyl derivative of 4-methylthio-6-pyrimidone (prepared from 12 g of 1[13]) was added 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide (prepared from 20 g of tetra-*O*-acetyl-D-ribofuranose) in dry acetonitrile (170 ml). After initial stirring the solution was left at 5° for 1.5 days followed by a further 2.5 days at room temperature. The solution was then evaporated to a syrup. Sodium bicarbonate, water and ethanol were added and the mixture was evaporated to dryness. The remaining traces of water were removed by coevaporation with absolute ethanol. The residue was extracted with chloroform. The solvent was removed and the residue was extracted again with chloroform. The residue obtained after solvent removal was dissolved in benzene (250 ml) and applied to a column (5.0 × 46 cm) of alumina (Merck) prepacked in benzene. The material was washed on with benzene (2 l.) and 200-ml fractions were collected. The fractionation was monitored by tlc on alumina HF 254 with chloroform as developer. At fraction 11 the eluting solvent was changed to benzene–ethyl acetate (19:1). At fraction 21 the solvent was changed to benzene–ethyl acetate (9:1). Fractions 26–46 were evaporated to a syrup; the yield of crude 1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-4-methylthio-6-pyrimidone was 4.6 g. This material was dissolved in methanolic ammonia (60 ml, methanol saturated at 0°) and the sealed vessel was left overnight at room temperature. The solution was filtered and the filtrate was evaporated to dryness. Acetamide was removed by sublimation at 60° under oil pump vacuum. The residue was then triturated with a mixture of ethanol and 2-propanol to yield 2.47 g (15%) of **2**, mp 147–151°. Two crystallizations from methanol afforded pure white material: mp 154–155°; $[\alpha]D$ +50.6° (*c* 1, water); λ_{max}^{KBr} 1645 cm^{-1} (C=O of pyrimidine), $\lambda_{max}^{pH\ 1}$ 270 mμ (ε 9860), 239 (19,200), $\lambda_{min}^{pH\ 1}$ 255 (8210), $\lambda_{max}^{pH\ 4}$ 269 (10,000), 238 (19,000) $\lambda_{min}^{pH\ 4}$ 253 (8200) $\lambda_{max}^{pH\ 11}$ 239 (34,800), sh 265 (13,700), $\lambda_{max}^{pH\ 14}$ 244 (10,500); pmr (D_2O) δ 2.40 (s, 3, 4-SCH_3), 3.84–4.10, 4.15–4.44 (m, 5, sugar ring H's), 5.96 (d, 1, $J_{1',2'}$ = 2.5 cps, 1′-H), 6.21 (s, 1, 5-H), 8.56 ppm (s, 1, 2-H).

Anal. Calcd for $C_{10}H_{14}N_2O_5S$: C, 43.75; H, 5.14; N, 10.22. Found: C, 43.64; H, 5.08; N, 10.12.

This compound was found to be homogeneous by tlc on SilicAR 7GF with ethyl acetate–methanol (9:1) as developer.

1-(β-D-Ribofuranosyl)-6-pyrimidone (3).—To 4-methylthio-1-(β-D-ribofuranosyl)-6-pyrimidone (**2**, 50 mg) in 2-methoxyethanol (20 ml) was added sponge nickel (500 mg previously washed with 2-methoxyethanol) and the mixture stirred under reflux for 3 hr. The mixture ws filtered through Celite and the filtrate was evaporated to dryness. The syrupy residue was applied to the short edge of a SilicAR 7GF plate (1 × 200 × 400 mm) and the plate was developed several times with ethyl acetate–methanol (9:1). The major component was excised and the adsorbent was extracted with absolute ethanol (300 ml). The extract was evaporated to a smaller volume whereupon crystallization occurred to yield 15 mg of white needles, mp 166–168°. The ir spectrum of this compound in KBr was superimposable upon that of the compound obtained by the method of Pfleiderer and Robins.[16] A mixture melting point showed no depression.

4-Methoxy-1-(β-D-ribofuranosyl)-6-pyrimidone (6).—1-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)-4-methylsulfonyl-6-pyrimidone (**7**, 0.70 g of dry foam) was added to a solution of sodium (0.30 g) in anhydrous methanol (40 ml). The resulting solution was left at room temperature overnight and then neutralized to pH 7 with glacial acetic acid. The solution was evaporated to dryness and the residue dissolved in a mixture of acetic anhydride (30 ml) and pyridine (30 ml). The solution was stirred at room temperature for 1 day and finally poured onto ice and the aqueous mixture extracted with dichloromethane. The dichloromethane solution was washed consecutively three times with 1 *N* hydrochloric acid, once with water and saturated sodium bicarbonate solution, and three times with water. The dried ($MgSO_4$) solution was evaporated to a syrup. This material was applied to the short edge of three SilicAR 7GF gel plates (2 × 200 × 400 mm) and the plates were developed several times using benzene ethyl acetate (2:1). The main band was excised and the adsorbent was extracted with methanol. The methanol was removed by evaporation and the residue extracted with dichloromethane. The dichloromethane was removed to give a dry syrup. This syrup was dissolved in anhydrous methanol (30 ml) and a small piece of sodium (50 mg) was added. After 2 hr at room temperature the stirred solution was neutralized to pH 7 by portionwise addition of Dowex 50 H^+ (X4, 200–400) resin. The resin was removed by filtration and washed well with methanol. The filtrate and washings were evaporated to dryness and the residual syrup was crystallized from ethanol–ethyl acetate to yield 0.20 g (48%), mp 77–80°; it resolidified and melted again at 118–120°. This material was dissolved in hot ethanol and the solution was decolorized with charcoal. After solvent removal **6** was crystallized from ethanol–ethyl acetate to give pure material: mp 129–130°; $[\alpha]^{25}D$ +49.4° (c 1, water); λ_{max}^{KBr} 1650 cm^{-1} (C=O of pyrimidine); $\lambda_{max}^{pH\ 1,4,11}$ 262 mμ (ε 6700), $\lambda_{min}^{pH\ 1,4,11}$ 243 (2200), $\lambda_{max}^{pH\ 14}$ 253 mμ (5900); pmr (D_2O) δ 3.82–4.03 (s at 3.90, 4-OCH_3 and s at 3.95, 5′-CH_2OH, 5), 4.12–4.46 (m, 3, 2′-, 3′-, and 4′-H's), 4.70 (solvent), 5.79 (s, 1, 5-H), 5.96 (d, 1, $J_{1',2'}$ = 2.0 cps, 1′-H), 8.54 ppm (s, 1, 2-H).

Anal. Calcd for $C_{10}H_{14}N_2O_6$: C, 46.51; H, 5.47; N, 10.85. Found: C, 46.20; H, 5.12; N, 10.55.

Prystas[4] reported mp 77–81° for **6**. This melting point would appear to be the melting point of an ethanol solvate and was obtained prior to the preparation of the analytical sample. Upon thorough drying **6** exhibits one melting point, *viz.* 129–130°

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Liquid Acetylene. Metalation and Carbonation Studies

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The novel use of liquid acetylene as both reactant and solvent under pressure below its critical temperature is reported. Alkali metals such as lithium, sodium and potassium are rapidly converted into the corresponding acetylides in high conversion using excess liquid acetylene containing catalytic amounts of ammonia or trimethylamine. Acetylide formation also takes place in undiluted liquid acetylene, but at a slower rate. A mechanism for acetylide formation in this medium and in the presence of catalytic amounts of donor molecules is discussed. A simple, one-step method for the preparation of sodium propiolate by the reaction of sodium, liquid acetylene and liquid carbon dioxide is presented. Trimethylamine is a highly effective catalyst for this system, although metalation and carbonation to sodium propiolate is possible in its absence.

Although the use of gaseous[1] and solvated acetylene[2,3] in synthetic operations is well documented, the use of the liquified gas as both reactant and solvent has been scarcely studied. Industrial explosions[4,5] at the turn of the century and the fact that the pure or diluted liquid can be detonated *via* ignition of the vapor phase[6] may explain this lack of interest.

The polymerization[7] of liquid acetylene has been claimed to yield *cis*-polyacetylene *via* a cationic mechanism. Also, the interaction of liquid acetylene with dimethyl and diethyl ethers yielded 1:1 complexes at temperatures below −100°, while attempts to chlorinate the liquid often resulted in explosions.[8,9]

Our object in studying liquid acetylene as a solvent–reactant system was to determine if it could be handled safely in synthetic operations, and to assess any possible mass action or solvation effects (faster rate, higher conversion, better product purity) which might benefit acetylene reactions, such as metalation, ethynylation, carbonation or complex formation. To guard against accidental explosion or detonation, work was generally carried out below the critical temperature of acetylene in a suitably designed pressure system, in an isolated building.

Recently, a barricaded reaction system for observing and carrying out reactions in liquid acetylene safely under pressure up to its critical temperature (35°) has been described.[10] Liquid acetylene was exposed to both polar and nonpolar diluents, and also to the action of alkali metal hydroxides to yield a variety of complexes. This reaction system was operated repeatedly during a 10-month period with no explosions or exothermic decompositions noted, and is the basis for new work reported in this publication.

Alkali Metal Acetylide Formation.—Table I shows that alkali metals (either as dispersions or coarse particles) react readily with liquid acetylene in the presence of catalytic to small amounts of ammonia. Sodium could also react with liquid acetylene, in the absence of ammonia, to give a 75% conversion to sodium acetylide in 5.5 hr. However, the reaction rate was considerably enhanced by the presence of ammonia. Essentially quantitative yields of acetylide could be realized in 1–3 hr using reaction loadings of 0.10–0.34 mol of alkali metal, 0.05–0.41 mol of NH_3 and 0.60–1.00 mol of liquid acetylene. Ammonia, used catalytically (0.5 mol of ammonia/g-atom of sodium) still effected a rapid, quantitative conversion to acetylide using a reaction loading of 0.1 g-atom of sodium, 0.60 mol of acetylene and 0.05 mol of ammonia. Similar results were also obtained with trimethylamine, the acetylide being used to synthesize sodium propiolate from Na, liquid C_2H_2 and CO_2 (*cf.* carbonation of sodium acetylide to sodium propiolate).

The use of excess liquid ammonia as a reaction solvent for acetylide formation and ethynylation is well known,[11] but its use as a catalyst in a liquid acetylene system has never been reported. Limited work with potassium and lithium showed that the respective acetylides were also readily formed in liquid acetylene. The lithium derivative, in contrast, disproportionated readily to the carbide (Li_2C_2) on standing at ambient room temperature. However, it is reported to be stabilized effectively by complexing with ethylenediamine.[12] The lower purity values (Table I) obtained for the dry, isolated acetylides, based on evolved acetylene, are believed due to moisture absorption during isolation and analysis. Some slow disproportionation to the carbide derivative on standing is also possible.

When all gaseous products (Table II) derived from the reaction of 0.20 g-atom of Na, 0.90 mol of liquid C_2H_2 and 0.05 mol of NH_3 were subjected to vapor chromatographic analysis for acetylene, ethylene, ethane and hydrogen, no hydrogen was observed, but the total moles of ethylene and ethane formed showed a 99% conversion to sodium acetylide based on eq 6 and 11. This value agreed well with the 98% conversion based on the weight of isolated acetylide (Table I, expt 5). Complete analysis of the total vapor and liquid phases (Table III) gave similar results with only a trace of hydrogen now detected. The above results show conclusively that alkali metal acetylides are formed in high conversion in the liquid acetylene system using a small amount of a basic catalyst.

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TABLE I

PREPARATION OF ALKALI METAL ACETYLIDES IN LIQUID ACETYLENE

Expt no.	Amt, mol: Metal		C_2H_2	NH_3	Reaction: Temp, °C	Pressure, psig	Time, hr	Isolated acetylide: Purity based on Metal	Purity based on C≡CH	Convn based on wt, %
1	0.10	Na	0.60	0.41	8–25	360–400	1.25	96	86	100
2	0.10	Na	0.60	0.10	5–21	400–478	2.5	96	86	102
3	0.10	Na	0.60	0.05	17–25	420–620	3	97	92	102
4	0.20[a]	Na	0.00	0.80	22–24	80–82	2			
5	0.20	Na	0.90	0.05	11–26	540–692	3	*c*		98
6	0.20[b]	Na	0.90	0.05	5–30	610–745	0.5	*d*	73	87
7	0.10	Na	0.45	0.00	21–26	520–560	5.5	*d*	62	75
8	0.10	K[f]	0.60	0.20	26–30	349–380	3	99	85	91
9	0.34	Li[e]	1.00	0.20	18–32	475–598	3			96

[a] Reaction of sodium dispersion with liquid ammonia in the absence of liquid acetylene, to determine if sodamide is formed as a reaction intermediate. No sodamide was formed. [b] Short reaction time; total reaction phases (liquid and gas) analyzed for C_2H_2, C_2H_4 and C_2H_6 by vapor fractometry (*cf.* Table III, expt A). [c] Product not analyzed for NaC_2H. However, vapor fractometry analyses for acetylene, ethylene and ethane material balance shows a 99% conversion to acetylide, which agrees well with 98% conversion based on weight (9.4 g) of isolated acetylide (*cf.* Table II). [d] Incomplete conversion based on isolated yield of acetylide; Na values have no significance hence not reported. [e] Lithium acetylide is not stable. It decomposed to the carbide (Li_2C_2) on standing a total of 7 days and lost weight gradually (10.5 → 6.1 g.) [f] Some loss (undetermined) of potassium sand on transfer and decantation; hence yield obtained is a minimum figure.

TABLE II

SODIUM ACETYLIDE FORMATION.[a] ANALYSIS OF REACTION VAPOR PHASE[b] BY GAS CHROMATOGRAPHY

Time, hr	Temp, °C	Ethane, %	Ethylene, %	Acetylene, %	Hydrogen, %
0[c]	8	0	0	100	0
0.12	28	0	1.5	98.5	0
0.15	0	0.3	2.7	97.0	0
0.50	26	0.3	3.2	96.5	0
1.00	24	0.4	3.5	95.9	0
1.50	22	0.3	3.8	96.0	0
3.00	21	0.5	4.1	95.4	0

[a] Reaction charge: 0.20 mol of Na, 0.90 mol of C_2H_2, 0.05 mol of NH_3 (*cf.* Table I, expt 5), % conversion to NaC_2H, 99%. [b] Only gas phase analyzed by careful venting to an evacuated gas sampling bottle (50 cc). [c] Sample taken 7 min after liquefication of acetylene and prior to ammonia addition. Zero reaction time defined as time of ammonia addition.

TABLE III

SODIUM ACETYLIDE FORMATION. ANALYSIS[a] OF REACTION LIQUID AND VAPOR PHASES BY GAS CHROMATOGRAPHY

	Temp, °C	Time, hr	% H_2	% C_2H_6	% C_2H_4	% C_2H_2	% N_2
A[b]	5–30	0.5	<0.1	0.3	2.4	56.3	41
B[b]	21–26	5.5	0.1	0.3	1.8	60.0	38

[a] Samples A and B were obtained by venting the reaction mixture slowly into a 32.8-l. steel gas tank followed by dilution with nitrogen to a total pressure of 800 mm. Before dilution, sample A exerted 520-mm pressure at 20°, sample B, 475 mm at 19°. [b] Reaction charges: sample A, 0.20 mol of Na, 0.90 mol of C_2H_2, 0.05 mol of NH_3 (*cf.* Table I, expt 6); sample B, 0.10 mol of Na, 0.45 mol of C_2H_2 (*cf.* Table I, expt 7).

Mechanism of Acetylide Formation.—The catalytic effect realized with both ammonia and trimethylamine in acetylide formation is best explained by the anion-radical mechanism shown below.

Support for such a mechanism is the extensive work reported in recent years on the formation and properties of solvated electrons, of which alkali metal–ammonia or amine solutions are prime examples.[13] Also, the reaction of diphenylacetylene (tolan) with alkali metal hydrocarbons in THF has been stated to involve intermediate anion-radical formation.[14]

The almost complete absence of free hydrogen and the formation of ethylene and ethane (Tables II and III) during the reaction also supports such a route. In contrast, acetylide formation in organic solvents[15] is accompanied by a preponderance of hydrogen evolution, although some reduction of acetylene is also noted.

Further, the reaction of sodium with ammonia under identical conditions yielded no sodamide showing this species is not present as a reaction intermediate during metallation in liquid acetylene. Traces of iron salts and air are necessary catalysts for the conversion of sodium to sodamide in liquid ammonia.[16,17] Sodamide, in turn, reacts rapidly with acetylene in liquid ammonia to form sodium acetylide quantitatively.[18] The over-all route to acetylide can be regarded as proceeding through two stages. The first (steps 1–6) accounts primarily for by-product ethylene, while the second (minor route) (steps 7–11) yields ethane.

$$Na\cdot + NH_3 \rightleftharpoons Na^+[NH_3]\cdot^- \quad (1)$$

$$CH{\equiv}CH + Na^+[NH_3]\cdot \rightleftharpoons \underset{I}{\cdot[CH{=}\ddot{C}H]Na^+} + NH_3 \quad (2)$$

$$I + CH{\equiv}CH \longrightarrow \underset{II}{[CH_2{=}\dot{C}H]} + NaC{\equiv}CH \quad (3)$$

$$II + Na^+[NH_3]\cdot^- \longrightarrow \underset{III}{[CH_2{=}\ddot{C}]^-Na^+} + NH_3 \quad (4)$$

$$III + CH{\equiv}CH \longrightarrow CH_2{=}CH_2 + NaC{\equiv}CH \quad (5)$$

Over-all route

$$3CH{\equiv}CH + 2Na \longrightarrow 2NaC_2H + CH_2{=}CH_2 \quad (6)$$

The further reaction of ethylene with ammoniated sodium $[Na^+NH_3]\cdot^-$ will eventually yield ethane (steps 7–11).

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$$Na^+(NH_3)\cdot^- + CH_2{=}CH_2 \longrightarrow {}^-[\dot{C}H_2\dot{C}H_2]Na^+ + NH_3 \quad (7)$$
IV

$$IV + CH{\equiv}CH \longrightarrow [CH_3\dot{C}H_2] + NaC{\equiv}CH \quad (8)$$
V

$$V + Na^+(NH_3)\cdot^- \longrightarrow {}^-[CH_3CH_2]Na^+ + NH_3 \quad (9)$$
VI

$$VI + CH{\equiv}CH \longrightarrow CH_3CH_3 + NaC{\equiv}CH \quad (10)$$

Over-all route

$$2Na + CH_2{=}CH_2 + 2CH{\equiv}CH \longrightarrow 2NaC_2H + CH_3CH_3 \quad (11)$$

Total stoichiometry for both stages

$$5CH{\equiv}CH + 4Na \longrightarrow 4NaC_2H + CH_3CH_3 \quad (6 + 11)$$

The further attack of $Na^+[NH_3]\cdot^-$ on ethylene *via* the second-stage mechanism (steps 7–10) is a minor route compared to the first stage. The amount of ethane experimentally observed (gas chromatography) averages only one-eighth the amount of ethylene produced (Tables II and III).

However, the fact that in the absence of ammonia, ethylene and ethane are still obtained indicates that electron transfer is still possible *via* the direct reaction of sodium with liquid acetylene to yield ion radical I. The rate of this reaction, however, is much slower than that observed with the sodium–ammonia species $[Na^+\text{-}NH_3]\cdot^-$, but steps 2–5 are still possible.

$$Na\cdot + CH{\equiv}CH \longrightarrow Na^+[\dot{C}H{=}\ddot{C}H]^-$$
I

The possible formation of butadiene *via* the dimerization of the acetylene anion radical $\dot{C}H{=}\ddot{C}H^-$ is believed to be an insignificant reaction due to the 99% material balance realized for products such as NaC_2H, ethylene and ethane (steps 1–11). Also its presence was not noted by gas chromatography.

The above mechanism is actually a simplification of a much more complicated solvation process. Both liquid acetylene and ammonia, mutually complexed (H bonded),[10] probably function together to complex and activate such species as $NH_3\cdot^-$, Na^+, $^-\cdot[CH{=}\ddot{C}H]$, $[CH_2{=}\dot{C}H]$, thereby facilitating the entire reaction sequence. Also, the reaction of III with acetylene (step 5) probably involves the transfer of H^+ from acetylene to III. This could be accomplished by the ionization of a C_2H_2–NH_3 complex or by NH_4^+ derived from the complex. The latter possibility is shown in Scheme I.

SCHEME I

$$C_2H_2 + NH_3 = C_2H_2\cdot NH_3 = C_2H^- + NH_4^+$$

$$[CH_2{=}\ddot{C}H]^-Na^+ + C_2H^- = NaC_2H + [CH_2{=}\ddot{C}H]^-$$
III

$$[CH_2{=}\ddot{C}H]^- + NH_4^+ \longrightarrow NH_3 + CH_2{=}CH_2$$

The large amount of hydrogen formed in organic solvents compared to its absence in liquid acetylene in turn indicates the former process involves intermediate radical (H·) formation besides proton transfer. Acetylide formation in organic media is a complicated surface process[15] involving a number of intermediate color changes. Alkali metal dispersions are mandatory, and at no time in the process is a homogenous solution observed. The ready formation of atomic and eventually molecular hydrogen from such active surfaces in organic solvents is believed more likely than in a homogenous liquid acetylene system where even KOH is dissolved[10] by complex formation.

TABLE IV

SODIUM PROPIOLATE FORMATION[a]

Expt no.	Na, g-atom	C_2H_2, mol	CO_2, mol	Cocatalyst, mol	Temp, °C	% conversion
1	0.18	0.90	0.50	0.05[b]	5–23	85
2	0.18	0.90	0.50	0	4–21	34
3	0.075[c]	0.80	0.28	0	−25–15	57
4	0.075[c]	0.40	0.28	0.49[d]	−8–27	55
5	0.18	0.90	0.50	0.05[e]	−9–20	10

[a] All runs used a 2-hr reaction time except expt 3 (1.25 hr). Average pressure range was 300–630 psig (−9 to 27°). [b] Trimethylamine. [c] Sodium acetylide used in place of sodium. [d] Dioxane. [e] Ammonia.

Carbonation of Sodium Acetylide to Sodium Propiolate.—A simple, one-step method for the preparation of sodium propiolate by the interaction of sodium, liquid acetylene and liquid carbon dioxide in the presence of a small amount of trimethylamine (TMA) has been developed.

$$Na + CH{\equiv}CH \xrightarrow{TMA} HC{\equiv}CNa$$

$$Na{-}C{\equiv}CH + CO_2 \longrightarrow HC{\equiv}CCO_2Na$$

The reaction takes place (Table IV, expt 1) under mild conditions (5–23°) during a 2-hr period to give an 85% conversion to sodium propiolate. Sodium and excess liquid acetylene are allowed to react for approximately 30 min in the presence of the cocatalyst, trimethylamine, before introducing liquid carbon dioxide.

Previous methods[19,20] involved the preformation of sodium acetylide in organic solvents (xylene, DMF, dioxane, etc.) or liquid ammonia. Acetylide prepared in organic solvents requires temperatures from 75 to 140°, while the use of liquid ammonia dictates the later removal of ammonia and the use of a substitute solvent before carbonation; otherwise, ammonium carbamate formation predominates. The sodium acetylide–solvent slurry is then transferred to an autoclave for carbonation with gaseous CO_2. Acetylide formed at elevated temperatures is less active, and is often contaminated with sodium carbide (Na_2C_2), which is either converted into by-product acetylenedisodium carboxylate ($CO_2NaC{\equiv}CCO_2Na$) or may be responsible for pyrophoric samples of sodium propiolate obtained when exposed to the atmosphere.

Table IV also shows that in the absence of trimethylamine only a 34–57% conversion is realized (expt 2 and 3), while the use of dioxane as cocatalyst (expt 4) gives no significant improvement (55%) in conversion. Ammonia (expt 5) was actually detrimental to the carbonation (10% conversion) owing to ammonium carbamate formation.

The interaction of liquid CO_2 and trimethylamine (TMA) under pressure at 5–20° was observed to yield a solid complex which decomposed as the pressure was released (*cf.* Experimental Section). This intermediate

(19) L. N. Owen, *et al.*, *J. Chem. Soc.*, **3**, 111 (1949).
(20) A. N. Kurtz, (to Union Carbide Corp.), U. S. Patent 3,211,662 (1963); Belgian Patent 63,6771 (1963).

TMA–CO_2 complex (probably soluble in liquid acetylene) may be an activated species involved in the rapid, low-temperature carbonation of sodium acetylide.

Experimental Section

Apparatus.—A reaction system for safely liquefying and handling acetylene was described previously.[10] The reactor used in the following experiments was a 125-cc stirred autoclave equipped with jacketed walls through which a heat exchange fluid (methanol) was circulated to control the reactor temperature.

Acetylene was added to the autoclave (usually at −30 to 0°) from a calibrated buret after assembling and pressure testing the equipment. Other materials (gases, liquefied gases, liquids) were introduced *via* standard techniques from pressure burets also calibrated and equipped with needle valves allowing accurate control of addition rates and quantities of materials added.

Solids, slurries, etc., were charged into the autoclave before assembling. In all cases the autoclave and the entire pressure system were purged with N_2 and dried thoroughly before each run. The heating–cooling system has already been described.[10]

Preparation of Alkali Metal Acetylides in Liquid Acetylene.—Acetylene was added to the alkali metal (dispersion in light mineral oil, or a freshly prepared sand in xylene) at various temperatures and pressures as shown in Table I. At −5°, the desired amount (by volume) of liquid ammonia was added (5–10 min). The mixture was allowed to warm gradually, until a mildly exothermic reaction occurred raising the reaction temperature to about 17°. Cooling for approximately 2 min was sometimes necessary to hold the temperature below 20°. The mixture was stirred from 1.25 to 5.5 hr during which time it slowly warmed to room temperature.

Hexane (50 ml) was introduced followed by slowly bleeding off the gases. The hexane slurry was removed, and the mixture centrifuged to separate hexane from the acetylide. Unnecessary exposure of the product to air and moisture was avoided during the isolation step. The solid was washed with hexane, followed by drying at room temperature in a vacuum desiccator. Products were analyzed for total alkali metal and acetylenic hydrogen content by well-known procedures.[21]

Reaction of Sodium and Acetylene in the Presence of Ammonia and Analysis of the Gases Bled Off.—The procedure described above for the preparation of sodium acetylide in the presence of ammonia was followed. Sodium dispersion (0.2 g-atom), liquid acetylene (0.9 mol) and ammonia (0.05 mol) were stirred 3 hr at 11–25° (540–692 psig). During this time gas samples were taken and analyzed by gc (20% dimethylsulfolane on Gas-Chrom-R) for ethane, ethylene and acetylene (see Table II). Retention times at ice–water temperature were ethane, 5 min; ethylene, 5.5 min; acetylene, 12 min. Hydrogen content was checked by gc using a column packed with 5A Molecular Sieves at room temperature (retention time 1 min).

A run was carried out reacting sodium (0.2 g-atom), acetylene (0.90 mol) and ammonia (0.05 mol) for 0.5 hr at 5–30° (610–745 psig). The entire gas content was collected in a 32.8-l. tank and analyzed by gc (see Table III, run A).

A run was carried out reacting sodium (0.10 g-atom) and acetylene (0.45 mol), in the absence of ammonia, for 5.5 hr at 21–26° (520–560 psig). The entire gas content was collected in a 32.8-l. tank and analyzed by gc (see Table III, run B).

Formation of Sodium Propiolate Starting with Sodium Dispersion in the Presence of Trimethylamine.—Sodium dispersion (12 cc, 0.178 g-atom, 40% in mineral oil), acetylene (45 cc, 0.9 mol), and trimethylamine (4.7 cc, 0.05 mol) were warmed from −5° to room temperature and stirred 0.5 hr. Occasional cooling was necessary to maintain room temperature. At 2–12° liquid CO_2 (37 cc, 0.5 mol) was added over a 15-min period. The mixture was stirred 2 hr during which time the temperature rose slowly to 23°.

The gases were bled off. The solid was washed with hexane to remove the small quantity of mineral oil, then dried in a vacuum oven at 40°. The weight of finely divided, light brown powder was 15.1 g. By analysis it contained 27.2% total sodium, 92.3% sodium propiolate and 4.4% sodium acetylide. No free sodium was detected. Conversions, based on total sodium, to sodium propiolate and sodium acetylide were 84.7 and 7.3%, respectively.

In the Absence of Ammonia or Trimethylamine.—Sodium dispersion (12 cc, 0.19 g-atom) and liquid acetylene (45 cc, 0.9 mol) were stirred 0.5 hr at room temperature. At 5–10° liquid carbon dioxide (37 cc, 0.5 mol) was added over a 0.5-hr period. The mixture was stirred 2 hr allowing the temperature to increase slowly to 21°.

The solid product was washed with hexane and pumped dry (weight 13.4 g). Free sodium was present because sparks could be seen when a small quantity of the solid was sprinkled on water. The solid contained 32.7% total sodium (partly as free metal), 11.8% sodium acetylide and 47.8% sodium propiolate. Based on total sodium the conversions to sodium acetylide and sodium propiolate were 17.3 and 33.7%, respectively.

Carbonation of Sodium Acetylide in Liquid Acetylene.—Sodium acetylide (79% pure, 3.6 g, 0.059 mol) was placed in the autoclave followed by closing and pressure testing with N_2. At −40° liquid acetylene was added (40 cc, 0.8 mol). Over a period of 15 min and at −25° liquid carbon dioxide (30 cc, 0.4 mol) was added. The mixture was stirred 1.25 hr at 8–15°, followed by bleeding off the gases.

The solid product weighed 5.8 g and contained 54% sodium propiolate and 4.5% unreacted sodium acetylide. The conversion to sodium propiolate, based on sodium acetylide used, was 57%. The recovery of sodium acetylide was 10.0%.

Registry No.—Acetylene, 74-86-2.

(21) L. Barnes, Jr., and L. J. Molinini, *Anal. Chem.*, **27**, 1025 (1955).

The Kinetics of the Hydrogenation of Cycloalkenes on Palladium–Alumina Catalysts[1]

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Reaction rates for the hydrogenation of bicyclo[2.2.1]heptene, cyclopentene, cyclohexene, cycloheptene, and cyclooctene from solution in cyclohexane on alumina-supported palladium catalysts are reported. The observed rates at 25.0° near 1 atm are first order in catalyst but they exhibit a fractional order dependence both upon the concentration of the cycloalkene and also upon the hydrogen pressure. The apparant activation energy for cyclohexene is 5.7 ± 0.5 kcal mol^{-1}. The fractional order dependence of the rates upon the cycloalkene concentration is explained in terms of a reversible chemisorption of the alkene, while the fractional order dependence upon hydrogen pressure is viewed to reflect an intrinsic zero-order dependence upon which is superimposed a first-order pore diffusional process involving hydrogen.

We have recently reported on the kinetics of the hydrogenation of a number of cycloalkenes from solution in cyclohexane using alumina-supported platinum catalysts near room temperature and hydrogen pressures near 1 atm.[2] Very considerable care was found to be essential to guarantee the absence of catalyst-poisoning impurities; otherwise the reaction rates were not reproducible. These reactions with platinum catalysts were found to be first order in hydrogen pressure and in the amount of catalyst added, but to be zero order in cycloalkene concentration. These findings led us to modify the Horiuti–Polanyi mechanism[3] for hydrogenation at platinum surfaces to have chemisorption of the alkene irreversible.

Our attention quite naturally turned to palladium catalysts. These are about as popular as platinum catalysts for the hydrogenation of nonaromatic carbon unsaturation. Indeed, for nonconjugated double bonds the two catalysts are often used interchangeably. The two are, however, quite different in several ways. Palladium is very selective in promoting the stepwise addition of pairs of hydrogen atoms to alkynes, allenes, and 1,3-dienes while platinum is not.[4] Platinum, on the other hand, promotes the isomerization only of exceptional alkenes under hydrogenation conditions;[2] in contrast, isomerization of alkenes on palladium is extensive and is even appreciably faster than hydrogen addition with some.[5] Likewise, the two catalysts differ considerably in stereochemical specificity where *cis*- and *trans*-dialkylcycloalkanes can be formed,[5a,b] in their ability to exchange deuterium for protium in alkenes and alkanes,[6] and in their promotion of the disproportionation of cyclohexenes.[7]

The reason for such differences in catalytic activity is obscure. One inference is that the details of the surface reactions which take place on these two catalysts differ considerably at the least; it is possible that there are fundamental differences in the surface reactions on the two catalysts.

A knowledge of the kinetics of a reaction being an important component of any meaningful discussion of its mechanism, we report here the results of kinetic studies of hydrogen addition to cycloalkenes from the liquid phase at palladium surfaces. These are counterpart to our earlier studies using platinum catalysts.[2]

Experimental Section

The Apparatus.—The hydrogenation apparatus used in this study was that developed for studies using platinum catalysts.[2]

Catalysts.—Hot aqueous solutions of *trans*-dinitrodiammine-palladium(II),[8] which had been several times recrystallized from water, were stirred for several hours with η-alumina[9] on the steam bath, following which the impregnated supports were filtered at the water pump and dried at 100°. These were then heated in a stream of oxygen in a muffle furnace, cooled under high purity nitrogen, and activated with purified electrolytic hydrogen at 350° as before.[2]

Two 150–200 mesh alumina supports were used in the research reported here. One had a surface of 208 m^2 g^{-1}; the other, 227 m^2 g^{-1}. Both were prepared by the method of Selwood[10] but the higher surface support was washed exhaustively with *hot* distilled water before being fired. This support also differed from the lower surface one by having much less alkaline material (traces *vs.* 2%) which could be extracted by boiling water.

One catalyst used in this research (PDG-1) was prepared using the lower area support. It had 0.74% palladium[11] but was appreciably less active than a second (PDG-2) which was prepared from the higher area support. The metal content of the latter as only 0.57%.

Solvents and Substrates.—The same painstaking care as before[2] was found to be required for the observed rates to be reproducible. If anything, these palladium catalysts are even more sensitive to catalyst-poisoning impurities than the platinum catalysts used in the previous study.

Catalyst and Cycloalkene Dependence.—In a typical experiment, 21.64 ± 0.05 mg of PDG-1 catalyst was placed in the reaction flask. The system was evacuated and flushed five times with hydrogen, then the hydrogen pressure was set near 760 mm, and 0.700 ± 0.005 ml of highly purified[2] cyclohexane was injected *via* the entry port. After 20-min agitation to equilibrate the catalyst and to attain temperature equilibrium at 25.0 ± 0.1°, 0.080 ± 0.005 ml of high purified[2] cyclohexene was added. The pressure was readjusted close to 760 mm, agitation was begun, and hydrogen volumes were noted and recorded at 30-sec intervals.

(1) We make grateful acknowledgment for support of this research from the National Science Foundation (GP 4656).

(2) A. S. Hussey, G. W. Keulks, G. P. Nowack, and R. H. Baker, *J. Org. Chem.*, **33**, 610 (1968).

(3) M. Polanyi and J. Horiuti, *Trans. Faraday Soc.*, **30**, 1164 (1934).

(4) See W. G. Young, R. L. Meier, J. Vinograd, H. Bollinger, L. Kaplan, and S. L. Linden, *J. Amer. Chem. Soc.*, **69**, 2046 (1947). See also E. F. Meyer and R. L. Burwell, Jr., *ibid.*, **85**, 2877 (1963).

(5) (a) S. Siegel and G. V. Smith, *ibid.*, **82**, 6087 (1960); (b) J-F. Sauvage, R. H. Baker, and A. S. Hussey, *ibid.*, **83**, 3874 (1961); (c) G. V. Smith and J. R. Swoap, *J. Org. Chem.*, **31**, 3904 (1966); (d) A. W. Weitkamp, *J. Catal.*, **6**, 431 (1966).

(6) See (a) E. F. Meyer and C. Kemball, *J. Catal.*, **4**, 711 (1965), and (b) K. Schrage and R. L. Burwell, Jr., *J. Amer. Chem. Soc.*, **88**, 4549 (1966), for recent examples.

(7) A. S. Hussey, T. A. Schenach, and R. H. Baker, *J. Org. Chem.*, **33**, 3258 (1968).

(8) N. L. Cull and H. B. Jonassen, *Inorg. Syn.*, **4**, 179 (1953).

(9) H. C. Stumpf, A. S. Russell, J. W. Newsome, and C. M. Tucker, *Ind. Eng. Chem.*, **42**, 1398 (1950); see also H. Pines and W. O. Haag, *J. Amer. Chem. Soc.*, **82**, 2471 (1960).

(10) P. W. Selwood, *Advan. Catal.*, **3**, 41 (1951).

(11) We are indebted to Dr. G. R. Lester, Universal Oil Products Co., Des Plaines, Ill., for the determination of the palladium content of these catalysts and the pore distribution in the supports.

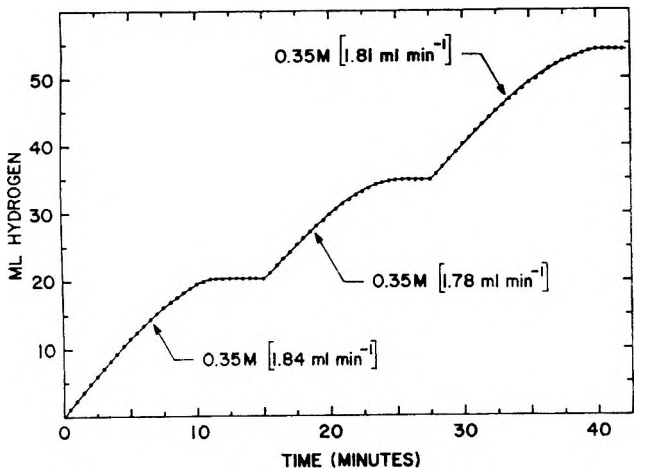

Figure 1.—Rate of hydrogen absorption: cyclohexene in cyclohexane; 21.64 mg of 0.74% Pd catalyst; 25.0°; 760 ± 1 mm. Initial concentrations: (a) 1.07 *M*; (b) 0.70 *M*; (c) 0.085 *M*.

When the hydrogenation of this first sample was complete, a second sample of 0.060 ± 0.005 ml of cyclohexene was injected and its hydrogenation was followed as above. A third 0.080 ± 0.005 ml sample of cyclohexene was then injected and the course of its hydrogenation was followed in the same way. These data are presented in graphical form in Figure 1, and the results from a number of experiments with cyclohexene as the substrate are presented in Table I. The data from experiments where poisoning was extensive (relatively very slow rates) were discarded. The data from experiments in which the hydrogen absorption rates for the second and third samples were appreciably slower than the rate for the first sample were also discarded because such a progressive slowing of rate reflects the accumulation of catalyst-poisoning impurities.[2]

The initial specific rates for hydrogen addition to the several cycloalkenes are summarized in Table II.

Pressure and Temperature Studies.—Similar three-sample experiments were employed in pressure and temperature studies. However, many of the pressure dependence studies were also carried out with a single 0.300 ± 0.005 ml sample of the cycloalkene in 0.300 ± 0.005 ml of cyclohexane. Reaction rates were observed at two or three *increasing* total pressure settings, one of which was near 760 mm. When somewhat slow rates were observed near 760 mm, the rates at the several pressures were normalized by this factor. Data from experiments where poisoning was extensive were discarded.

Typical data for the pressure dependence studies are summarized in Figure 2 and in Table III.

The initial rates of reaction of cyclohexene at different temperatures (Table IV, first sample of three-sample experiments) have been corrected for the change in solubility of hydrogen in cyclohexane with temperature[12] and for the change in the partial pressure of hydrogen in the reaction flask which results from the change in vapor pressure of cyclohexane with temperature.[13] From the slope of a log rate *vs.* T^{-1} plot the apparent activation energy is calculated to be 5.7 ± 0.5 kcal mol^{-1}.

Deuterium Addition.—A solution of 0.30 ml of cyclohexene in 0.60 ml of cyclopentane with 10.24 mg of PDG-2 catalyst was shaken under 1 atm of deuterium (99.7%) for 50 sec. The material was flash evaporated (liquid nitrogen trap) and then separated into solvent, cyclohexane (3.4%), and cyclohexene (96.6%) by glpc. Mass spectrometric analysis (Consolidated Electrodynamics Model 21-104, 15-V ionization potential) furnished parent peak data from which the deuterium distributions were calculated (corrected for natural abundance of hydrogen and carbon isotopes): cyclohexane, d_0 (17.2), d_1 (37.4), d_2 (38.9), d_3 (4.16), d_4 (1.25), d_5 (0.50), d_6 (0.24), d_7 (0.12), d_8 (0.07), d_9 (0.06), d_{10} (0.03), d_{11} (0.02), d_{12} (0.01), d_{av} (1.39); cyclohexene, d_0 (96.7), d_1 (2.8), d_2 (0.3), d_3 (0.2), d_4 (trace), d_{av} (0.40).

(12) P. Frohlich, E. J. Tauch, J. J. Hogan, and A. A. Peer, *Ind. Eng. Chem.*, **23**, 548 (1931); see also M. W. Cook, D. N. Hanson, and B. J. Alder, *J. Chem. Phys.*, **26**, 748 (1957).

(13) "International Critical Tables," Vol. III, 1928, p 222.

TABLE I

INITIAL RATES OF HYDROGENATION OF CYCLOHEXENE USING PALLADIUM CATALYSTS[a]

Pressure, mm	Catalyst, mg	Rate, ml min^{-1}	Specific rate[b]
	PDG-1[c]		
756	9.39	1.17	73
765	10.12	1.17	69
753	12.59	1.49	69
760	12.77	1.44	66
750	13.47	1.70	73
750	15.53	1.80	67
756	18.96	2.23	69
753	25.15	2.90	67
750	34.50	4.45	75
			Av 70 ± 3[d]
	PDG-2[e]		
757	8.81	2.36	204
763	10.47	2.39	175
758	10.98	3.00	208
762	11.75	3.19	208
763	12.08	2.82	179
761	12.92	3.11	184
762	13.20	3.60	208
			Av 195 ± 14[d]

[a] From solution in cyclohexane, 25.0 ± 0.1°. [b] Rates expressed as mol min^{-1} g-atom^{-1}. [c] 0.74% Pd. [d] Standard deviation. [e] 0.57% Pd.

TABLE II

INITIAL RATES OF HYDROGENATION OF CYCLOALKENES USING PALLADIUM CATALYSTS[a]

Cycloalkene[b]	Initial rate[c,d] PDG-1[e]	PDG-2[f]
Bicyclo[2.2.1]heptene	450 ± 20 (2)	
Cyclopentene	129 ± 10 (9)	400 ± 20 (4)
Cyclohexene[g]	70 ± 3 (9)	195 ± 14 (7)
Cycloheptene	66 ± 4 (4)	218 + 12 (3)
Cyclooctene	4.0 ± 0.2 (4)	18 ± 1 (2)

[a] From solution in cyclohexane, 25.0 ± 0.1°, 760 ± 5 mm total pressure. [b] Concentration ~1 *M*. [c] Number of experiments in parentheses. [d] Rates expressed as mol min^{-1} g-atom^{-1}. [e] 0.74% Pd. [f] 0.57% Pd. [g] Apparent activation energy, 5.7 ± 0.5 kcal mol^{-1}.

Results

The collection of the rate data reported here has been beset with the frustrating experimental problem of the necessity for the complete exclusion of rate-slowing impurities. The palladium catalysts appear to be even more sensitive to trace impurities than were the platinum catalysts used in our previous kinetic study. Moreover, when platinum catalysts are used, the rates of hydrogenation are zero order in cycloalkene concentration; hence a divergence of the rate plots from linearity immediately signals the presence of rate-slowing impurities.[2] The rates of hydrogenation of cycloalkenes at palladium surfaces, however, are functions of their concentrations. Consequently, as the rate plots have an inherent curvature (Figure 1), traces of catalyst poisons simply superimpose some additional curvature to these plots and the presence of poisons is not immediately obvious.

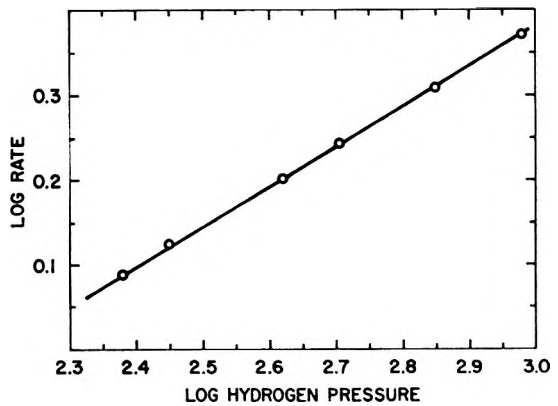

Figure 2.—Dependence of initial hydrogen absorption rate on hydrogen pressure: cyclooctene in cyclohexane; 0.57% Pd catalyst, 25.0°; concentration ≥ 1 *M*. (Rate in ml of H_2 min^{-1} g of $catalyst^{-1}$ at STP.)

TABLE III

KINETICS FOR THE HYDROGENATION OF CYCLOALKENES ON ALUMINA-SUPPORTED PALLADIUM CATALYSTS[a]

rate = k[cycloalkene]^m[P_{H_2}]^n

	Catalyst			
	PDG-1[b]		PDG-2[c]	
Cycloalkene	m	n	m	n
Bicyclo[2.2.1]-heptene	0.20 ± 0.05	~1		
Cyclopentene	0.26 ± 0.05	0.57 ± 0.05	0.26 ± 0.05	0.56 ± 0.05
Cyclohexene	0.34 ± 0.05	0.45 ± 0.05	0.33 ± 0.05	0.47 ± 0.05
Cycloheptene	0.27 ± 0.05	0.43 ± 0.05	0.33 ± 0.05	0.48 ± 0.05
Cyclooctene	0.23 ± 0.05	0.23 ± 0.05	0.24 ± 0.05	0.48 ± 0.05

[a] From solution in cyclohexane at 25.0 ± 0.1°. Initial concentration ≥ 1 *M*. [b] 0.74% Pd. [c] 0.57% Pd.

TABLE IV

TEMPERATURE COEFFICIENT FOR THE HYDROGENATION OF CYCLOHEXENE ON PALLADIUM[a]

$1/T \times 10^3$	Log rate[b,c]
3.47	1.889
3.36	2.058
3.30	2.112
3.25	2.177
3.20	2.243
3.14	2.276

[a] From solution in cyclohexane. [b] At STP, ml of hydrogen min^{-1} g of $catalyst^{-1}$, corrected for change of hydrogen solubility and hydrocarbon partial pressure with temperature. [c] Using 0.74% Pd catalyst (PDG-1).

In the platinum-catalyzed study,[2] a sample-bracketting procedure allowed us to compare the rates of hydrogenation of the several alkenes with considerable confidence because it was so easy to tell when rate-slowing impurities were present. However, in the studies reported here using palladium catalysts, the presence of such impurities is not obvious (except when it is extensive) until the data have been analyzed. As a consequence we found it impractical to use the sample-bracketting procedure which we had used before. Rather, we have resorted to a three-successive-sample procedure through which the presence of rate-slowing impurities is detectable because of its cumulative effect on the rates observed for the second and third samples.

Because we were not able immediately to detect the presence of traces of rate-slowing impurities, the total data collected for the palladium-catalyzed hydrogenations are somewhat less precise than those which were obtained using platinum. We have, in effect, collected hydrogen absorption data which converge toward the maximum rate of a completely poison-free system. In the experiments where poisoning was extensive the initial rates were relatively very slow, tending toward one-half the fastest initial rates. Apparently, about one-half of the catalytic activity of these palladium catalysts is very sensitive to such poisons but the remainder of the catalytic activity is much less sensitive. These slow initial rate data were discarded.

Where the presence of poisons was not immediately obvious, the rates observed for the first sample tended to fall into the lower range of a group of very fast initial rates, but the rates for the second and third samples became progressively slower. We therefore applied the requirement that the initial rates of the second and third samples be very close to that of the first. This criterion allowed us to identify experiments in which rate-slowing impurities were significant. We were then able to discard all of the low values in the high-rate group in good conscience, leaving the edited data which are summarized in Table I and II. The initial rates (mol min^{-1} $g\text{-}atom^{-1}$) are the slopes of the tangents of rate plots of the experimental data at the beginning of the hydrogenations when hydrogen absorption rates are nearly linear. We summarize them in this form in Table II simply for convenient comparison with the specific rates reported earlier for platinum catalysts.[2]

Dependence of Rate on Amount of Catalyst.—The data of Table I include initial rates using a range of catalyst weight from *ca.* 5 to 35 mg. The rates are clearly first order in the amount of catalyst and, within experimental error, doubling the amount of catalyst doubled the initial rate of hydrogen absorption. Likewise the slopes of tangents at equal cycloalkene concentrations along the curving hydrogen uptake plots (Figure 1) gave rates which were first order in the amount of catalyst. Thus, neither hydrogen transport from the gas phase into the liquid phase nor diffusion of hydrogen through the solution to the catalyst surface[2,14] limits the rates which we observe under our experimental conditions. The possibility of diffusional limitations within the catalyst pores remains, however. It will be discussed later.

Notice that it would probably not be possible to hydrogenate bicyclo[2.2.1]heptene using our more active PDG-2 catalyst without imposing serious hydrogen transport or hydrogen diffusion limitations on the rates of hydrogen absorption observed.

Dependence on Substrate Concentration.—From rate data such as that presented in Figure 1 one can obtain values for the exponent m in the rate expression

$$\text{rate} = k[\text{E}]^m[P_{H_2}]^n[\text{catalyst}] \quad (1)$$

where k is the rate constant for the over-all reaction, $[\text{E}]^m$ is the molar cycloalkene dependence, and $[P_{H_2}]^n$ is the hydrogen dependence. These values for m are summarized in Table III. They are about 0.3 and

(14) H. S. Davis, G. Thomson, and G. S. Crandall, *J. Amer. Chem. Soc.*, **54**, 2340 (1932); H. C. Yao and P. H. Emmett, *ibid.*, **81**, 4125 (1959).

are not greatly different. These data *for a particular hydrogen pressure* can be accommodated by Langmuir–Hinshelwood kinetics and the rate expression

$$\text{rate} = k'K_E[E]/(1 + K_E[E] + K_H[H_2]) \quad (2)$$

where k' is the over-all rate constant at the particular hydrogen pressure, K_E is the chemisorption constant of the alkene, [E] is its molar concentration, K_H is the chemisorption constant for hydrogen from solution, and $[H_2]$ is its molar concentration. The kinetics do not allow a choice between eq 2, however, and a simpler rate expression

$$\text{rate} = k'K_E[E]/(1 + K_E[E]) \quad (3)$$

which assumes that hydrogen does not interfere with the chemisorption of alkene.

Dependence of Rate on Hydrogen Pressure.—The data from experiments using cyclooctene and our PDG-2 catalyst are summarized in Figure 2 which is a plot of log initial rate *vs.* log P_{H_2}. The slopes of such plots for the several cycloalkenes give values for n, the order of hydrogen in rate expression 1. These values are also summarized in Table III where the rates are seen to vary within experimental error with the square root of hydrogen pressure, except for bicycloheptene and cyclooctene using PDG-1 catalyst.

Discussion

Dependence of Rate on Substrate Concentration.—We have earlier proposed that the kinetics of hydrogen addition and the nonintervention of isomerization in the face of extensively isotopically exchanged cycloalkane are best accommodated by a chemisorption of cycloalkenes on platinum surfaces which is effectively irreversible.[2,15] A reversible chemisorption of cycloalkenes on palladium surfaces, in accord with rate expression 2 or 3, would seem at first to offer a satisfactory explanation for the extensive isomerization which intervenes when palladium is the hydrogenation catalyst. It would also seem to explain the difference in stereochemical consequences with palladium compared with platinum catalysts.[5]

It has been pointed out,[16] however, that very different assumptions about the mechanism of a sequence of reactions taking place at the surface of solid catalyst, such as we deal with here, often lead to rate expressions which are of identical mathematical form as expressions

$$H_2 + 2^* \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} 2H^*$$

$$E + 2^* \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} E^{**} \text{ (diadsorbed alkane)}$$

$$E^{**} + H^* \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} 2^* + HE^* \text{ (monoadsorbed alkane)}$$

$$HE^* + H^* \underset{k_{-4}}{\overset{k_4}{\rightleftharpoons}} H_2E + 2^*$$

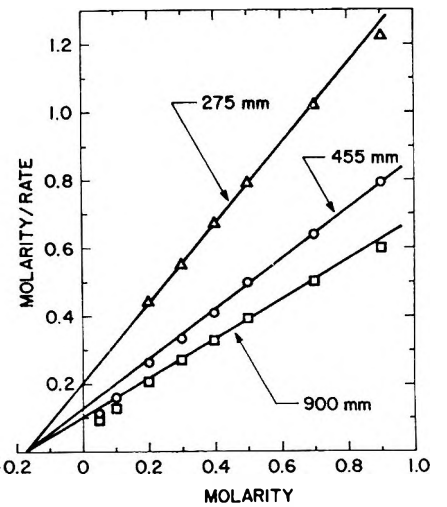

Figure 3.—Plots of cyclohexene molarity/rate *vs.* cyclohexene molarity in cyclohexane: 0.74% Pd catalyst; 25.0°. (Rate in mol sec^{-1} g-$atom^{-1}$.)

2 and 3. Hence it is not possible to make a choice among the several alternatives on the basis of the kinetic data alone and we must call upon other information in order to be able to refine the general model[17] so that it is accord with the details of palladium-catalyzed hydrogenations.

First, it has been shown conclusively that cycloalkanes do not dissociatively chemisorb on palladium catalyst under our conditions;[5a,b] hence the addition of the second hydrogen (associative desorption of cycloalkane) can be regarded to be irreversible. Second, the very extensively exchange product which is formed when deuterium is used (see Experimental Section and ref 5d) is compelling evidence that the addition of the first hydrogen is highly reversible. Third, the appearance of HD in the gas phase shows that hydrogen adsorption is also. We are then left only with the questions (1) whether adsorption of alkene is reversible or not and (2) whether alkene and hydrogen compete with one another in the adsorption process.

Let us ignore the question of the reversibility of alkene chemisorption for the moment to consider a variation of the general Horiuti–Polanyi model for hydrogen addition in which the adsorptions of hydrogen and alkene are independent of one another, and the addition of the first hydrogen is highly reversible but the addition of the second hydrogen is irreversible in accord with the discussion above. A steady-state treatment based on these assumptions leads to eq 4

$$\text{rate} = \frac{k_2k_3k_4[E]\Theta_H^2}{k_2[E](k_{-3} + k_3\Theta_H + k_4\Theta_H) + k_3k_4\Theta_H^2 + k_{-2}k_{-3} + k_{-2}k_4\Theta_H} \quad (4)$$

if chemisorption of alkene is reversible. The last two terms in the denominator disappear if chemisorption of alkene is irreversible, but in either event eq 4 is of the same mathematical form as eq 2 and 3. At constant pressure, the fraction of the surface occupied by hydrogen, Θ_H, would be constant in this model and,

(15) A. S. Hussey, R. H. Baker, and G. W. Keulks, *J. Catal.*, **10**, 258 (1968).

(16) M. Boudart, "Kinetics of Chemical Processes," Prentice-Hall, Inc., Englewood Cliffs, N. J., 1968, p 104.

(17) M. Polanyi and J. Horiuti, *Trans. Faraday Soc.*, **30**, 1164 (1934).

if eq 4 is rearranged to eq 5 it is seen that a plot of

$$[\mathrm{E}]/\mathrm{rate} = \left[\frac{k_{-3} + k_3\Theta_\mathrm{H} + k_4\Theta_\mathrm{H}}{k_3k_4\Theta_\mathrm{H}^2}\right][\mathrm{E}] + \left[\frac{1}{k_2} + \frac{k_{-2}(k_{-3} + k_4\Theta_\mathrm{H})}{k_2k_3k_4\Theta_\mathrm{H}^2}\right] \quad (5)$$

[E]/rate *vs.* [E] should be linear with quite different intercepts depending upon whether adsorption of alkene is reversible or irreversible. If the latter obtains and $k_2 \gg 1$, the intercept will be at the origin. This is true for platinum-catalyzed systems[2] where $k_2 \gg k_{-2}$. If adsorption is reversible, k_{-2} will be finite and the intercept will be positive.

The data for cyclohexene at three different hydrogen pressures are plotted in this way in Figure 3, where the plots are seen to be linear, except at very low concentrations, and the intercepts to be positive. Notice, furthermore, that the data for the three pressures extrapolate to a common intercept with the abscissa in accord with an adsorption of alkene which is independent of the adsorption of hydrogen. The departure from linearity at low concentration may come about because Θ_H is not independent of [E]. However, we prefer an alternate explanation which will be discussed in the next section, and we propose that the hydrogen addition reaction in palladium-catalyzed systems near 1 atm involves reversible adsorptions of hydrogen and alkene which are independent of one another, a reversible addition of the first hydrogen, and an irreversible addition of the second.

The Depencence of Rate on Hydrogen Pressure and the Question of Pore Diffusion Limitations.—The empirical dependence of the observed rates on the square root of hydrogen pressure (Table III) is a matter of concern because such a dependence can be interpreted to mean that the rate-determining step of the sequence is the addition of the first hydrogen atom. The transition state for such a rate-critical step would include a *single* hydrogen atom, whence a square-root dependence on hydrogen pressure logically follows. Such an interpretation is quite at odds with our assumptions in the model which we have developed in the preceding section. Fortunately, an alternate explanation for the observed rate dependence is available.

When a catalyst with an extensive internal pore structure is used, diffusion within the torturous pores may limit the availability of reactants at the internal catalytic surfaces.[18] In our system the deficient reactant will certainly be hydrogen because its concentration in the bulk solution is so small relative to that of the cycloalkene.[13] Diffusion being a first-order process with a small activation energy, the observed orders for reaction will tend toward unity and the observed activation energies will tend to be small[19] when diffusion limitations are superimposed. Thus an intrinsic zero-order reaction will tend toward half order and half-order reactions will tend toward three-quarters order, etc. Consequently, we are led to interpret the hydrogen dependence which we observe to reflect an *intrinsic zero-order process* upon which a first-order hydrogen pore diffusion process is superimposed.

We have no single piece of unequivocal evidence to support the imposition of pore diffusion limitations upon the observed rates in these experiments but there are several implications within our experimental data which lend support. The total effect of these arguments is rather convincingly in favor of this explanation for the hydrogen dependence which is observed.

First, the very extensive exchange observed when cyclohexene is deuterated[17] would seem to require the formation of monoadsorbed alkane to be reversible. Second, the Thiele moduli and the Weisz moduli[18] as estimated from our particle size (150–200 mesh), surface areas (>200 $m^2\,g^{-1}$), pore volumes (>2.5 $cm^3\,g^{-1}$), D_eff for hydrogen (0.5 to 7.5 $\times$ 10^{-5} $cm^2\,sec^{-1}$),[19,20] and the reaction rates (Table II) are several times larger than the maximum values below which diffusional effects can be ignored.[18] Third, the apparent activation energies are small.[19] Fourth, the hydrogen dependence falls to about one-quarter order when *slowly* hydrogenated cyclooctene is hydrogenated using our *less active* PDG-1 catalyst, but appears to approach first order when very rapidly hydrogenated bicycloheptene is the substrate (Table III).

Pore diffusional limitations are most convincingly demonstrated to be present by using catalyst particles of successively smaller size. We are not able mechanically to reduce our particle size without exposing the catalyst to rate-slowing impurities. It is possible, however, literally to explode particles of strong adsorbants by suddenly exposing them to materials which strongly adsorb on them[21] and when 1.0 to 2.0 μl of water is added in the course of a hydrogenation experiment such as that summarized in Figure 1, the rates are observed to increase. The effect is variable but is often as much as 80%.[22] The same effect is observed with acetic acid and with methanol, but not with 1,4-dioxane, and a second addition of protic solvents causes the rates to decrease. This effect seems likely to be the result of a breaking open of the catalyst particle to expose more metal surface to the reactants.

Finally, the rates of hydrogenation become much slower when the cycloalkene is nearly completely reduced (Figure 1). If pore diffusional effects are indeed involved in the initial fast rates, the hydrogen deficiency within the pores should become progressively less pronounced toward the end of the reaction. That is to say, more and more of the catalytic surface in the interior of the particle should be able to participate, up to the point where cycloalkene diffusional effects begin to be encountered. Accordingly, the rate of decrease of rate with cycloalkene concentration toward the end of the reaction should be less than that predicted by rate expressions 2, 3, and 4. Hence the existence of a pore diffusion effect is an alternate explanation for the divergence of the plots of Figure 3 from linearity.

We believe that the weight of the evidence supports

(18) C. N. Satterfield and T. K. Sherwood, "The Role of Diffusion in Catalysis," Addison-Wesley Publishing Co., Inc., Palo Alto, Calif., 1963, pp 56–71.

(19) The activation energy for the diffusion of hydrogen in cyclohexane is 2.9 kcal mol^{-1}: N. E. Khazamora and L. R. Linshitz, *Khim. Prom.*, (8), 579 (1963). See *Chem. Abstr.*, **60**, 2348*d* (1964).

(20) See ref 18, pp 11–30.

(21) D. H. Bangham, *Proc. Roy. Soc.*, **A147**, 175 (1934).

(22) We had observed this phenomenon before when bicyclo[2.2.1]heptene was hydrogenated using our platinum catalysts.[2] After the catalysts had been used to hydrogenate this very forcefully chemisorbed alkene, they often showed *increased* activity in the hydrogenation of cyclohexene. At that time we had no understanding of why this should be so.

the contention that a pore diffusional effect superimposed on an intrinsic zero-order dependence is responsible for the square-root hydrogen dependence which is observed. A zero-order dependence on hydrogen pressure is quite consistent with hydrogen/palladium ratios of ~0.6 near 1 atm at 25°.[23] The palladium crystallites at the exterior of the support, and those close to it, can be regarded to be reservoirs of hydrogen. It follows that a zero-order hydrogen dependence should be observed on palladium films but we do not have any evidence to this point.

Registry No.—Bicyclo[2.2.1]heptene, 498-66-8; cyclopentene, 142-29-0; cyclohexene, 110-83-8; cycloheptene, 628-92-2; cyclooctene, 931-88-4; cyclohexane, 110-82-7.

(23) F. A. Lewis, "The Palladium Hydrogen System," Academic Press, New York, N. Y., 1967, p 4.

Base-Catalyzed Intermolecular Condensation of α,β-Unsaturated Ketones. Self-Condensation of Styryl Isobutyl Ketone to Epimeric Diketones, $C_{26}H_{32}O_2$, and a Triketone, $C_{39}H_{48}O_3$. Stereochemistry of Michael Cyclization

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Received July 8, 1968

The self-condensation of styryl isobutyl ketone (**1**) in ethanolic sodium hydroxide solution leads to a cyclic diketone dimer, all-*trans*-3,5-diphenylisopropyl-4-(3-methylbutanoyl)cyclohexanone (**2a**), and a triketone trimer, 3,5-diphenyl-2-isopropyl-4-(2-isopropyl-7-methyl-5-oxo-3-phenyloctanoyl)cyclohexanone (**4**). In aqueous sodium hydroxide, **1** produces an acyclic dimer, 1,5-diphenyl-4-isopropyl-9-methyl-1-decene-3,7-dione (**3a**), a compound shown to be a precursor of **2a**. Pyrolysis of trimer **4** produces **1** and **2b**, an epimer of **2a**. Heating **2a** in refluxing dioxane with sodium methoxide catalyst leads to a mixture of **2a**, **2b**, and a third cyclic dimer, **2c**. The configurations of these condensation products have been established by deuterium-exchange experiments and nmr spectroscopy. The stereochemistry of the relevant addition reactions and a comparison with the related Michael aldol cyclization are examined and discussed.

Study of the stereochemistry of Michael cyclization arising from an acyclic precursor appears in only one previous report.[1] Stereochemistry of the related Michael aldol cyclization (Robinson annelation reaction) has been examined; most of these reactions involve Michael addition of a cycloalkanone enolate to an α,β-unsaturated ketone, followed by aldol cyclization to form a new ring.[2] Most other studies of Michael addition stereochemistry have dealt with the formation of acyclic diastereoisomers,[2f,g,3-5] or products of an addition to an activated endocyclic double bond.[2a,c,6-8] We have extended our studies of the base-catalyzed self-condensation of α,β-unsaturated ketones[9] to an examination of the stereochemistry of Michael cyclization products obtained by self-condensation of styryl isobutyl ketone. In this example, unlike many other types of Michael addition, the mechanism does not involve the complicating features of enolization stereochemistry. Product equilibration by enolization is a post-Michael addition process in this case.

The base-catalyzed self-condensation of styryl isobutyl ketone (**1**), in contrast to reactions of other

$$C_6H_5CH{=}CHCOCH_2C_3H_7\text{-}i$$
1

styryl alkyl ketones which have been examined,[9,10] leads to several crystalline condensation products rather than a single cyclic diketone dimer. Isomeric acyclic and cyclic diketones, $C_{26}H_{32}O_2$, and a triketone, $C_{39}H_{48}O_3$, have been prepared in the present work.

The base-catalyzed self-condensation of styryl isobutyl ketone has been studied by other workers.[9b,10c,11,12] In *ethanolic* sodium hydroxide solution the formation of a crystalline dimer, $C_{26}H_{32}O_2$, has been reported, and previously we showed its structure to be **2a**.[9b] We have now prepared dimers **2b** and **2c**, both of which have been shown to be epimers of **2a**. In *aqueous* sodium hydroxide Metayer[11] obtained a product, mp 141°, which he described as a dimer; we have shown it to be a trimer, $C_{39}H_{48}O_3$.

Condensation Products and Structure.—Self-condensation of styryl isobutyl ketone in *aqueous* sodium

(1) F. Wingler and H. Reiff, *Ann. Chem.*, **705**, 96 (1967).

(2) (a) W. S. Johnson, S. Shulman, K. L. Williamson, and R. Pappo, *J. Org. Chem.*, **27**, 2015 (1962); (b) J. A. Marshall and W. I. Fanta, *ibid.*, **29**, 2501 (1964); (c) H. G. O. Becker, U. Fratz, G. Klose, and K. Heller, *J. Prakt. Chem.*, (4) **29**, 142 (1965); (d) A. T. Nielsen, *J. Org. Chem.*, **30**, 3650 (1965); (e) T. A. Spencer, H. S. Neel, and D. C. Ward, *ibid.*, **31**, 434 (1966); (f) M. M. Robison, M. G. Pierson, L. Dorfman, and B. F. Lambert, *ibid.*, **31**, 3206, 3213 (1966); (g) L. Jung, *Bull. Soc. Chim. Fr.*, 4692, 4696 (1967); (h) A. T. Nielsen and W. J. Houlihan, *Org. Reactions*, **16**, 11 (1968).

(3) A. Wettstein, K. Heusler, H. Ueberwasser, and P. Wieland, *Helv. Chim. Acta*, **40**, 323 (1957).

(4) M. P. Hughes, Ph.D. Thesis, Rice University, 1964; *Dissertation Abstr.*, **25**, 1570 (1964).

(5) A.-M. Baradel, J. Dreux, R. Longeray, P. Laszlo, and H. Rivière, *Bull. Soc. Chim. Fr.*, 3543 (1966).

(6) E. D. Bergmann, D. Ginsburg, and R. Pappo, *Org. Reactions*, **10**, 179 (1959).

(7) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp 367–368.

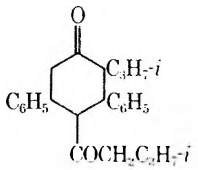
(8) (a) R. A. Abramovitch and J. M. Muchowski, *Can. J. Chem.*, **38**, 557 (1960); (b) S. V. Kessar, J. P. Nagpal, and K. K. Khullar, *J. Indian Chem. Soc.*, **39**, 381 (1962); (c) M. E. Wall, F. I. Carroll, and G. S. Abernathy, *J. Org. Chem.*, **29**, 604 (1964); (d) N. L. Allinger and C. K. Riew, *Tetrahedron Lett.*, 1269 (1966); (e) R. A. Abramovitch and D. L. Struble, *Tetrahedron*, **24**, 357 (1968).

(9) (a) A. T. Nielsen, D. W. Moore, and K. Highberg, *J. Org. Chem.*, **26**, 3691 (1961); (b) A. T. Nielsen and H. J. Dubin, *ibid.*, **28**, 2120 (1963); (c) A. T. Nielsen, H. Dubin, and K. Hise, *ibid.*, **32**, 3407 (1967); (d) A. T. Nielsen and S. Haseltine, *ibid.*, **33**, 3264 (1968).

(10) (a) R. Dickinson, I. M. Heilbron, and F. Irving, *J. Chem. Soc.*, 1888 (1927); (b) I. M. Heilbron and F. Irving, *ibid.*, 2323 (1928); (c) I. M. Heilbron and F. Irving, *ibid.*, 931 (1929); (d) I. M. Heilbron, R. N. Heslop, F. Irving, and J. S. Wilson, *ibid.*, 1336 (1931).

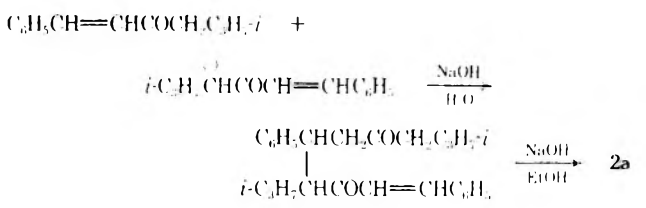
(11) M. Metayer, *Rec. Trav. Chim. Pays-Bas*, **71**, 153 (1952).

(12) C. V. Gheorghiu and B. Arwentiev, *J. Prakt. Chem.*, (2) **118**, 295 (1928).



2a, mp 207–208°
b, mp 170–172°
c, mp 94–96°

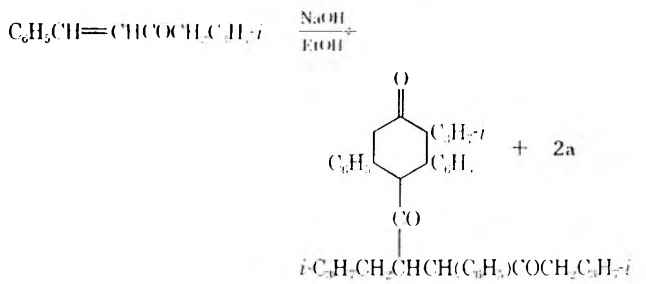
hydroxide at 50° (15–24 hr) gave as the principal product the acyclic Michael adduct **3a** (18–23% yield). The elemental analysis, molecular weight, spectra, and chemical behavior support structure **3a.** In ethanolic



3a, mp 115–117°

sodium hydroxide solution **3a** is converted essentially quantitatively into cyclic dimer **2a**; no other products result under a variety of conditions. Diketone **3a** is the first reported acyclic styryl alkyl ketone dimer.[13,14] Such acyclic dimers have been postulated as primary Michael adduct intermediates in the base-catalyzed self-condensation of styryl alkyl ketones.[9b-d]

Self-condensation of styryl isobutyl ketone in *ethanolic* sodium hydroxide gave, in addition to cyclic dimer **2a** (22–38% yield), a trimeric triketone, $C_{39}H_{48}O_3$, in 43–46% yield. Elemental analysis, molecular weight, spectra, and chemical behavior support structure



4, mp 143–145°

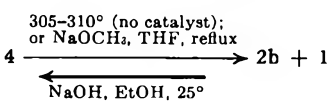
4. No evidence of olefinic unsaturation appears in the infrared and ultraviolet spectra.

Compound **4** appears to be the first trimer obtained by self-condensation of an α,β-unsaturated ketone. It also represents the first 3:3 aldehyde:ketone aldol condensation product to be described.[2h,9c]

(13) Acyclic, olefinic 1,5-diketones have been isolated as dimeric products of base-catalyzed self-condensation of a few other α,β-unsaturated ketones including (a) 4-methyl-1-phenyl-2-penten-1-one [R. Anet, *J. Org. Chem.*, **26**, 246 (1961)]; (b) 1-cyclopropyl-4-methyl-2-penten-1-one;[9a] and (c) 1,3-diphenyl-2-buten-1-one (dypnone) [H. Meerwein, *Chem. Ber.*, **53**, 1829 (1920)]. The dimers isolated in examples a and b were shown to be β,γ-unsaturated 1,5-diketones. Like **3a** they are derived from monomers containing isopropyl groups.

(14) The acyclic diketone dimer derived from mesityl oxide [*i.e.*, $(CH_3)_2C(CH_2COCH_3)CH_2COCH{=}C(CH_3)_2$] could not be isolated, but has been trapped as a bromo derivative: B. Furth and J. Wiemann, *Bull. Soc. Chim. Fr.*, 1819 (1965).

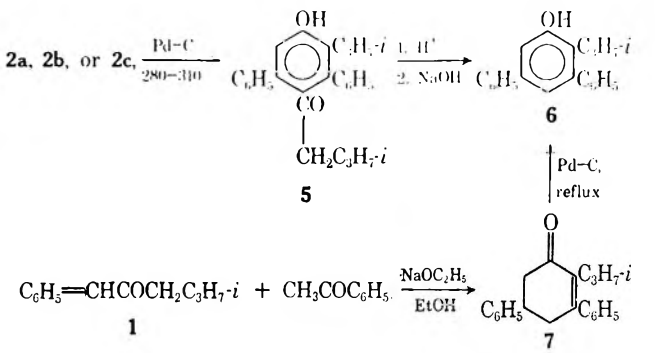
Heating trimer **4** at 305–310° for a few minutes resulted in retro-Michael cleavage in the side chain to yield only cyclic dimer **2b** and styryl isobutyl ketone **1**. The retrogression could also be effected by heating **4** under reflux in tetrahydrofuran with sodium methoxide catalyst. Trimer **4** was synthesized by base-catalyzed condensation of **1** with dimer **2b**.



A third cyclic dimer (**2c**) and dimer **2b** were obtained by heating dimer **2a** under reflux in dioxane with sodium methoxide catalyst. Nearly quantitative conversion of **2c** into **2b** occurred rather rapidly in ethanolic sodium hydroxide at 25°. This conversion could also be effected by heating **2c** in the absence of a catalyst at 300–310°.

The structures of cyclic dimers **2b** and **2c** were established by dehydrogenation, as with **2a**, by heating with palladium–charcoal to produce 3,5-diphenyl-2-isopropyl-4-(3-methylbutanoyl)phenol (**5**) (Scheme I), identical with a sample of this substance obtained from **2a**.[9b,15] Reverse Fries rearrangement, followed by saponification, led to phenol **6**, which was synthesized by dehydrogenation of 3,5-diphenyl-2-isopropyl-2-cyclohexen-1-one (**7**). The latter ketone was obtained in a Michael aldol cyclization departing from styryl isobutyl ketone (**1**) and acetophenone (Scheme I).

SCHEME I

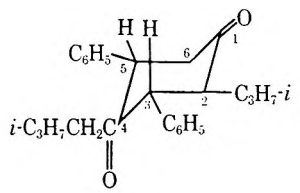


Stereochemistry.—Three stable diastereoisomers having cyclic dimer structure **2** are to be expected in basic medium (assuming a chair form of the cyclohexanone ring with favored equatorial substituents), since substituents at C-2 and C-4 may easily change configuration by equilibration. Exchange of all six enolizable hydrogens in **2a** and **2b** occurred within a few minutes in refluxing deuterioethanol–sodium ethoxide as shown by the nmr spectrum of the recovered deuterated product.

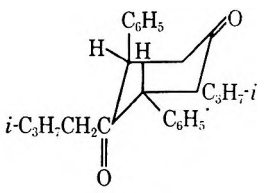
The two nonexchangeable C-3 and C-5 ring benzyl protons in hexadeuterio **2a** appear as a singlet at τ 6.67, and in hexadeuterio **2b** as two singlets at τ 6.30 and 6.18. These data suggest an all equatorially substituted structure for **2a**.

(15) The major product of dehydrogenation of **2b** is dimer **2a** (20% yield), believed to result by hydrogenation of certain products or intermediates formed by dehydrogenation of **2b**. Dimer **2a** was observed to have much greater thermal stability than **2b**. Dehydrogenation of dimer **2a** under the conditions employed with **2b** led to 31% recovery of **2a** and a 23% yield of phenol **5**.[9b] The relative low yield (5%) of **5** from **2b**, produced without recovery of **2b**, is believed to be due to the low thermal stability of **2b** under the reaction conditions. The thermal stability of the cyclic dimers decreases in the order **2a** > **2b** > **2c**.

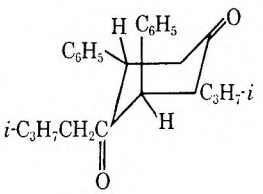
Additional evidence for structure **2a** is shown by the nmr spectra in Table I. In **2a** the C-4 substituents are symmetrically disposed with respect to the C-3 and C-5 phenyl substituents; the signal of the strongly



2a



2b



2c

shielded magnetically equivalent isopropyl methyl protons of the C-4 3-methylbutanoyl group appears as a 6.5-Hz doublet centered at τ 9.78. By contrast, in **2b** the C-4 isopropyl methyl signal appears as a pair of magnetically nonequivalent,[16] less shielded 6.5-Hz doublets centered at τ 9.47 and 9.59; in **2c** these doublets appear at τ 9.23 and 9.32. The isobutyl methylene doublet is also strongly shielded in **2a** (τ 8.83), but less so in **2b** (τ 8.33). In acyclic dimer **3a** this doublet appears at τ 7.88, and in styryl isobutyl ketone at τ 7.52.

TABLE I

NMR PEAKS OF ISOPROPYL METHYL GROUPS[a] AND STEREOCHEMISTRY OF STYRYL ISOBUTYL KETONE CONDENSATION PRODUCTS

	i-C_3H_7 at C-2[b]		*i*-C_3H_7CHCO– at C-4[b]		*i*-$C_3H_7CH_2$,	C_6H_5 confign at
Compd	τ	$\Delta\tau$	τ	$\Delta\tau$	acyclic, τ	C-3, C-5[d]
2a	8.96, 9.11	0.15	9.78, 9.78[c]	0.00[c]		e, e
2b	8.92, 9.11	0.19	9.47, 9.59	0.12		e, a
2c	8.98, 9.37	0.39	9.23, 9.32	0.09		a, e
4	8.97, 9.03	0.06	9.47, 9.63	0.16	9.22[c]	e, a
3a	8.89, 9.01	0.12			9.23[c]	
1					9.03[c]	

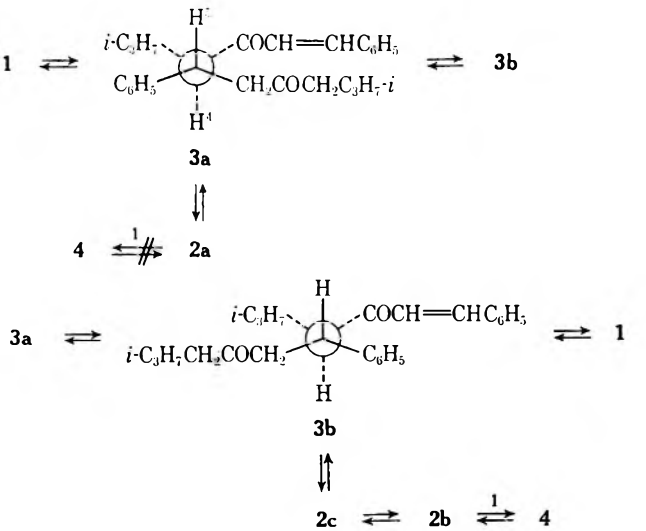
[a] Center of doublet ($J \cong$ 6.5–7.0 Hz), measurement in deuteriochloroform with tetramethylsilane internal reference. [b] C-2 and C-4 positions of cyclohexanone ring except in **3a**. [c] Isopropyl methyl signals magnetically equivalent within limits of resolution. [d] e = equatorial; a = axial.

Available evidence suggests that in **2b** the C-5 phenyl is axial with the remaining substituents equatorial; in **2c** only the C-3 phenyl is axial. Isomer **2b** is thermodynamically more stable than **2c**, as was pointed out above. Comparison of the C-2 isopropyl methyl signals in the three isomers (Table I) reveals nearly identical chemical shifts for the 6.5-Hz methyl doublet pair in **2a** and **2b**, but different chemical shifts in **2c**. Also, it is noted that the methyl chemical shift differences due to magnetic nonequivalence in **2a** and **2b** are similar ($\Delta\tau$ = 0.15 and 0.19, respectively) and much less than the value found for **2c** ($\Delta\tau$ = 0.39). Together, these values suggest an identical configuration of C-2 isopropyl and C-3 phenyl in **2a** and **2b**, which is different from the configuration of these groups in **2c**.

Other cyclic styryl alkyl ketone dimers[9,10] are believed to have an all-*trans*-equatorial configuration like that of **2a**.

Two acyclic styryl isobutyl ketone dimers are possible. Only one of these could be isolated in the present work. It is believed to have configuration **3a** (Scheme II), a conclusion based principally on chemical evidence which also disfavors configuration **3b**. A preferred conformation with *trans* disposition of C-4, C-5 hydrogens is in agreement with the nmr spectrum.

SCHEME II



Acyclic dimer **3a** produces cyclic dimer **2a** under a wide variety of reaction conditions; yields are often quantitative and other products are not produced. In particular, under the usual reaction conditions (ethanolic sodium hydroxide, 25°), whereby styryl isobutyl ketone (**1**) produces trimer **4**, no products other than **2a** are produced from **3a** *even in the presence of a large excess of* **1**. In another experiment, 50% **3a**, and no other product, was recovered from a reaction in which **2a** is formed in 30% yield, suggesting that the equilibration **3b** ⇄ **3a** does not occur under these conditions. Preparation of **2a** from **3a** in deuterioethanol–sodium ethoxide led only to hexadeuterio **2a**.

Acyclic dimer **3b** could not be isolated. It is believed that its isolation is disfavored under all reaction conditions, and that it undergoes very rapid cyclization to **2c**, followed by rapid conversions of **2c** to **2b** and **4**.

The conversion **3a** → **2a** appears to be a product-development-controlled process.[17] Stereochemistry of enolization is not involved in this apparently kinetically controlled Michael cyclization; anion protonation at C-6 represents the final Michael step (nonstereochemically important), and subsequent enolization at C-2 or C-4 can result in equilibration only as a post-

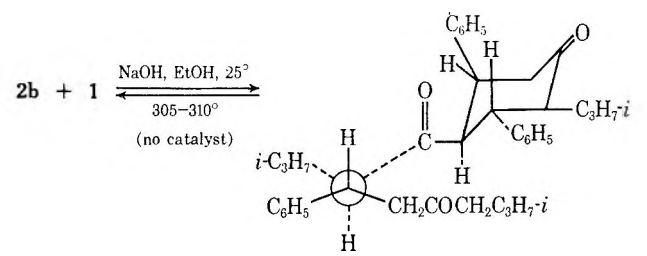
(16) (a) M. Kajtár and L. Radics, *Chem. Commun.*, 784 (1967); (b) T. S. Sorensen, *Can. J. Chem.*, **45**, 1585 (1967).

(17) H. C. Brown and J. Muzzio, *J. Amer. Chem. Soc.*, **88**, 2811 (1966).

Michael addition event. Dimer **2a** is formed under reaction conditions which do not permit its retrogression to **3a**, nor equilibration of **3a** to **3b**. Furthermore, the epimerization **2b** → **2a** is disallowed. The cyclization of **3a** could lead to a maximum of four diastereoisomers, *two of which could equilibrate at C-2 and C-4 to produce* **2b** under the reaction conditions. No **2b** is formed. It is suggested that in the transition state leading to the most stable product, **2a**, there is a *trans* disposition of all bulky groups, at or removed from the bond-forming site. This situation is also found in a Michael aldol cyclization involving formation of a six-membered ring having four asymmetric centers, although a very small amount (*ca.* 5%) of a less stable product (COH epimer) is formed under conditions of kinetic control.[2d] This result agrees with an earlier suggestion that more stereoselectivity is to be expected in the Michael addition, relative to the aldol condensation.[2d]

Conversion of cyclic dimer **2a** to dimers **2b** and **2c** in refluxing dioxane–sodium methoxide requires a retrogression of **2a** to acyclic dimer **3a** (Scheme II), and very likely an equilibration **3a** ⇄ **3b** as well. A higher temperature and an aprotic solvent permit a less stable isomer (**2c**) in the equilibrium.[4,5] Chilling, followed by neutralization of the catalyst, leads to isolation of **2c**. Assuming a *trans* orientation of C-4 and C-5 groups resulting by Michael cyclization of **3b**, in the manner envisioned for **3a**, the initial cyclization product from **3b** should be **2c**, which can then readily equilibrate to **2b** by enolization at C-2 and C-4.

The configuration of trimer **4** is suggested by its synthesis from cyclic dimer **2b** and styryl isobutyl ketone, and the formation of these components and no others (no **2a**) by heating **4** at 310°. Although **4** can also arise



4

from **2c**, **4** is believed to have the same configuration of substituents in the cyclohexane ring as does **2b**, since **2b** has been shown to be thermodynamically much more stable, relative to **2c**, in ethanolic sodium hydroxide.

The nmr spectrum of **4** supports the assigned stereochemistry (Table I). In **4** the values for the chemical shifts of the C-2 isopropyl methyls (τ 8.97, 9.03) and the chemical shift difference of these methyls due to magnetic nonequivalence ($\Delta\tau$ = 0.06) are smaller and resemble more closely the corresponding values for **2a** and **2b** than the values for **2c**. Also, these values for the signals of the methyls of the 3-methylbutanoyl group attached at C-4 are nearly identical in **2b** and **4**, but different from the values for **2a** and **2c**. These facts suggest an identical configuration of C-2 isopropyl and C-3 phenyl in **2a**, **2b**, and **4**, which is different from that in **2c**, as well as an identical configuration of C-4 substituent and C-5 phenyl in **2b** and **4** which is different from the configuration of these groups in **2a** and **2c**.

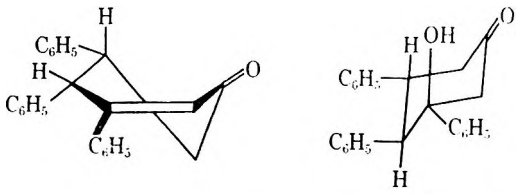
The C-4 side-chain configuration in **4** may exist as illustrated by the Newman projection. The nmr spectra of **4** and acyclic dimer **3a** are very similar with respect to the peaks in the spectrum of those substituents located in the region of the acyclic diastereoisomerism. An isobutyl methyl doublet appears at τ 9.22 (9.23) and a sharp phenyl signal at τ 2.63 in both compounds. The peaks of the single acyclic protons in **4** (shown in a favored *trans* conformation as with **3a**) could not be sufficiently resolved to make assignments.

The reaction sequence which leads to trimer **4** is not necessarily established by synthesis of **4** from dimer **2b** and styryl isobutyl ketone (**1**). However, the available data suggest no reasonable precursors other than **2b**, **2c**, and **1**. Dimers **2a**, **3a**, and **3b** appear to be excluded. The failure of **2a** to react with **1** to form any trimer may be attributed to a steric factor which reduces the reactivity, or inhibits the formation, of the required enolate anion of **2a**. Cyclization of **3a** to **2a** evidently occurs more rapidly than other condensation reactions which **3a** might undergo under the reaction conditions. Failure of **3a** to form a trimer by reaction with **1** suggests the likelihood that acyclic dimer **3b** is also not a precursor of trimer **4**. Acyclic dimer **3b** appears to cyclize even more rapidly than **3a**, since **3a** could be isolated as a reaction product in aqueous medium where no **2a** is formed, but where **4** and no **3b** form. Also, the higher yield of **4** relative to **2a** from **1** in ethanolic sodium hydroxide could be explained by assuming a more rapid cyclization of **3b** to **2c** relative to the **3a** → **2a** cyclization. Finally, formation of **4** from **3a** or **3b** requires that the three required, successive Michael additions occur in a sequence different from that whereby **4** is formed from **2b** or **2c**. The sequence from **3a** or **3b** would make it difficult to explain the observed stereochemistry of **4**, since by this route one might expect a trimer in which all cyclohexane substituents are equatorial.

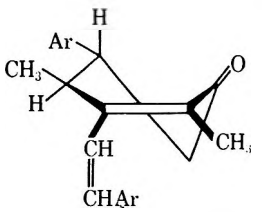
Formation of trimer **4** is unique. Other styryl alkyl ketones have not been observed to form trimers.[9,10] It is believed that the required enolate anion derived from **2b** or **2c** is a potent nucleophile, perhaps owing to its poor solvation, and is not too hindered to prevent Michael addition to a molecule of monomer. (It should be possible to prepare a mixed trimer from **2b** and a different monomer.) High crystallinity, low solubility, high melting point, and slow rate of retrogression to reactants may facilitate isolation of trimer **4**.

Michael stereochemistry results of the present investigation agree with those reports on Michael aldol cyclization departing from acyclic precursors obtained by Michael additions.[1,2d,f,5,9d] The monocyclic products formed in each of these base-catalyzed reactions (which include examples of kinetic and thermodynamic control) have *trans* stereochemistry in the carbon–carbon bond initially derived by Michael addition.

Compound **8** (thermodynamically favored[5]) is an exception (C-4, C-5 *cis*). The related cyclization products **9** (kinetically favored and formed from the same reactants as **8**[5]), and **10**[9d] both have C-4, C-5 *trans* stereochemistry. However, the exception may



9



10, Ar = 2-$CH_3OC_6H_4$

be explained by recognizing that in cyclohexene compounds (existing in a favored chair conformation[18-20]) eclipsing by a C-1 phenyl substituent on the double bond results in a favored pseudoaxial configuration of C-6 phenyl, and certain other C-6 substituents, particularly in a molecule lacking C-4 substituents.[5,20,21]

Experimental Section[22]

3,5-Diphenyl-2-isopropyl-4-(3-methylbutanoyl)cyclohexanone (Isomer 2a) and 3,5-Diphenyl-2-isopropyl-4-(2-isopropyl-7-methyl-5-oxo-3-phenyloctanoyl)cyclohexanone (4). Procedure A. Condensation of Benzaldehyde with Methyl Isobutyl Ketone.—To benzaldehyde (106 g, 1.0 mol) and methyl isobutyl ketone (100 g, 1.0 mol) dissolved in 680 ml of absolute ethanol was added 60 ml of 25% aqueous sodium hydroxide solution. The reaction flask was swept with nitrogen and sealed with a ground-glass stopper. The temperature rose spontaneously to a maximum of 39° within 5 min and the solution became orange-red. The solution was stored in the dark at room temperature. Crystals appeared in the solution within 15 hr and continued to separate for *ca.* 4 days, after which time very little further crystallization was observed. After a total reaction time of 1 week the mixture was filtered to yield 105.6 g of white crystals, mp 135–180°; concentration and chilling of the filtrate yielded 21.7 g, mp 130–140°. Crystallization of the first crop from ethyl acetate (900 ml) gave 32.5 g of **2a**, mp 207–208°, in addition to 9.5 g, mp 180–204°, obtained by concentration of the filtrate: total yield, 42 g, 22.3%; λ_{max} 248 mμ (ε 182), 253 (260), 259 (374), 266 (316), 268 (192), 295 (96); analytical data are in Table II.

Concentration of the ethyl acetate filtrate to dryness gave 60.0 g, mp 130–140°, which was combined with the crude second crop above (total yield of crude **4**, 81.7 g, 43.5%). Crystallization from ethanol gave 63.5 g of chunky prisms, mp 141–143°. Recrystallization gave 42.8 g: mp 143–145°; λ_{max} 248 mμ (ε 303), 253 (438), 259 (638), 265 (560), 268 (390), 299 (207); analytical data are in Table II.

Concentration of the filtrates remaining from the above crystallization gave 49.1 g of dark-red, viscous oil which was distilled to yield 1.33 g of crude benzyl alcohol, bp 68–71° (1.0 mm), and 12.7 g (6.8%) of styryl isobutyl ketone, bp 105–106° (0.4 mm). The viscous brown residue (34.2 g) crystallized from 100 ml of 95% ethanol deposited 0.17 g of crude dimer **2a**, mp 180–195°, and no other crystalline product.

The aqueous alkaline part remaining from the reaction work-up was acidified with hydrochloric acid to yield 2.77 g of material, mp 115–120°; recrystallization gave benzoic acid, mp 121–122°.

Procedure B. Self-Condensation of Styryl Isobutyl Ketone.—To styryl isobutyl ketone[11] (10.0 g, 0.053 mol) in 50 ml of absolute ethanol was added 1.6 ml of 25% aqueous sodium hydroxide solution. After standing 12 days at 25° in a nitrogen atmosphere there was obtained 4.70 g of crystals, mp 135–195°; from the filtrate by concentration and chilling there was obtained 1.92 g of **2a**, mp 205–206°, and 1.76 g of crude trimer **4**, mp 128–130°. Recrystallization of the first crop gave 1.87 g of **2a**, mp 204–206° (total yield of **2a**, 3.79 g, 38%). The remainder was crude trimer (total yield 4.59 g 46%).

1,5-Diphenyl-4-isopropyl-9-methyl-1-decene-3,7-dione (3a).—A mixture of styryl isobutyl ketone[11] (10 g, 0.053 mol), sodium hydroxide (1.0 g) and 2 ml of water was stirred at 50° for 15 hr. The mixture was cooled and extracted with ether. The extracts were washed with water and dried; the solvents were evaporated to leave 9.16 g of yellow oil. Crystallization from ethanol gave 1.57 g of diketone **3a**, mp 90–105°. From the filtrate by distillation there was obtained 6.78 g (67.8%) of recovered styryl isobutyl ketone, bp 105–110° (0.3 mm), and 0.97 g of residue. Crystallization of the residue from ethanol gave 0.2 g of crude trimer **4**, mp 120–130° (recrystallization from ethanol gave 0.15 g, mp 138–140°), and 0.20 g of additional diketone **3a**, mp 90–110°; total yield of **3a** 1.77 g (17.7%). Recrystallization from ethanol gave 0.8 g, mp 113–115°. Further recrystallization gave small needles: mp 115–117°; analytical data are in Table II; λ_{max}^{EtOH} 288 mμ (ε 21,000) [styryl isobutyl ketone λ_{max}^{EtOH} 289 mμ (ε 19,400)]. The nmr spectrum of **3a** shows two 16-Hz vinyl doublets (two *trans*-olefinic protons) centered at τ 2.71 and 3.62, a 6.5-Hz isobutyl methyl doublet centered at τ 9.23, and a pair of 6.5-Hz methyl doublets centered at τ 8.89 and 9.01; the two phenyl signals are observed at τ 2.63 and 2.80. The C-4 proton (H-4) signal appears at τ 6.95 (dd, $J_{4,5}$ = 8, J = 6 Hz), the C-5 proton (H-5) at τ 6.28 (eight-line multiplet, J = 6, 8, 9 Hz), and the two C-6 methylene protons as overlapping doublets centered at τ 7.16 (J = 6 Hz) and 7.18 (J = 8 Hz).

In a parallel 50-g run employing a reaction time of 24 hr there was obtained a 23% yield of diketone **3a**, 2% of trimer **4**, 2% of cyclic dimer **2b**, 1% of cyclic dimer **2a**, and 32% of recovered styryl isobutyl ketone. Treatment of the noncrystalline reaction product remaining (after removal of products **1**, **2a**, **3a**, and **4**) with ethanolic sodium hydroxide failed to yield any additional crystalline product. The shorter reaction time of the first run provides **3a** in slightly lower yield, but the material isolated is much more easily purified.

Cyclization of 1,5-Diphenyl-4-isopropyl-9-methyl-1-decene-3,7-dione (3a) to Cyclic Dimer 2a.—A 94.7-mg sample of acyclic diketone **3a** and 15 mg of sodium methoxide in 5 ml of absolute ethanol was heated at 70° for 7.5 hr. The cooled solution deposited 72.3 mg of cyclic diketone **2a**, mp 202–203°. The filtrate was neutralized with acetic acid, and chilled to −15° to deposit 19 mg of **2a**, mp 203–204°. Concentration of the filtrate to dryness and dilution with water gave 2.4 mg, mp 195–200°, and 1.0 mg, mp 165–195°; total yield of **2a**, 94.7 mg (100%).

Acyclic diketone **3a** (100 mg), 0.5 ml of 1 *N* sodium hydroxide (aqueous), and 5 ml of 95% ethanol heated at reflux for 1 min gave 30 mg of **2a**, mp 186–197°, and 50 mg of recovered **3a**, mp 87–97°. A parallel experiment employing a 5-min reflux time gave a 67% yield of **2a**, mp 199–205°.

Acyclic diketone **3a** (100 mg), 10 ml of ether, and 1 ml of 0.1 *N* aqueous sodium hydroxide solution were stirred at 25° for 4–6 hr; there resulted only unreacted **3a** which was crystallized from ethanol to yield 78–87 mg, mp 108–112°. Ketone **3a** (100 mg), sodium hydroxide (100 mg), water (2 ml), and benzene (10 ml) were stirred at 50–60° for 4 hr; there resulted 87 mg of unreacted **3a**, mp 102–103°.

Preparation of 3,5-Diphenyl-2-isopropyl-4-(3-methylbutanoyl)-cyclohexanone Isomers 2b and 2c from 2a.—A 20.0-g sample of cyclic dimer **2a** in 200 ml of dioxane containing 0.26 g of sodium methoxide was heated under reflux for 69 hr. After cooling the solution, neutralization of the catalyst with acetic acid, and removal of the solvent, the residue was crystallized from ethanol to yield 7.74 g, mp 195–198°, and 1.10 g, mp 170–185°, of recovered **2a** (44% total). By concentration and chilling of the filtrate there was obtained 1.74 g of crude dimer **2b**, mp 150–165°, 3.83 g of crude dimer **2b**–**c** mixture, mp 90–115°, and 5.24 g of viscous, noncrystalline material. Several recrystallizations of the crude dimer **2b** from ethanol gave 0.36 g, mp 165–170°. Further recrystallization gave 0.17 g of **2b**: mp 168–170°; an

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(19) F. R. Jensen and C. J. Bushweller, *ibid.*, **87**, 3285 (1965).
(20) B. Rickborn and S.-Y. Lwo, *J. Org. Chem.*, **30**, 2212 (1965).
(21) E. G. Garbisch, Jr., *ibid.*, **27**, 4249 (1962).
(22) Melting points were determined on a Kofler block and are corrected. Ultraviolet spectra were determined on a Cary Model 11 spectrophotometer (95% ethanol solvent), infrared spectra on a Perkin-Elmer Model 137 spectrophotometer, and nmr spectra on a Varian A-60 spectrometer (10–20% solutions in deuteriochloroform unless otherwise stated). Mass spectra were determined on a Hitachi Model RMU-6E. Magnesium sulfate was employed as a drying agent. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

TABLE II

PROPERTIES OF STYRYL ISOBUTYL KETONE CONDENSATION PRODUCTS

Compd	Bp (mm) or mp, °C	Infrared bands (KBr), cm⁻¹ C=O	Infrared bands (KBr), cm⁻¹ CH out-of-plane	Elemental analyses[a] % C	Elemental analyses[a] % H	Mol wt[b]
2a	207–208[c]	1720, 1690	700 s, 755 m, 767 w	83.07	8.53	376[d], 363[e]
2b	170–172[f]	1700	700 s, 737 m, 763 w, 780 m	82.96	8.88	376[d]
2c	94–96	1710, 1690	700 s, 757 m, 776 w	82.64	8.70	376[d]
3a	115–117	1710, 1640	700 s, 756 m	83.34	8.61	380[e]
4	143–145[g]	1710, 1680	703 s, 712 (sh) m, 752 w, 763 m	83.08	8.72	564,[d] 563[e]
1	105–106 (0.4 mm)[h]	1680, 1640[i]	690 s, 749 s[i]			

[a] Calcd for $C_{26}H_{32}O_2$ and $C_{39}H_{48}O_3$.: C, 82.93; H, 8.57. [b] Calcd for $C_{26}H_{32}O_2$: mol wt, 376.52. Calcd for $C_{39}H_{48}O_3$: mol wt, 564.77. [c] Lit. mp 202°,[10c] 205–206°,[9b] 209°.[11] [d] Determination by mass spectroscopy. [e] Determination by vapor osmometry. [f] Lit.[11] mp 170–171°. [g] Lit.[11] mp 141°. [h] Lit.[11] bp 159–160° (17 mm). [i] Measurement on neat liquid.

analytical sample had mp 170–172°; λ_{max} 248 mμ (ε 248), 253 (308), 259 (368), 266 (301), 268 (203), 295 (98); analytical data are in Table II.

Recrystallization of the crude dimer **2b–c** mixture from ethanol gave 2.0 g, mp 115–118°. Further recrystallization gave prisms of a 1:1 **2b–c** compound, mp 118–121°; recrystallization from hexane did not change the melting point. The mixture, which could not be separated by crystallization, was resolved by chromatography on silica gel (elution with benzene) to give equal weights of dimer **2b**, mp 170–172°, after recrystallization from ethanol, and **2c**, mp 94–96°, after recrystallization from heptane; analytical data are in Table II; the ultraviolet spectrum of **2c** is practically identical with that of **2a** and **2b**.

The infrared spectra of isomeric dimers **2a**, **b**, and **c** were virtually identical except for the 735–780-cm⁻¹ CH out-of-plane deformation region (KBr); *cf.* Table II. Differences in the nmr spectra of these isomers are discussed in the text.

Preparation of 3,5-Diphenyl-2-isopropyl-4-(3-methylbutanoyl)-cyclohexanone Isomer 2b. A. By Thermal Cleavage of Trimer 4.—A 6.0-g sample of trimer **4** was heated in a test tube with a flame at 305–310° for 12 min and at 320° for 1 min (thermometer bulb in liquid). After cooling the sample in a stream of nitrogen and crystallization of the residue from ethanol (25 ml) there was obtained 1.84 g (46%) of dimer **2b**, mp 163–166°. Recrystallization gave 0.85 g of long needles, mp 167–170°. Further recrystallization raised the melting point to 169–170°. Chilling of the filtrate gave 1.24 g (21%) of recovered trimer **4**, mp 130–145°. Concentration of the filtrate to dryness gave 2.77 g of oil which was distilled to yield 1.13 g (56%) of styryl isobutyl ketone, bp 108–110° (0.5 mm), and 1.66 g of residue. The styryl isobutyl ketone was identified by infrared spectra comparison with an authentic sample and its semicarbazone derivative, mp 170–172° [melting point undepressed when mixed with an authentic sample, mp 170–172° (lit.[23] mp 167°)].

B. By Base-Catalyzed Cleavage of Trimer 4.—A solution of 1.0 g of trimer **4** and 27 mg of sodium methoxide in 10 ml of tetrahydrofuran was heated under reflux for 21 hr. The solution was neutralized by addition of acetic acid and concentrated to dryness. Crystallization of the residue from ethanol gave 0.85 g of recovered **4**, mp 140–142°, and 21 mg of dimer **2b**, mp 165–168°. A similar experiment in refluxing absolute ethanolic sodium ethoxide gave 17% recovery of crude **4** and gummy material, but no other crystalline product.

C. By Thermal Epimerization of Cyclic Dimer 2c.—A 55.7-mg sample of dimer **2c** was heated in a small test tube at 300–310° for 2 min. Crystallization from ethanol gave 5.5 mg of dimer **2b**, mp 165–168°. Addition of 0.1 ml of 10% aqueous sodium hydroxide to the filtrate, followed by standing at room temperature for 3 hr, led to formation of an additional 15.0 mg of dimer **2b**, mp 169–170°.

D. By Base-Catalyzed Epimerization of Cyclic Dimer 2c.—A 3.9-mg sample of dimer **2c** in 0.5 ml of ethanol containing a few drops of 10% aqueous sodium hydroxide was allowed to stand at room temperature. Within *ca.* 1 hr crystals of isomer **2b** began to separate. After 16 hr the mixture was chilled to −15° for 2 hr, and then filtered to yield 3.3 mg of dimer **2b**, mp 167–169°.

Samples of dimer **2b** prepared by the above five methods all showed identical infrared spectra. Pairs of the samples prepared by the different methods, when mixed, each showed no depression in melting point.

A 100-mg sample of **2b** in 10 ml of ethanol containing 0.1 ml of 10% aqueous sodium hydroxide solution was allowed to stand at room temperature for 9 days; there resulted 39 mg of recovered **2b**, mp 160–165°, and no other crystalline product.

Pyrolysis of Styryl Isobutyl Ketone Dimers. A. Cyclic Dimers 2a, b, and c.—A 1.0-g sample of cyclic dimer **2a** heated under reflux (*ca.* 315–320° in the liquid) for 5 min followed by crystallization from ethanol led to recovered **2a**, 0.55 g, mp 201–203°, and 0.05 g, mp 191–197°. No other crystalline product could be isolated from the filtrate.

Similarly, a 0.50-g sample of cyclic dimer **2b** heated at 300 ± 5° for 5 min gave 0.37 g of recovered **2b**, mp 166–167°, after crystallization from ethanol, and no other crystalline product. Treatment of the filtrate with 20 mg of sodium methoxide, followed by heating on the steam bath for 5 min, led only to isolation of 0.03 g of additional **2b**, mp 165–170°. Thermal epimerization of cyclic dimer **2c** into isomer **2b** is described above.

B. Acyclic Dimer 3a.—A 0.50-g sample of acyclic dimer **3a** was heated under reflux for 4 min; during the heating the temperature within the liquid dropped from 320 to 305°. Cooling gave an oil which was dissolved in 10 ml of absolute ethanol containing 80 mg of sodium methoxide. Heating the resulting solution on the steam bath for 5 min, followed by chilling, led to isolation of 0.07 g of cyclic dimer **2a**, mp 200–205°.

Synthesis of Trimer 4.—A 55-mg sample of cyclic dimer **2b** and 275 mg of styryl isobutyl ketone (10 mol equiv) were dissolved in 4 ml of ethanol containing 0.1 ml of 10% aqueous sodium hydroxide; the solution was allowed to stand at room temperature for 16 hr. The resulting clear yellow solution was acidified with acetic acid and concentrated to a small volume. Chilling at −15° gave 32.9 mg (40%) of crude trimer **4**, mp 125–140°, and no other crystalline product. Recrystallization of the crude product from ethanol gave trimer **4**, mp 140–141°, identified by its infrared spectrum. When mixed with a sample of **4** obtained by the self-condensation of styryl isobutyl ketone, the melting point was not depressed.

A parallel experiment employing acyclic dimer **3a** failed to yield trimer **4**. A 188-mg sample of acyclic dimer **3a** and 1.88 g of styryl isobutyl ketone (20 mol equiv) were dissolved in 5 ml of ethanol containing 0.5 ml of aqueous sodium hydroxide solution; the solution was allowed to stand at room temperature for 15 hr. Crystals of cyclic dimer **2a** separated, 185 mg, mp 205–206°. Chilling the filtrate at −15° for 2 days led to 45 mg of additional **2a**, mp 195–205°.

Preparation of 1,3,6,6-Tetradeuterio-3,5-diphenyl-2-isopropyl-4-(2,2-dideuterio-3-methylbutanoyl)cyclohexanone Isomers (Hexadeuterio 2a and b).—A solution of 100 mg of cyclic dimer **2a** in 10 ml of ethanol-O-*d* containing sodium ethoxide (prepared by addition of 70 mg of sodium to the alcohol) was heated under reflux for 3 hr. Concentration to near dryness, followed by dilution of the residue with water, gave 80 mg of hexadeuterio **2a**, mp 200–202°. A 10-min reflux period led to a similar result. [A 1-hr reflux period with ethanolic sodium bicarbonate led only to exchange of the C-6 ring methylene protons as evidenced by a marked reduction in intensity of the nmr signal of these protons (multiplet at τ 7.3).] The nmr spectrum of hexadeuterio **2a** showed only the ten phenyl protons as a sharp singlet (τ 2.72), the two ring benzyl protons as a sharp singlet at τ 6.67, and the two isopropyl methine protons as a complex multiplet centered at τ 8.48; the remainder of the spectrum is discussed in the text. Signals observed in **2a** for the exchangeable enolizable protons at C-2, C-4, and C-6 in the cyclohexanone ring, and in the isobutyl methylene group, were absent in hexadeuterio **2a**.

In a similar experiment, 200 mg of cyclic dimer **2b** in 10 ml of

(23) (a) C. V. Gheorghiu and B. Arwentiev, *J. Prakt. Chem.*, (2) **118**, 249 (1928); (b) I. M. Heilbron and F. Irving, *J. Chem. Soc.*, 941 (1929).

deuterioethanol containing sodium ethoxide, prepared by addition of 10 mg of sodium to the alcohol, was heated under reflux for 7 min. Distillation of the solvent (in about 5 min) to reduce the volume to 5 ml, followed by chilling at −15°, led to 100 mg of hexadeuterio **2b**, mp 165–169°. Dimer **2b** was found to be much less stable than isomer **2a** in refluxing ethanolic sodium ethoxide. Heating under the above conditions for periods longer than 30 min resulted in destruction of dimer **2b**. However, complete deuterium exchange of all enolizable hydrogens occurred very rapidly within 5–10 min with isomers **2a** and **2b** under the conditions described. The nmr spectrum of hexadeuterio **2b** was different from that of hexadeuterio **2a**. The phenyl protons appeared as a τ 2.3–2.9 multiplet with a principal signal at τ 2.53, the two ring benzyl protons as singlets at τ 6.18 and 6.30, and the two isopropyl methine protons as a multiplet centered at *ca.* τ 8.3; the remainder of the spectrum is discussed in the text. As with hexadeuterio **2a**, proton signals of all six enolizable protons were absent in the spectrum of hexadeuterio **2b**.

Attempts to prepare deuterio derivatives of cyclic dimer **2c** and acyclic dimer **3a** were unsuccessful. Cyclic dimer **2c** rapidly exchanged and epimerized into dimer **2b**, and acyclic dimer **3a** was converted quantitatively into hexadeuterio **2a** under the deuterium-exchange conditions (refluxing deuterioethanol–sodium methoxide for *ca.* 5–10 min). Trimer **4** was readily destroyed under these reaction conditions. However, a low yield of a sample was recovered after 5-min heating on the steam bath, mp 138–140°, which contained deuterium; almost complete exchange of hydrogen for deuterium of the C-6 ring methylene protons (d, τ 7.18), and side-chain methylene protons (multiplets at τ 7.83 and 8.25) occurred, as evidenced by the disappearance of these peaks in the recovered sample; the remaining enolizable protons were incompletely exchanged.

3,5-Diphenyl-2-isopropyl-2-cyclohexen-1-one (7).—To styryl isobutyl ketone (18.8 g, 0.10 mol) and acetophenone (12.0 g, 0.10 mol) dissolved in 100 ml of absolute ethanol was added a solution of sodium ethoxide prepared from 0.46 g of sodium dissolved in 15 ml of absolute ethanol. The solution was allowed to stand at 25° for 17 hr, then heated under reflux for 24 hr. The red-orange solution was neutralized with acetic acid and concentrated to dryness. The gummy residue was extracted with methylene chloride and the extracts were concentrated to yield 22.8 g of viscous red oil; crystallization from ethanol gave 1.24 g of crude cyclic dimer **2a**, mp 175–195°. The filtrate was distilled to yield 1.0 g of recovered acetophenone. The residue (19.7 g) was crystallized from hexane–cyclohexane to yield 2.0 g of additional **2a**, mp 170–200°. The filtrate was concentrated and the residue dissolved in benzene containing 0.1 g of camphorsulfonic acid; the solution was then heated under reflux for 16 hr. The solution was concentrated and the residue dissolved in hot hexane, treated with decolorizing charcoal (Darco G-60), filtered, and cooled to −15°. The gummy crystals (4.62 g) which were deposited were fractionally crystallized from hexane to yield 0.50 g of cyclohexenone **7**: mp 88–90°; recrystallization from hexane raised the melting point to 90–91°; $\nu_{KBr}^{cm^{-1}}$ 1640 (C=O), 1600 (C=C); λ_{max}^{EtOH} 204 mμ (ε 17,900), 260 (9800).

Anal. Calcd for $C_{21}H_{22}O$: C, 86.85; H, 7.64; mol wt, 290.4. Found: C, 87.20; H, 7.60; mol wt, 321 (vapor osmometry).

3,5-Diphenyl-2-isopropyl-4-(3-methylbutanoyl)phenol (5).—A 0.4-g sample of cyclic dimer **2b** and 0.05 g of 10% palladium–charcoal were mixed and heated in a nitrogen atmosphere at 280–290° for 15 min, and at 300–310° for 5 min. The cooled residue was extracted with methylene chloride and the filtrates were concentrated to yield 0.37 g of residue which was crystallized from ethanol to yield 80 mg (20%) of dimer **2a** as long needles, mp 200–203° (when mixed with an authentic sample of **2a** the melting point was not depressed). No **2b** could be recovered. The filtrate was concentrated to dryness and the residue crystallized from benzene to yield 20 mg (5%) of crude **5**, mp 190–200°; recrystallization gave **5**, rhombic prisms, mp 200–201°; when mixed with an authentic sample, mp 202–203°, the melting point was not depressed (lit.[9c] mp 202–203°).

3,5-Diphenyl-2-isopropylphenol (6).—A mixture of 1.0 g of 3,5-diphenyl-2-isopropyl-2-cyclohexen-1-one (**7**) and 0.3 g of 10% palladium on charcoal was heated under gentle reflux in a nitrogen atmosphere for 10 min. The mixture was extracted with hot chloroform, filtered, and the filtrate concentrated to dryness. Crystallization of the residue from hexane gave 0.44 g (44%) of crude phenol **6**, mp 105–108°. Recrystallization from hexane gave needlelike prisms: mp 111–114° (lit.[9c] mp 114–115°); when mixed with an authentic sample, mp 114–115°, the melting point was not depressed; λ_{max}^{EtOH} 206 mμ (ε 38,000), 235 (27,000), 264 (16,500), 300 (4450).

Anal. Calcd for $C_{21}H_{20}O$: C, 87.46; H, 6.99. Found: C, 87.57; H, 7.05.

Registry No.—**1**, 2892-18-4; **2a**, 18346-83-3; hexadeuterio **2a**, 18366-75-1; **2b**, 18346-82-2; hexadeuterio **2b**, 18366-76-2; **2c**, 18366-77-3; **3a**, 10596-48-2; **4**, 18366-78-4; **6**, 18354-80-8; **7**, 18354-81-9.

Acknowledgment.—The authors are indebted to Drs. Wayne R. Carpenter and Thomas G. Archibald for assistance in securing the mass spectra and for helpful discussions.

Photorearrangement of β,γ-Unsaturated Ketones. Application to the Synthesis of Bridged Bicyclic Ketones

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Ultraviolet irradiation of β,γ-unsaturated ketones such as **3**, **5**, and **7** in which the double bond occupies an exocyclic position with respect to the carbonyl group has been found to give rise exclusively to unsaturated bridged bicyclic ketones. The photorearrangements were shown to be completely reversible, the apparent photostationary states lying substantially in favor of **3**, **5**, and **7**. Although ketones **4**, **6**, and **8** do not predominate at equilibrium, isolation can be achieved by preparative-scale gas chromatography. These conversions therefore provide synthetic entry to previously unknown and otherwise difficultly accessible carbonyl compounds. The spectra and physical properties of these ketones are presented in some detail.

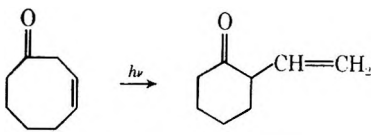
Light-induced transformations of β,γ-unsaturated ketones have been the subject of recent intensive study. The capability of such formally nonconjugated molecules for photochemical excitation and subsequent chemical change is linked to the enhanced n → π* absorption generally associated with the β,γ-unsaturated carbonyl chromophore.[2] In brief, it is now recognized that cyclic and acyclic β,γ-unsaturated ketones may undergo three general types of phototransformation depending upon the structure of the

(1) The Ohio State University Postdoctoral Fellow, 1967–1968.

(2) (a) A. Moskowicz, K. Mislow, M. A. W. Glass, and C. Djerassi, *J. Amer. Chem. Soc.*, **84**, 1945 (1962); (b) D. E. Bays, R. C. Cookson, and S. Mackenzie, *J. Chem. Soc., B*, 215 (1967).

particular molecule: carbon monoxide expulsion,[3] Norrish type-I cleavage, often accompanied by allylic rearrangement,[4] and conjugated cyclopropyl ketone formation.[5] Photoreduction of a β,γ-unsaturated ketone has been observed in one instance.[6]

The molecular change involved in the allyl migration of an acyl radical as seen, for example, in the conversion of 1 into 2[4l,m] is unprecedented in ground-state chemistry and suggests several diverse synthetic applications. The present paper describes the photorearrangement of bicyclic ketones in which the β,γ-olefinic linkage



1 2

occupies an exocyclic position with respect to the carbonyl group.

Results

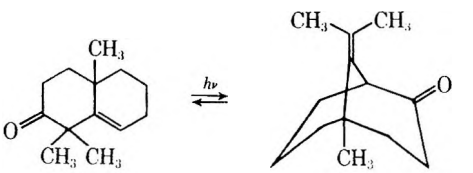
Irradiation of **3** in dilute pentane solution with a Hanovia 450-W mercury arc and Vycor optics led to the rapid establishment of a photostationary state consisting of the starting ketone **3** and a single photoproduct (see Table I).[7a] Further irradiation (beyond 60 min) did not appear to alter the ratio of the two components but gave a poorer recovery of the ketones presumably because of polymer formation. Preparative-scale vpc served to provide pure samples of the liquid photoketone which was characterized as its semicarbazone derivative. In agreement with structure **4**, this photoisomer exhibited an intense infrared (ir) band (in CCl_4) at 5.84 μ and an ultraviolet (uv) spectrum in isooctane solution [λ_{max} 286 mμ (ε 145) and 300 sh (125)] suggestive of a nonplanar β,γ-unsaturated ketone.[2] The nuclear magnetic resonance (nmr) spectrum, which is fully compatible with this structural assignment, displays, *inter alia*, a high field singlet at δ 1.43 assigned to the saturated methyl group at C-5, singlets at 1.68 and 1.92 attributable to the isopropylidine methyl groups, and a broad pattern (1 H) at 3.37 indicative of an allylic α-keto proton.[8-10] The substance does not exhibit absorption below δ 3.4. Final evidence that **3** and **4** are interrelated structurally by a noncomplicated photorearrangement process was obtained by irradiation of purified samples of **4**. A

Table I

Time-Composition Data for the Photorearrangements of 3, 5, and 7

Irradiation period, min	3, ratio 3:4[a]	5, ratio 5:6[a]	7, ratio 7:8[a]
15	13.0:1	4.2:1	7.3:1
25		4.0:1	
30	10.0:1		6.7:1
35		3.8:1	
45	9.9:1		
55		3.9:1	
60			6.6:1

[a] Only two components were seen in each series of experiments.



3 4

(3) (a) J. E. Starr and R. H. Eastman, *J. Org. Chem.*, **31**, 1393 (1966); (b) P. Dowd and K. Sachdev, *J. Amer. Chem. Soc.*, **89**, 715 (1967); (c) L. D. Hess and J. N. Pitts, *ibid.*, **89**, 1973 (1967).

(4) (a) G. Büchi and E. M. Burgess, *ibid.*, **82**, 4333 (1960); (b) P. E. Eaton, *Tetrahedron Lett.*, 3695 (1964); (c) R. Criegee and J. Furrer, *Chem. Ber.*, **97**, 2949 (1964); (d) D. I. Schuster, M. Axelrod, and J. Auerbach, *Tetrahedron Lett.*, 1911 (1963); (e) G. O. Schenk and R. Steinmetz, *Chem. Ber.*, **96**, 520 (1963); (f) R. L. Cargill, M. E. Beckham, A. E. Seibert, and J. Dorn, *J. Org. Chem.*, **30**, 3647 (1965); (g) N. C. Yang and D. M. Thap, *Tetrahedron Lett.*, 3671 (1966); (h) E. Baggiolini, E. G. Herzog, S. Iwasaki, R. Schorta, and K. Schaffner, *Helv. Chim. Acta*, **50**, 297 (1967); (i) E. F. Kiefer and D. A. Carlson, *Tetrahedron Lett.*, 1617 (1967); (j) L. D. Hess, J. L. Jacobson, K. Schaffner, and J. N. Pitts, Jr., *J. Amer. Chem. Soc.*, **89**, 3684 (1967); (k) W. F. Erman and H. C. Kretschmar, *ibid.*, **89**, 3842 (1967); (l) L. A. Paquette and R. F. Eizember, *ibid.*, **89**, 6205 (1967); (m) J. K. Crandall, J. P. Arrington, and J. Hen, *ibid.*, **89**, 6208 (1967); (n) D. E. Bays and R. C. Cookson, *J. Chem. Soc., B*, 226 (1967); (o) R. G. Carlson and J. H. Bateman, *Tetrahedron Lett.*, 4151 (1967); (p) M. Fischer and B. Zech, *Chem. Ber.*, **101**, 2360 (1968); (q) L. A. Paquette, R. F. Eizember, and O. Cox, *J. Amer. Chem. Soc.*, **90**, 5153 (1968).

(5) (a) L. P. Tenney, D. W. Baykin, Jr., and R. E. Lutz, *ibid.*, **88**, 1835 (1966); (b) J. R. Williams and H. Ziffer, *Chem. Commun.*, 194 (1967); (c) J. R. Williams and H. Ziffer, *ibid.*, 469 (1967); see also ref 4q.

(6) R. L. Cargill, J. R. Damewood, and M. M. Cooper, *J. Amer. Chem. Soc.*, **88**, 1330 (1966).

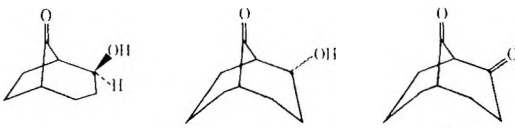
(7) (a) The percentage compositions cited in Tables I and II were determined with a Varian-Aerograph Hy-Fi gas chromatograph[7b] and the values are uncorrected for differences in flame ionization response of the isomeric ketone pairs. This type of analysis was deemed most satisfactory, albeit that the values are not precisely correct, in view of the low concentrations of the bridged bicyclic ketones early in the irradiation experiments with **3**, **5**, and **7**. The internal consistency of the technique is obvious from the data in the two tables. (b) On the other hand, the values given in the text are product composition values derived from preparative-scale reactions (see Experimental Section), analysis of which has been made by thermal conductivity vapor phase chromatography (vpc). Because differences in thermal conductivity response are generally minimal, the photostationary-state values obtained by this technique are considered more accurate.

(8) A referee has raised the question that the ir, uv, and nmr spectra of this photoproduct may be abnormal, thereby allowing for several alternative structural possibilities such as i–iii. Although we have not been successful

i ii iii

in our varied attempts to degrade or to synthesize in unequivocal fashion the bridged bicyclic ketones (see footnote 9), this point does not seem well taken since the nmr chemical shift data completely rule out such alternative formulations. It is also difficult to reconcile the complete reversibility of the photoisomerization (*vide infra*) with these alternatives. Furthermore, we are not prepared to accept the premise that the spectral properties of the photoisomers need be abnormal (see particularly ref 10).

(9) Despite this disadvantage, the photoisomerization pathway appears to be the only available route to such bridged ketones (with the exception of **9**) at the present time. We have tried without success to convert by means of a variety of reactions the ketols iv [N. A. LeBel and L. A. Spurlock, *J. Amer. Chem. Soc.*, **84**, 4360 (1962)] and v [A. C. Cope, D. L. Nealy, P. Scheiner, and G. Wood, *ibid.*, **87**, 3130 (1965)] and the diketone vi [J. R. Hargreaves and P. W. Hickmott, *Tetrahedron Lett.*, 4173 (1966)] into the desired β,γ-unsaturated ketones. Further, efforts to degrade **6** to vi by means of the ozonolysis procedure of Meinwald and Gassman [*J. Amer. Chem. Soc.*, **82**, 5445 (1960)] were to no avail, further degradation to more highly oxygenated material being observed.



iv v vi

(10) C. H. DePuy and P. R. Story, *J. Amer. Chem. Soc.*, **82**, 627 (1960).

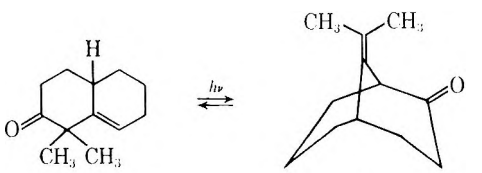
TABLE II
TIME-COMPOSITION DATA FOR THE PHOTOREARRANGEMENTS OF 4, 6, AND 8

Irradiation period, min	4, ratio 3:4[a]	6, ratio 5:6[a]	8, ratio 7:8[a]
10	1.4:1	0.9:1	0.6:1
20	4.3:1	2.0:1	2.4:1
30	7.6:1	3.1:1	5.2:1
40	9.5:1	3.7:1	6.8:1
50	9.7:1	3.8:1	6.9:1
60	9.7:1		

[a] Only two components were seen in each series of experiments.

photostationary state which was virtually identical with that observed when proceeding from **3** was rapidly attained (see Table II).[7a]

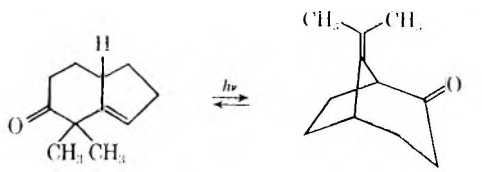
Similarly, ketone **5** was found to give rise to **6** when irradiated under identical conditions; again, a photostationary state was rapidly established (see Table I). It is interesting that the nonbridged ketone **5** predominates to the extent of approximately 77%, whereas



5 6

in the case of **3** the product distribution is such that **3** is present to the extent of about 94%.[7b] Photoketone **6** exhibited a 5.84-μ carbonyl band in the ir which is characteristic[11] of a cyclohexanone. The uv spectrum (isooctane) [λ_{max} 293 mμ (ϵ 130), 302 (130), and 311 sh (100)] is characteristic of a β,γ-unsaturated carbonyl chromophore.[2,10] The 60-MHz nmr spectrum showed the isopropylidene methyl groups as singlets at δ 1.73 and 1.66. In addition, the allylic α-keto proton was seen at δ 3.25 and the allylic bridgehead proton at 3.07; this is to be compared with the nmr spectrum of **4** which lacks the latter absorption because of the presence of a methyl group at that position.

Irradiation of tetrahydroindanone **7** in dilute pentane solution again rapidly effected the establishment of a photoequilibrium with a lone photoketone which also displayed 5.83-μ ir carbonyl absorption characteristic of a six-membered ring ketone. The nmr

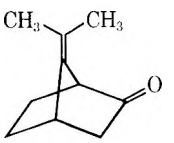


7 8

spectrum was very similar to that of **6** with three-proton singlets at δ 1.75 and 1.62 and broadened one-proton signals centered at 3.30 and 3.03. The uv spectrum in isooctane exhibited maxima at 288 mμ sh (ϵ 360), 296 (420), 305 (390), and 317 (225). These data and analogy to the rearrangement of **3** and **5** indicated that this photoketone is 8-isopropylidenebicyclo[3.2.1]octan-2-one (**8**).

(11) L. J. Bellamy, "The Spectra of Complex Molecules," 2nd ed, John Wiley & Sons, Inc., New York, N. Y., 1958.

In the case of **8**, there is observed an increase in λ_{max} and also in the extinction coefficient over that for its two higher homologs, **4** and **6**. These data suggest somewhat improved interaction between the carbonyl group and the double bond in **8**, in full agreement with the observation of such interaction in Dreiding models of **4**, **6**, and **8** and with the spectral parameters previously reported for congener **9** [λ_{max} 308 mμ (ϵ 423)].[10]



9

The photostationary state in this last instance was found to consist of approximately 88% **7** and 12% **8**,[7b] independent of the direction from which the equilibrium was approached (Tables I and II).

The behavior of α,β-unsaturated cyclic ketones under conditions of electron impact has been the subject of considerable study.[12] It is now recognized that such systems often undergo mechanistically interesting alkyl and aryl rearrangements. Because β,γ-unsaturated ketones have been little studied, and particularly in view of the isomeric nature of the three ketone pairs **3**–**8**, we were led to examine their mass spectra (see Table III). The mass spectra of ketones **3**, **5**, and **7** differ markedly from those of their bridged bicyclic isomers. Not only do these ketones give rise to abundant molecular ions, but fragmentations involving M − 43 and M − 55 ions occur to a significant extent. In contrast, bridged bicyclic ketones **6** and **8** exhibit very weak molecular ions and considerable fragmentation to low molecular weight ions. The base peak in both cases is found at m/e 43. The mass spectrum of **4** is quite complicated. From such data it is clear that electron-impact fragmentation (70 eV) of the two ketone pairs does not proceed exclusively by α-keto cleavage to afford identical allylic radical cations. Thus, although a number of organic compounds display parallel behavior on electron impact and pyrolysis,[13] such a comparison apparently cannot be extended in the present case to include photolysis.

Discussion

The photochemical interconversion of ketone pairs **3-8** unquestionably involves initial $n \rightarrow \pi^*$ excitation of the carbonyl group and cleavage of the allylic α-carbonyl bond. Migration of the acyl function to the alternate terminus of the allyl moiety can proceed in concerted fashion and therefore may not involve discrete diradical intermediates. The possible concerted nature of this photochemical change finds its basis in orbital symmetry considerations of such 1,3 suprafacial[14] sigmatropic shifts.[9]

Although the present report establishes the fact that

(12) R. L. N. Harris, F. Komitsky, Jr., and C. Djerassi, *J. Amer. Chem. Soc.*, **89**, 4765 (1967), and pertinent references cited therein.

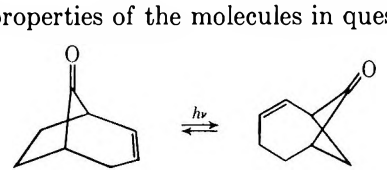
(13) M. P. Cava and R. J. Spangler, *ibid.*, **89**, 4550 (1967); D. C. DeJongh, R. Y. Van Fossen, and C. F. Bourgeois, *Tetrahedron Lett.*, 271 (1967), and references cited therein.

(14) The geometrical restraints placed upon ketones **6**–**11** by the arrangement of atoms can only lead to suprafacial shifts.

Table III
m/e Values and Per Cent Relative Abundance for Various Fragment Ions of Ketones 3–8

Compd	*m/e* (% relative abundance)
4	39 (58), 40 (14), 41 (90), 43 (30), 51 (23), 52 (16), 53 (52), 54 (12), 55 (65), 57 (19), 65 (32), 66 (15), 67 (58), 69 (36), 77 (52), 78 (16), 79 (75), 80 (20), 81 (63), 82 (16), 91 (75), 92 (16), 93 (100), 94 (28), 95 (49), 105 (45), 106 (17), 107 (69), 108 (30), 109 (20), 110 (26), 117 (14), 119 (20), 121 (65), 122 (20), 123 (17), 131 (14), 133 (17), 135 (51), 136 (55), 137 (58), 149 (63), 150 (26), 159 (20), 163 (11), 164 (13), 177 (65), 192 (80), 193 (13)
6	41 (50), 42 (63), 43 (100), 57 (24), 71 (12), 79 (14), 123 (12), 135 (12), 178 (15)
8	39 (13), 41 (38), 42 (74), 43 (100), 56 (14), 57 (32), 71 (20), 72 (11), 164 (5)
3	39 (47), 40 (10), 41 (100), 51 (15), 53 (36), 55 (43), 57 (14), 65 (18), 67 (35), 69 (26), 77 (36), 78 (12), 79 (48), 80 (10), 81 (49), 91 (55), 92 (13), 93 (82), 94 (20), 95 (35), 105 (27), 106 (13), 107 (55), 108 (20), 109 (13), 110 (20), 120 (15), 121 (51), 122 (14), 123 (14), 133 (12), 135 (39), 136 (40), 137 (50), 149 (51), 150 (18), 159 (10), 163 (10), 164 (11), 177 (56), 192 (84), 193 (13)
5	39 (52), 41 (83), 43 (50), 51 (18), 52 (11), 53 (37), 55 (34), 65 (21), 67 (59), 69 (20), 77 (47), 78 (17), 79 (95), 80 (22), 81 (42), 91 (61), 92 (18), 93 (67), 94 (26), 95 (14), 105 (24), 106 (10), 107 (65), 108 (18), 119 (20), 121 (43), 122 (18), 123 (91), 124 (12), 135 (96), 136 (35), 163 (12), 178 (100), 179 (13)
7	39 (45), 41 (50), 43 (17), 51 (17), 52 (10), 53 (26), 55 (20), 65 (21), 66 (11), 67 (28), 77 (39), 78 (13), 79 (53), 80 (28), 81 (12), 91 (56), 92 (12), 93 (86), 94 (12), 105 (28), 107 (89), 108 (55), 109 (100), 110 (12), 120 (42), 121 (34), 122 (12), 131 (12), 136 (11), 164 (85), 165 (10)

4, **6**, and **8** can be synthesized photochemically from readily available precursors, it was disappointing to observe that these bridged ketones do not exceed their nonbridged counterparts at the apparent photostationary states.[15] Germane to this question of product distribution is the recent report by Erman and Kretschmar[4k] that the more strained cyclobutanone **11** predominates over **10** at photoequilibrium (1.7:1). Two other examples studied by these workers followed the same course. However, the examples presented herein and earlier[4] demonstrate unequivocally that product distribution is determined solely by the photochemical properties of the molecules in question and is



10 **11**

not related to their relative thermodynamic stabilities. In particular, utmost caution should be exercised in attempts to correlate wavelength and intensity of n → π* absorption bands of such β,γ-unsaturated ketones with product distribution, particularly when broad spectrum light sources are employed. The precise output of such lamps at the different wavelengths is frequently difficult to assess; therefore, correlations with available uv absorption data cannot be made justifiably. Whether product distribution will be predictable when appropriate monochromatic light sources are used under strictly controlled conditions remains to be determined.

(15) R. B. Woodward and R. Hoffmann, *J. Amer. Chem. Soc.*, **87**, 2511 (1965).

Experimental Section[16]

1,1,4a-Trimethyl-1,3,4,4a,5,6,7-heptahydronaphthalen-2-one (3).—This ketone was prepared in the manner described by Marshall and Hochstetler[17] and Yanagita, Hirakura, and Saki.[18] From 10.0 g of 4a-methyl-3,4,4a,5,6,7,8-heptahydronaphthalen-2-one[19] there was obtained 8.24 g of a colorless liquid, bp 73.5–75.5° (0.5 mm), which was a mixture of two components in the ratio 8.05:1. Pure **3** was obtained by regeneration (pyruvic acid) of the recrystallized (*sec*-butyl alcohol) semicarbazone: mp 222–224° dec. The purified ketone displayed mp 32–33.5° (lit.[18] mp 31.5–32.5°); $\lambda_{max}^{isooctane}$ 228 mμ (ε 35), 296 sh (35), and 305 sh (30); $\delta_{TMS}^{CCl_4}$ 5.51 (triplet, J = 4.3 Hz, 1 H, vinyl proton), 2.6–1.4 (complex pattern, 10 H, methylene protons), 1.17 (singlet, 6 H, C-1 dimethyl protons), and 0.98 (singlet, 3 H, C-4a methyl group).

9-Isopropylidene-5-methylbicyclo[3.3.1]nonan-2-one (4).—A solution of 2.00 g (10.4 mmol) of **3** in 600 ml of pentane was irradiated for 30 min under a nitrogen atmosphere with a 450-W medium-pressure Hanovia Type L mercury arc in a quartz immersion well apparatus fitted with a Vycor filter. Removal of the solvent *in vacuo* at 25° gave a colorless oil (1.96 g) which was shown by vpc (column A,[20] 155°) to be a mixture of unchanged **3** and a single photoproduct (**4**) in the ratio 14.4:1. This mixture was subjected to preparative-scale vpc separation (column A,[20] 140°) to afford 1.53 g (76.5%) of **3** and 0.107 g (5.4%) of **4**: mp *ca.* 25°; $\lambda_{max}^{CCl_4}$ 5.84, 6.84, 7.28, 8.00, 8.36, 8,57, 8.94, 9.15 μ; $\lambda_{max}^{isooctane}$ 286 (ε 145), 300 sh mμ (ε 125); $\delta_{max}^{CCl_4}$ 3.37 (broad signal, 1 H, allylic α-keto proton), 2.5–1.5 (complex pattern, 10 H, methylene protons), and 1.92, 1.68, and 1.43 (singlets, 3 H each, methyl groups). This ketone was characterized as its semicarbazone, mp 185–187° dec (from methanol).

Anal. Calcd for $C_{14}H_{23}N_3O$: C, 67.43; H, 9.30; N, 16.85. Found: C, 67.54; H, 9.24; N, 16.87.

1,1-Dimethyl-1,3,4,4a,5,6,7-heptahydronaphthalen-2-one (5).—This compound was prepared according to the method of Marshall and Andersen.[21] From 10.0 g of 3,4,4a,5,6,7,8-heptahydronaphthalen-2-one[22] there was obtained 11.7 g of crude product which by vpc analysis (column B,[20] 150°) was a mixture of two major components in the ratio 2.5:1. Purification of **5** was achieved by means of the semicarbazone, mp 185.5–187° (from methanol), to give a colorless oil: bp 86–87° (0.7 mm) [lit.[21] bp 62–64° (0.25 mm)]; $n^{25}D$ 1.5045; $\lambda_{max}^{isooctane}$ 289 mμ (ε 80), 297 (85), 306 (75), and 317 (40); $\delta_{TMS}^{CCl_4}$ 5.53 (doublet of triplets, $J_{8,7}$ = 3.9 Hz, $J_{8,4a}$ = 1.7 Hz, 1 H, vinyl proton), 2.9–1.3 (complex pattern, 11 H, methylene protons), and 1.21 and 1.13 (singlets, 3 H each, methyl groups).

9-Isopropylidenebicyclo[3.3.1]nonan-2-one (6).—Irradiation of a solution of 1.50 g (8.45 mmol) of **5** in 450 ml of pentane in the above apparatus for 30 min afforded, after concentration *in vacuo* at 0°, 1.48 g of a yellow oil which was shown by vpc (column A,[20] 130°) to be a mixture of unchanged **5** and a single photoproduct **6** in the ratio 3.4:1. Preparative-scale vpc separation (column B,[20] 135°) of this mixture afforded 0.592 g (39.5%) of **5** and 0.104 g (6.9%) of **6**: $\lambda_{max}^{CCl_4}$ 5.84, 6.92, 7.30, 7.55, 8.14, 9.16 μ; $\lambda_{max}^{isooctane}$ 293 mμ (ε 130), 302 (130), and 311 sh (100); $\delta_{TMS}^{CCl_4}$ 3.25 and

(16) Melting points were determined with a Thomas–Hoover melting point apparatus and are corrected. Ir spectra were recorded with a Perkin-Elmer Infracord Model 137 spectrometer fitted with sodium chloride prisms. Uv spectra were determined with a Cary 14 recording spectrometer. Nmr spectra were obtained with a Varian A-60 spectrometer purchased with funds made available through the National Science Foundation. The mass spectra were measured with an AEI MS-9 mass spectrometer at an ionizing energy of 70 eV. The microanalyses were performed by the Scandinavian Microanalytical Laboratory, Herlev, Denmark.

(17) J. A. Marshall and A. R. Hochstetler, *Chem. Commun.*, 732 (1967).

(18) M. Yanagita, M. Hirakura, and F. Saki, *J. Org. Chem.*, **23**, 841 (1958).

(19) J. A. Marshall and W. I. Fanta, *ibid.*, **29**, 2501 (1964).

(20) Column A: 0.25 in. × 5.5 ft aluminum column packed with 20% SE-30 on 60/80 mesh Chromosorb W. Column B: 0.25 in. × 5.5 ft aluminum column packed with 20% SF-96 on 60/80 mesh Chromosorb W. All preparative gas chromatographic work was accomplished with Varian-Aerograph A-90P3 gas chromatographs fitted with thermal conductivity cell detectors.

(21) J. A. Marshall and N. H. Andersen, *J. Org. Chem.*, **31**, 667 (1966).

(22) G. S. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Amer. Chem. Soc.*, **85**, 207 (1963).

3.07 (broad signals, 1 H each, bridgehead protons), 2.9–1.5 (complex pattern, 10 H, methylene protons), and 1.73 and 1.66 (singlets, 3 H each, isopropylidene methyl groups). This ketone was characterized as its semicarbazone, mp 205–207° dec (from methanol).

Anal. Calcd for $C_{13}H_{21}N_3O$: C, 66.35; H, 9.00; N, 17.86. Found: C, 66.46; H, 8.98; N, 17.74.

4,4-Dimethyl-4,6,7,7a-tetrahydroindan-5-one (7).—Treatment of 10.0 g of 3,6,7,7a-tetrahydroindan-5-one[22] according to the procedure of Marshall, Andersen, and Johnson[23] gave 5.43 g of a colorless liquid, bp 52–55° (0.5 mm), which contained approximately 77% **7**. Purification was achieved *via* its semicarbazone, mp 209–210.5° dec (from methanol), to give **7**: bp 55.5–56.5° (0.6 mm); $n^{25}D$ 1.4935; $\lambda_{max}^{isooctane}$ 289 mμ (ε 90), 298 (95), 308 (85), and 319 (45); $\delta_{TMS}^{CCl_4}$ 5.34 (doublet of doublets, $J_{3,2}$ = 2 Hz, $J_{3,7a}$ = 2 Hz, 1 H, vinyl proton), 3.0–1.3 (complex pattern, 9 H, methylene protons), and 1.22 and 1.20 (singlets, 3 H each, methyl groups).

8-Isopropylidenebicyclo[3.2.1]octan-2-one (8).—A solution of 1.50 g (9.15 mmol) of **7** in 450 ml of pentane was irradiated for 30 min under the predescribed conditions. Removal of the solvent *in vacuo* at 25° gave 1.49 g of a light yellow oil which was shown by vpc (column A or B,[20] 130°) to be a mixture of unchanged **7** and a single photoproduct **8** in the ratio 7.6:1. Preparative vpc (column B,[20] 130°) of this mixture led to the isolation of 0.874 g (58%) of **7** and 0.130 g (8.7%) of **8**: $\lambda_{max}^{CCl_4}$ 5.83, 6.89, 7.04, 7.28, 7.65, 8.10, 9.74 μ; $\lambda_{max}^{isooctane}$ 288 sh mμ (ε 360), 296 (420), 305 (390), and 317 (225); $\delta_{TMS}^{CCl_4}$ 3.30 and 3.03 (broad signals, 1 H each, bridgehead protons), 2.7–1.75 (complex pattern, 8 H, methylene protons), and 1.75 and 1.62 (singlets, 3 H each, isopropylidene methyl groups). This ketone was characterized as its semicarbazone, mp 205–206° dec (from methanol).

Anal. Calcd for $C_{12}H_{19}N_3O$: C, 65.12; H, 8.65; N, 18.99. Found: C, 65.18; H, 8.64; N, 19.06.

Photoequilibration Experiments.—Solutions (*ca.* 1%) of ketones **3**–**8** in pentane were placed under a nitrogen atmosphere in quartz test tubes, affixed to the exterior of the quartz well, and irradiated in the manner described above. The progress of the reactions were monitored by vpc analysis on a Varian-Aerograph Hy-Fi Model 600D gas chromatograph. Aliquots were obtained by piercing the septum-sealed test tubes with a syringe of the proper size.

Registry No.—**3**, 4668-61-5; **3** semicarbazone, 18366-32-0; **4**, 18346-76-4; **4** semicarbazone, 18346-77-5; **5**, 2020-07-7; **5** semicarbazone, 5164-39-6; **6**, 18346-78-6; **6** semicarbazone, 18346-79-7; **7**, 18366-35-3; **7** semicarbazone, 18366-36-4; **8**, 18346-80-0; **8** semicarbazone, 18346-81-1.

(23) J. A. Marshall, N. H. Andersen, and P. C. Johnson, *J. Amer. Chem. Soc.*, **89**, 2748 (1967).

Notes

Ferrocene Studies. II. The Reaction of Ferrocenyllithium with Aromatic Aldehydes[1]

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In general, organometallic compounds react with aromatic aldehydes to give secondary alcohols. A recent exception is the reported formation of 2-aroylpyrroles from the reaction of pyrrylsodium with aromatic aldehydes.[2] This reaction was proposed by Raines to proceed through an alkoxide reduction involving a second mole of the aldehyde.

We now wish to report that the reaction of ferrocenyllithium (I) with aromatic aldehydes in tetrahydrofuran gave aryl ferrocenyl ketones (II). Thus *p*-chlorbenzaldehyde, tolualdehyde, anisaldehyde, and ferrocenecarboxaldehyde gave the appropriate aryl ferrocenyl ketone (II) and no secondary alcohol when either a 3:1 or 1:1 *M* ratio of the aldehyde was added to ferrocenyllithium (I) in tetrahydrofuran. The expected alcohol was obtained (together with the ketone) only when benzaldehyde was allowed to react in a 1:1 molar ratio. With an excess of aldehyde, benzaldehyde also gave rise to ketone and no alcohol.

This reaction apparently follows a course similar to that proposed by Raines[2] in the pyrrole series. Thus when phenylferrocenylmethanol (III) was treated with *n*-butyllithium, alkoxide IV was formed as indicated by the formation of the ether V upon the addition of methyl iodide. When benzaldehyde was added to IV benzoylferrocene (II, Ar = C_6H_5) was obtained (Scheme I).

The ferrocenyllithium (FcLi) was prepared from bromoferrocene in tetrahydrofuran.[3] That complete lithiation of the bromoferrocene had occurred was checked by direct carbonation to form ferrocenecarboxylic acid. In all cases liquid aldehydes were purified by distillation under a nitrogen atmosphere before use and the tetrahydrofuran was distilled freshly from lithium aluminum hydride. In all cases a significant amount of ferrocene appears as a product of the reaction. This could arise by a simple proton abstraction from impurities or solvent, as a product from some mechanistic pathway, or more likely as the result of hydrolysis of unused ferrocenyllithium which had not reacted with the aldehyde. The later reasoning would

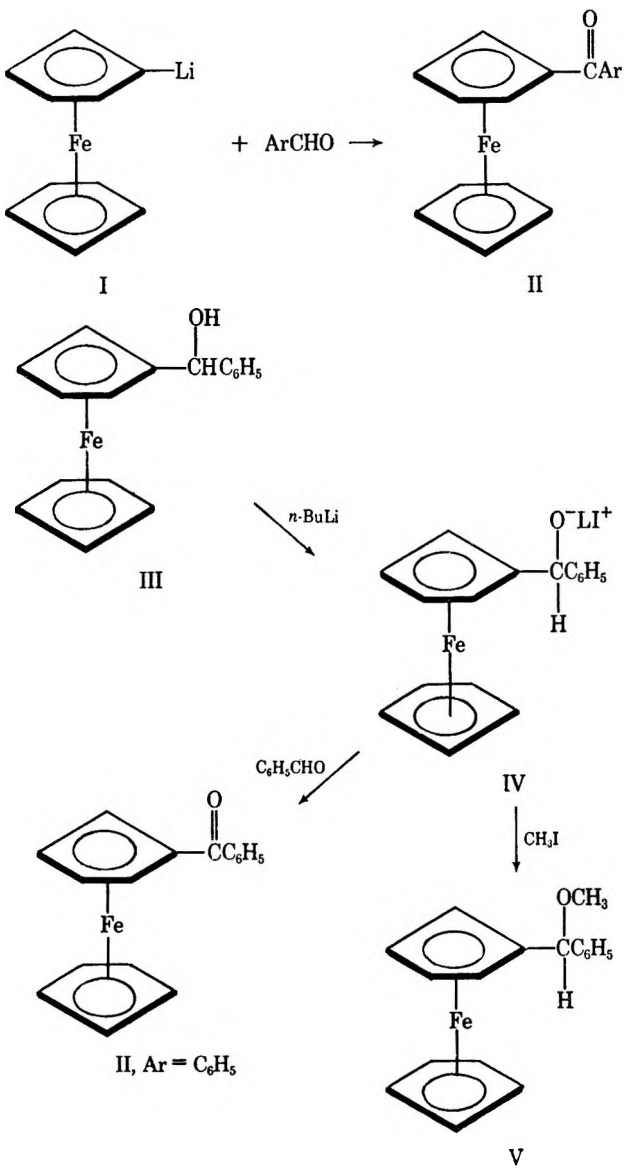
(1) Part I.: F. D. Popp and J. A. Kirby, *J. Chem. Eng. Data*, **8**, 604 (1963). We should like to thank the Norwich Pharmacal Co. for financial support of a portion of this work.

(2) S. Raines, *J. Org. Chem.*, **32**, 227 (1967).

(3) H. Rosenburg, J. M. Barton, and M. M. Hollander, Abstracts of 2nd Annual International Symposia on Organometallic Chemistry, Madison, Wis., Aug 30–Sept 3, 1965. We should like to thank Dr. Rosenberg for his helpful comments in regard to this preparation.

also explain the formation of triferrocenylmethanol from the reaction of ferrocenyllithium with ferrocenealdehyde. Several unidentified compounds were obtained in a number of reactions. Although no rigorous attempt was made to identify these products, anisaldehyde and tolualdehyde gave products which appear to be diarylferrocenylcarbinols. The possible presence of tertiary carbinols and the isolation of carboxylic acids from two reactions might indicate possible oxidation of aldehyde to acid followed by a Hammick-type reaction with the ketones.

SCHEME I



It is of interest to note that in the case of the 1:1 reaction of benzaldehyde with ferrocenyllithium (where the carbinol was found), the yield of carbinol could be increased by the use of excess *n*-butyllithium. Finally it should be noted that when phenylferrocenylmethanol was subjected to the separation and purification scheme used in these reactions no evidence of ketone formation could be noted, indicating that the ketone arose from the reaction and not as an artifact from purification.

Experimental Section[4]

Bromoferrocene was synthesized from chloromercuriferrocene[5] by the method of Fish and Rosenblum[5] with the following modifications. The reaction was worked up immediately after the rapid addition of the 10% sodium thiosulfate solution by the addition of 100–125 g of crushed ice followed by extraction with Skellysolve B. The addition of crushed ice was repeated before each extraction. In this manner large runs can be carried out while keeping the volume to a reasonable size. In a typical run 8.4 g of chloromercuriferrocene gave after chromatography and drying 4.6 g (86.5%) of bromoferrocene, mp 30–31°.

Ferrocenyllithium.—The lithiation of bromoferrocene was accomplished according to a procedure followed by Rosenberg and coworkers.[3] In a typical experiment 1.5 ml of 2.51 *M* (3.77 mmole) *n*-butyllithium in hexane was added over 10 min to a stirred solution of 1.0 g (3.77 mmol) of bromoferrocene in 35 ml of anhydrous tetrahydrofuran at 0°. After stirring for an additional 30 min at 0° the various aldehydes were added to the solution as described below.

Condensation of Ferrocenyllithium with Benzaldehyde. A. Excess Benzaldehyde.—To a 3.77-mmol solution of ferrocenyllithium as described above was added at 0° over a period of 10 min 4.025 g (37.9 mmol) of benzaldehyde. After stirring for 12 hr at room temperature, 20 ml of distilled water and 40 ml of ether were added and the organic layer was separated. The organic layer was washed successively with two 50-ml portions of a 10% sodium bisulfite solution and two 50-ml portions of distilled water and dried over magnesium sulfate. Concentration gave an oil which on chromatography with Skellysolve B gave 0.25 g (34%) of ferrocene and 0.60 g (55%) (eluted with benzene–ether) of benzoylferrocene. In addition to the usual methods of identification[4] this material was reduced[6] to the expected carbinol.

B. Molar Amounts of Reactants.—In the same manner 3.77 mmol of ferrocenyllithium and 3.77 mmol of benzaldehyde gave the three products as indicated in Table I together with a small amount of unidentified solid, mp 74–77° (not benzylferrocene).

Anal. Found: C, 74.17; H, 5.62; Fe, 19.43.

TABLE I

FERROCENYLLITHIUM AND AROMATIC ALDEHYDES

Aldehyde	Ratio of FcLi to ArCHO	Ferrocene	Products,[a] % O ‖ FcCAr	Products,[a] % OH | FcCHAr
C_6H_5CHO	1:10	34	55	0
	1:1	50	16	16
	1:1 (x's BuLi)	22	12	42
FcCHO	1:3	36	41	0
	1:1	31	12	0
p-$CH_3OC_6H_4CHO$	1:3	33	66	0
	1:1	21	10	0
p-$CH_3C_6H_4CHO$	1:3	53	12	0
	1:1	54	6	0
p-ClC_6H_4CHO	1:3	50	23	0
	1:1	10	11	0

[a] See Experimental Section for other products in specific reactions.

C. Molar Amounts of Reactants with Excess *n*-Butyllithium.—In the same manner 3.77 mmol of ferrocenyllithium (from 3.77 mmol of bromoferrocene and 5.42 mmol of *n*-butyllithium) and 3.77 mmol of benzaldehyde gave the three products as indicated in Table I together with a very small amount of unidentified yellow oil.

(4) All melting points are corrected and taken in capillaries. Analyses by Spang Microanalytical Laboratory, Ann Arbor, Mich. All aldehydes were purified immediately before use and the tetrahydrofuran was distilled from lithium aluminum hydride before use. The preparation of ferrocenyllithium and all reactions of ferrocenyllithium were carried out under a nitrogen atmosphere. Chromatographic separations were by dry column chromatography [B. Loev and M. M. Goodman, *Chem. Ind.* (London), 2026 (1967)]; we should like to thank Dr. Loev for helpful comments regarding this technique. All known compounds were identified by comparison of melting point and infrared and nmr spectra with authentic samples.

(5) R. W. Fish and M. Rosenblum, *J. Org. Chem.*, **30**, 1253 (1965).

(6) N. Weliky and E. S. Gould, *J. Amer. Chem. Soc.*, **79**, 2742 (1957).

Condensation of Ferrocenyllithium with Other Aldehydes.[7] **Excess Ferrocenecarboxaldehyde.**—Concentration gave diferrocenylketone[8] and an oil (five components by tlc) which on chromatography gave ferrocene, ferrocenecarboxaldehyde and unstable red oils.

Molar Amount of Ferrocenecarboxaldehyde.—Concentration gave 5% of ferrocenecarboxylic acid and an oil which on chromatography gave the products in Table I, 8% of triferrocenylmethanol, and two unidentified solids, mp 120–122 and 142°, in low yield.

Excess and Molar Amount of Tolualdehyde.—Chromatography gave the products in Table I and a solid (16% from excess, 15% from molar), mp 117–118° (from heptane), believed to be ditolylferrocenylcarbinol.

Anal. Calcd for $C_{25}H_{24}FeO$: C, 75.77; H, 6.10; Fe, 14.09. Found: C, 75.34; H, 6.06; Fe, 14.44.

Molar Amount of Anisaldehyde.—Chromatography gave the products in Table I and 9% of a solid, mp 76–78° (from heptane), believed to be dianisylferrocenylcarbinol.

Anal. Calcd for $C_{25}H_{24}FeO_3$: C, 70.10; H, 5.65; Fe, 13.04. Found: C, 70.45; H, 5.82; Fe, 12.82.

Excess and Molar Amount of *p*-Chlorobenzaldehyde.—Concentration gave *p*-chlorobenzoic acid (8% from excess, 49% from molar) and an oil which on chromatography gave the products in Table I. The *p*-chlorobenzoylferrocene had mp 119–120° from heptane.

Anal. Calcd for $C_{17}H_{13}ClFeO$: C, 62.90; H, 4.04; Fe, 17.21. Found: C, 63.06; H, 4.16; Fe, 17.08.

This ketone gave a 2,4-dinitrophenylhydrazone, mp 226°, from methylene chloride–heptane.

Anal. Calcd for $C_{23}H_{17}ClFeN_4O_4$: N, 11.95. Found: N, 11.96.

Reaction of Benzaldehyde with Lithium Phenylferrocenylmethoxide.—To 0.230 g (0.787 mmol) of phenylferrocenylmethanol[9] in 15 ml of anhydrous THF at 0° was added 1 ml of 2.51 *M* *n*-butyllithium in hexane. After 15 min the solution was allowed to warm to room temperature and 1 ml of benzaldehyde was added. The reaction mixture was stirred for 12 hr at room temperature and treated as above to give 0.122 g (50%) of benzoylferrocene.

Reaction of Methyl Iodide with Lithium Phenylferrocenylmethoxide.—In the same manner as above, addition of 1 ml of methyl iodide in place of the benzaldehyde gave a 90% yield of V.

Registry No.—I, 1271-15-4; dianisylferrocenylcarbinol, 12310-26-8; *p*-chlorobenzoylferrocene, 12310-23-5; 2,4-dinitrophenylhydrazone of *p*-chlorobenzoylferrocene, 12310-24-6; ditolylferrocenylcarbinol, 12310-25-7.

(7) The procedures used are identical with those indicated for benzaldehyde. Major products are indicated in Table I and this section lists minor products isolated.

(8) Samples of diferrocenyl ketone were generously supplied by Drs. M. Rausch and S. Goldberg.

(9) M. Cais and A. Eisenstadt, *J. Org. Chem.*, **30**, 1148 (1965).

Ring Closure of 2,2′-Diiodobiphenyl

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Collette, *et al.*,[1] have carried out the facile ring closure of the iodoso compounds from 2-iodobiphenyl and its homologs. By this procedure diphenyleniodonium salts have been made in high yield (99%). According to Beringer, *et al.*,[2] the reaction mechanism probably involves electrophilic substitution by the conjugate acid formed by the action of sulfuric acid on the iodoso compound.

In the present work the ring closure of 2,2′-diiodobiphenyl has been carried out to give the bisiodonium salt (**1**). The reaction mixture also affords a small amount of the well-known diphenyleniodonium salt (**3**). The formation of **3** is interesting because it represents electrophilic substitution in which the conjugate acid replaces iodine.

In order to explain the formation of **3** and the nature of the displaced iodine which also must be an electrophile, 2,2′-diiodobiphenyl dissolved in peracetic acid was allowed to stand at *room temperature* for 1 week. During this time 91% of the starting material ring closed to form the iodonium salt and no bisiodonium salt was detected. Diphenyleniodonium iodate **4** (70%) separated as a white solid and there was also isolated the iodonium salt as diphenyleniodonium chloride (21%). A reasonable explanation is that in acetic–peracetic acid solution the iodine present as the iodoso group is displaced and is a better leaving group than hydrogen. In cold concentrated sulfuric acid solution the iodoso group is a better electrophile than it is in the weaker acetic acid. It is also possible that a more favorable structure for hydrogen replacement exists due to a restriction about the biphenyl bond. This may be due to the bulk of the conjugate acid functions and to a repulsion between like charges on the conjugate acid functions. In this connection it is interesting to note that Mascarelli[3] found that when 2,2′-diiodosobiphenyl or the tetrachloride was kept in water for some months the aqueous solution when treated with sulfur dioxide afforded diphenyleneiodonium iodide.

The less drastic conditions for ring closure, described by Collette, *et al.*,[1] are not satisfactory for the formation of **1**. Under these conditions the final reaction mixture contains unreacted 2,2′-diiodobiphenyl, a small amount of **3** and some monoiododiphenyleniodonium salt (**2**) (Scheme I).

The diphenyleniodonium salts and the bisiodonium salts described in the present paper should be useful synthetic reagents. We have found that **3** in water with cuprous chloride and ammonium hydroxide at the refluxing temperature affords carbazole (65%). The pyrolysis of **1** as the diiodide and **2** as the iodide affords, respectively, 2,2′,6,6′-tetraiodobiphenyl and 2,2′,6-triiodobiphenyl.

Experimental Section

2,2′-Diiodobiphenyl was prepared by the pyrolysis of diphenyleniodonium iodide.[1]

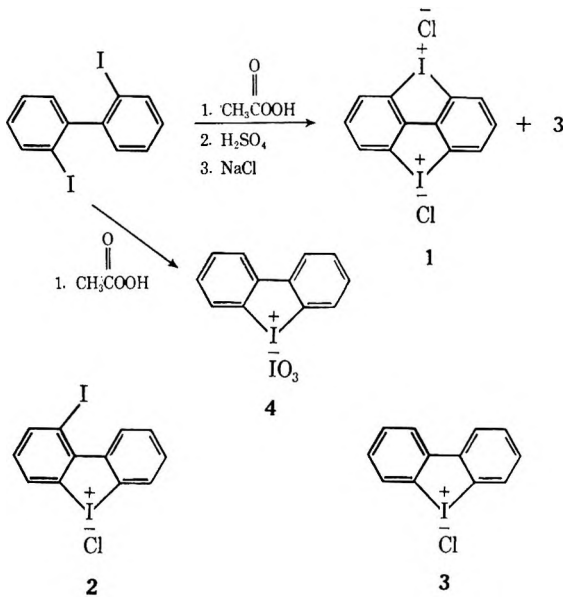
Peracetic Acid Oxidation and Cyclization. (*All preparations with organic peracids should be carried out behind a safety shield.*)—2,2′-Diiodobiphenyl (1.7 g) was added to peracetic acid[1] (50 ml) and allowed to stand for 72 hr at room temperature. The reaction mixture which now contained the iodoso compound was cooled in an ice–water bath and added dropwise and with stirring to concentrated sulfuric acid (25 ml) cooled in an ice–water bath. Some white solid separated and the

(1) J. Collette, D. McGreer, R. Crawford, F. Chubb, and R. B. Sandin, *J. Amer. Chem. Soc.*, **78**, 3819 (1956).

(2) F. M. Beringer, M. Drexler, E. M. Gindler, and C. C. Lumpkin, *ibid.*, **75**, 2705 (1953).

(3) L. Mascarelli, *Gazz. Chim. Ital.*, **43** (I), 26 (1913).

SCHEME I



mixture was allowed to stand at room temperature for 48 hr. The reaction mixture was poured into ice–water (500 ml) and the solid was collected and washed with water (1.0 l. at 70°). To the combined filtrate was added sodium chloride until precipitation was complete, which afforded III as the chloride.

Anal. Calcd for $C_{12}H_8ICl$: Cl, 11.28. Found: Cl, 10.99.

The residue was dissolved in boiling water (6.0 l.) and filtered while hot. To the hot filtrate was added sodium chloride until precipitation was complete, which afforded I as the dichloride, yield 0.5 g.

Anal. Calcd for $C_{12}H_6I_2Cl_2$ (0.0662- and 0.1310-g samples): AgI + AgCl, 0.1049, 0.2076 g. Found: AgI + AgCl, 0.1048, 0.2106 g.

When the procedure which brings about the facile ring closure of 2-iodobiphenyl[1] (5 g) was followed, the reaction mixture contained unreacted 2,2′-diiodobiphenyl, a small amount of III (0.1 g) and a relatively large amount of pale yellow II (1.1 g) which was isolated as the chloride.

Anal. Calcd for $C_{12}H_7I_2Cl$: Cl, 8.06. Found: Cl, 8.15, 8.39.

The brilliant yellow diiodide of I was prepared by the usual procedure.[1]

Anal. Calcd for $C_{12}H_8I_4$: I, 77.20. Found: I, 76.85.

The diiodide of I (1.5 g) was added to dimethyl sulfoxide (25 ml) and heated to 180° for 0.5 hr or until solution was complete. The solution was poured into 100 ml of ice–water and the solid tetraiodobiphenyl was recovered by filtration and was recrystallized from alcohol–benzene to afford brown crystals (1.0 g), mp 258°. A pale yellow-brown analytical sample melted at 262–263°.

Anal. Calcd for $C_{12}H_6I_4$: I, 77.26. Found: I, 77.22, 77.14.[4]

In a similar manner the iodide of II was prepared.

Anal. Calcd for $C_{12}H_7I_3$: I, 71.61. Found: 71.44.

The iodide was decomposed in hot dimethyl sulfoxide and afforded the triiodobiphenyl (54%). It was recrystallized three times from alcohol to give pale yellow crystals, mp 151–152°.

Anal. Calcd for $C_{12}H_7I_3$: I, 71.61. Found: I, 71.29, 71.38.[4]

A solution of 2,2′-diiodobiphenyl (2.4 g) in peracetic acid (70 ml) was allowed to stand for 1 week at room temperature (30°). White solid diphenyleniodonium iodate (1.9 g) separated and was recrystallized from water.

Anal. Calcd for $C_{12}H_8I_2O_3$: I, 55.94. Found: I, 55.57, 55.94.

An aqueous solution of the iodate was treated with sodium bisulfite and afforded pale yellow diphenyleniodonium iodide.

Anal. Calcd for $C_{12}H_8I_2$: I, 62.56. Found: I, 63.19.

The iodide was decomposed in hot dimethyl sulfoxide to produce 2,2′-diiobiphenyl, mp 109–110°. A mixture melting point with an authentic sample showed no depression.

There was also isolated from the above diphenyleniodonium iodate reaction filtrate the iodonium salt as the chloride (0.4 g).

(4) Microanalyses by Micro-Tech Laboratories, Inc., Skokie, Ill.

Anal. Calcd for $C_{12}H_8ICl$: 11.28. Found: Cl, 11.22, 11.41.

Diphenyleniodonium chloride or the sulfate (3 g) was dissolved in boiling water (2 l.) and to the solution was added cuprous chloride (10 g) followed by a *very slow* and *careful* addition of concentrated ammonium hydroxide (100 ml). The mixture was refluxed for 1 hr and carbazole (65%) was recovered by filtration and extraction by the usual procedure.

Registry No.—2,2′-Diiodobiphenyl, 2236-52-4; **1** dichloride, 18399-12-7; **2** chloride, 18399-13-8; 2,2′,6,-6′-tetraiodobiphenyl, 18399-10-5; **2** iodide, 18354-33-1; 2,2′,6-triiodobiphenyl, 18399-11-6; **3** chloride 4673-26-1; **3** iodide, 1010-76-0; **4** 18399-16-1.

Acknowledgments.—We are very grateful for the continued help and encouragement given to us by Professor Harry Gunning. We are also very grateful to Miss D. Roberts and Mrs. A Dunn for elemental microanalysis. We also express our thanks to the National Research Council of Canada, for financial aid.

Reactions of Chloroacetone in Basic Media

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In the interest of ascertaining the susceptibility of chloroacetone to function as a donor enolate at the chlorine-bearing carbon, the behavior of this ketone to various basic conditions was examined. Initial experiments revealed the essentially titrametric velocity with which chloroacetone reacts with aqueous alkali to afford quantitatively acetol as determined by the blue tetrazolium assay method.[1] Despite this extremely rapid hydrolysis of chloride, however, deuterium exchange and correspondingly formation of the pertinent anion at the chloromethylene center is a more rapid process. Thus when chloroacetone was allowed to react with 0.1 equiv of sodium deuterioxide in D_2O–CH_3OD, the nmr spectrum of the surviving chloroacetone, isolated after a 2-min reaction period, exhibited a 3:1 proton area ratio at τ 7.69 and 5.90 consistent with 1-chloro-1-monodeuterioacetone. In the absence of alkali, chloroacetone did not undergo measurable deuterium exchange after 0.5 hr.

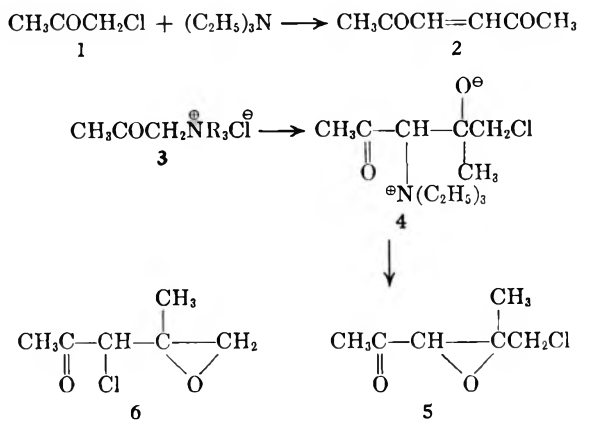
Attempts to mediate condensations of chloroacetone *via* its pyridinium salt (**3**, NR_3 = pyridine)[2] proved ineffective apparently in virtue of the relatively stable character of the latter species. With triethylamine condensation proceeded in two independent directions according to the media employed. In aprotic media such as glyme the two components did not react in a simple manner to give the quaternary salt **3** (R = C_2H_5) but instead gave triethylamine hydrochloride

(1) See Experimental Section; also A. S. Meyer and M. C. Lindberg, *Anal. Chem.*, **27**, 813 (1955), and references therein.

(2) C. Dreser, *Arch. Pharm.*, **236**, 334 (1898).

together with *trans*-diacetylethylene (2)[3] as the major isolable product (Scheme I). When reaction, on the

SCHEME I



other hand, was effected in protic media such as methanol, a Darzens-type reaction ensued with formation of the oxido chloro ketone **5** as a mixture of diastereoisomers.

Analysis of **5** by vapor phase chromatography revealed two very close-lying peaks in the ratio of 1:1 with retention times of 13 and 14 min, respectively. Each of the two corresponding substances exhibited a parent mass ion of 148/150 and the fragmentation pattern of both was essentially the same. The appearance of a mass peak at 99 (loss of CH_2Cl) supported structure **5** over **6**. Definitive for structure **5** was its zero response to alkaline tetrazolium assay, a method quantitatively applicable to α-halo ketones such as chloroacetone, 21-chloro-20-ketopregnanes, etc.[1,4] The nmr spectrum of **5** further exhibited doublet peaks at the various pertinent regions in conformity with expectations based on a mixture of diastereoisomers.

The essentially exclusive formation of **5** in the self-condensation of chloroacetone in alcoholic triethylamine is perhaps best accommodated as arising *via* an intermediate betaine **4** wherein preferred extrusion of the triethylammonium group *vis-a-vis* chlorine would be expected to be favored. Isolation, in fact, of an unstable trimethylammonium salt (**3**, R = CH_3) derived from chloroacetone at low temperature has been reported.[5] The reaction of chloroacetone with triethylamine in aprotic media probably proceeds *via* nucleophilic coupling with subsequent dehydrochlorination, a process formally indistinguishable from dimerization of an intermediate keto carbene resulting from α elimination.

The reaction of chloroacetone with methanolic triethylamine in the presence of 2 equiv of benzaldehyde yielded the Darzens product, benzalacetone oxide, also obtained previously employing the conventional strong base (CH_3ONa) technique.[6]

Experimental Section

Chloroacetone Solvolysis.—To a stirred solution of 3.0 ml of chloroacetone, 5 ml of methanol and 5 ml of water at 24° was added rapidly 4.0 ml of 1 *N* potassium hydroxide (0.1 mol/mol of chloroacetone). The rate of solvolysis was followed as a function of changed in pH with time on a recording pH meter. After an initial very steep rise, the pH value dropped rapidly and reached a value of pH 7 in 1.3 min.

Blue Tetrazolium Assay.[7]—The reagents used were (1) **tetramethylammonium hydroxide** (1 ml of a 10% aqueous solution) diluted to 100 ml with 95% ethanol, and (2) blue tetrazolium (5 mg/ml in 95% ethanol).

Sample solutions were (1) chloroacetone (105.9 μg/ml in methanol) and (2) epoxy chloro ketone **5** (78.8 μg/ml in methanol).

Procedure.—Chloroacetone was used as the standard for the color calibration curve. Aliquots of the chloroacetone solution (0.1–1.0 ml) were diluted to 1.0 ml with methanol and treated with 10 ml of tetramethylammonium hydroxide solution. After 1 min 1 ml of blue tetrazolium reagent was added and the sample was held at 24° for 45 min. The optical density at 5250 Å was determined on a Cary Model 14 recording spectrophotometer.

A plot of sample weight *vs.* optical density at 5250 Å provided a standardization curve and demonstrated the color linearity of chloroacetone. No discernible color was observed for 3,4-oxido-4-chloromethylpentanone-2 (**5**).

Chloroacetone–Deuterium Exchange.—To a vigorously stirred solution of 8.0 ml of deuterium oxide, 8.0 ml of methanol-d_1 and 5.0 g of chloroacetone was added rapidly a solution of 0.3 g of sodium methoxide in 2.0 ml of deuterium oxide. The reaction mixture was stirred for 2 min and then diluted with 100 ml of ether. The ethereal layer was separated, dried ($MgSO_4$) and the solvent removed. Distillation of the residue gave 4.4 g of chloroacetone: bp 62–63° (85 mm); nmr ($CDCl_3$) τ 5.90 (s, 1, CHDCl) and 7.69 ppm (s, 3, CH_3CO).

***trans*-1,2-Diacetylethylene (2).**—A mixture of 20 ml of chloroacetone, 32 ml of triethylamine and 50 ml of dimethoxyethane was stirred at 26° for 18 hr. At the end of this period the reaction mixture was diluted with 150 ml of ether and the ethereal solution washed with dilute hydrochloric acid, water, and dried ($MgSO_4$). The solvents were removed *in vacuo* and the dark residue was distilled, product fraction bp 100–110° (18 mm). The distilled material crystallized on standing at room temperature. Recrystallization from hexane gave 2.7 g of *trans*-1,2-diacetylethylene: mp 74–76°; uv max (CH_3OH) 228 mμ (E 1285); ir ($CHCl_3$) 5.95 (C=CC=O) and 6.18 μ (C=C); the mixture melting point with an authentic sample[8] was not depressed.

3,4-Oxido-4-chloromethylpentanone-2 (5).—A mixture of 100 ml of methanol, 50 ml of chloroacetone and 40 ml of triethylamine under a nitrogen atmosphere was stirred at 24° for 18 hr. The solvent was removed *in vacuo* and the residue was slurried with 400 ml of ether. Triethylamine hydrochloride was removed by filtration. The filtrate was washed with dilute hydrochloric acid, dried ($MgSO_4$), concentrated *in vacuo* and distilled to afford 18.2 g of the epoxy chloro ketone **5** as a pale yellow liquid, bp 99–108° (12 mm). Analytical material was obtained by chromatography on silica G and distillation: bp 98–100° (15 mm); ir 5.80 μ (C=O); glpc (20% SE-30/Chromosorb W, 100°) equal area peaks at 13 and 14 min; nmr ($CDCl_3$) τ 6.4 (d, 2, CH_2Cl), 7.7 (d, 3, CH_3CO) and 8.5 ppm (m, 4, CH_3 and CH).

Anal. Calcd for $C_5H_9ClO_2$: C, 48.47; H, 6.10: Cl, 23.85. Found: C, 48.73; H, 6.06; Cl, 23.56.

4-Phenyl-3,4-oxidobutanone-2.—A solution of 10 ml of chloroacetone, 16 ml of triethylamine, 27 ml of benzaldehyde and 20 ml of methanol was combined at 0° and held at 24–26° for 48 hr. At the end of this period the reaction mixture was concentrated *in vacuo* at <40°. The residue was diluted with 150 ml of ether and filtered. The ethereal solution was washed with dilute hydrochloric acid, sodium bicarbonate, dried ($MgSO_4$), concentrated *in vacuo* and distilled through a 15-cm stainless steel gauze packed column. The product fraction, bp 86–89° (1 mm), crystallized spontaneously. Recrystallization from ether–hexane gave 5.84 g of product: mp 52–53° (lit.[9] mp 52–53°); ir ($CHCl_3$)

(3) K. F. Armstrong and R. Robinson, *J. Chem. Soc.*, 1650 (1934).
(4) Unpublished observations from these laboratories.
(5) L. Niemilowicz, *Monatsh. Chem.*, **7**, 241 (1886).
(6) (a) T. I. Temnikova and V. F. Martynov, *J. Gen. Chem. USSR*, **15**, 499 (1945); *Chem. Abstr.*, **40**, 4694 (1946); (b) H. Kwart and L. G. Kirk, *J. Org. Chem.*, **22**, 116 (1957).
(7) Based on the method of W. J. Mader and R. R. Buck, *Anal. Chem.*, **24**, 666 (1952).
(8) Prepared according to M. W. Goldberg and P. Müller, *Helv. Chim. Acta*, **21**, 1699 (1938).
(9) E. Weitz and A. Scheffer, *Ber.*, **54**, 2327 (1921).

5.85 μ (C=O); nmr ($CDCl_3$) τ 2.65 (s, 5, aromatic), 5.98 (d, 1, J = 2 Hz), 6.50 (d, 1, J = 2 Hz) and 7.83 ppm (s, 3, CH_3CO).

Registry No.—1, 78-95-5; 2, 820-69-9; 5, 18266-87-0.

Acknowledgment.—The authors wish to thank Mr. A. B. White, Physical Measurements Department, for the blue tetrazolium assay determinations.

Reactions of Group IV Organometallic Compounds. VII.[1] Ring-Opening Reactions of β-Propiolactone with Various Trimethyltin Compounds

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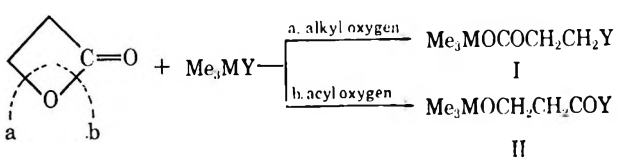
β-Propiolactone is the simplest four-membered cyclic ester among various cyclic compounds showing rather low basicity[2] associated with large ring strain. It is known to react readily with a large number of nucleophilic reagents through ring opening. Nucleophilic attack takes place either on sp^2 carbon atom which is the usual position for various open chain or higher membered cyclic esters, or on sp^3 carbon atom. The mode of the ring opening reaction was influenced by both the nature of nucleophiles and experimental conditions.

When trimethylmetal(IV) organometallic compounds are used as acceptor molecules to β-propiolactone, the following two modes of pathways are possible—(a) alkyl oxygen bond fission to give trimethylmetal(IV) β-substituted propionate (I) and (b) acyl oxygen bond fission to give β-keto-substituted ethoxytrimethylmetal(IV) (II).



In previous publications,[3-5] the mode of fission of β-propiolactone was found to depend on the central metal moiety. For the reaction with amino derivatives of trimethylmetal(IV) compounds with this substrate, the alkyl oxygen fission occurs when M = Si or Ge and the alkyl oxygen fission when M = Sn. These findings enforced us to study the effect of substituents (Y) on the mode of cleavage of β-propiolactone. Trimethyltin derivatives were chosen as suitable models since the corresponding trimethylsilyl or trimethylgermanium analogs showed only limited reactivity toward β-propiolactone on account of the considerable depression of basicity by (p–d)π interaction for some substituents with the metal.

Results

Determination of the Preferential Mode of Cleavage.—Relative amounts of products II/I were determined for the reaction of each 10.0 mmol of β-propiolactone and trimethyltin compounds in 2.00 ml of ethylene dichloride at 80°. As the reactivity of trimethyltindiethylamide was extremely high, treatment of β-propiolactone was carried out at 0° in the concentrations described above. β-Trimethylstannoxypropion-N,N-diethylamide, arising from selective acyl oxygen fission [II, Y = $N(C_2H_5)_2$], was isolated as a predominant product for the reaction of trimethyltin diethylamide with β-propiolactone. Preferential cleavage through the acyl oxygen bond was also observed for the reaction with trimethyltin methoxide, giving methyl β-trimethylstannoxypropionate (II, Y = OMe). At the same time, considerable amounts of product through alkyl oxygen fission (I, Y = OMe) were also detected by nmr and infrared spectrometry. From nmr peak areas of methoxy proton, relative amounts of II/I were estimated in the same manner as that described[1]—II/I = 7.7. Although this product ratio was found to depend on the polarity of the reaction media, the predominant mode was acyl oxygen bond fission for a variety of solvents.[1] The corresponding trimethylsilyl analog, trimethylmethoxysilane, did not react at all with β-propiolactone on account of the large stabilization due to (p–d)π overlap between silicon and oxygen.

A drastic change of mode of fission was however suggested when trimethyltin methylsulfide was utilized as an addendum toward β-propiolactone. After standing overnight, the reaction mixture was distilled under reduced pressure and the main product was isolated in 60% yield. This product showed characteristic nmr and infrared spectra for trimethyltin carboxylate[6] and was identified as trimethyltin β-methylthiopropionate (I, Y = SMe). The relative ratio of products for this system was determined in an analogous way as its oxygen analog from the relative intensity of methylthio protons in the reaction mixture—II/I = 0.15.

The preferential alkyl oxygen bond fission was also found for trimethyltin bromide and chloride. The reaction mixture of β-propiolactone and trimethyltin bromide gave an addition product which could be crystallized from acetone and was identified as trimethyltin β-bromopropionate (I, Y = Br) in 85% yield. Unfortunately, exact amounts of I and II could not be obtained because of the absence of key nmr proton signals and the low stability of the acyl halide structure in II (Y = Br). For the reaction with trimethyltin chloride, behavior was the same as the corresponding bromide, giving trimethyltin β-chloropropionate (I, Y = Cl) which arose through alkyl

(1) Part VI: K. Itoh, S. Kobayashi, S. Sakai, and Y. Ishii, *J. Organometal. Chem.*, **10**, 451 (1967).
(2) Y. Yamashita, T. Tsuda, M. Okada, and S. Iwatsuki, *J. Polym. Sci.*, Part *A-1*, **4**, 2121 (1966).
(3) K. Itoh, S. Sakai, and Y. Ishii, *J. Org. Chem.*, **31**, 3948 (1966).
(4) K. Itoh, S. Sakai, and Y. Ishii, *Tetrahedron Lett.*, 4941 (1966).
(5) K. Itoh, Y. Kato, S. Sakai, and Y. Ishii, *Kogyo Kagaku Zasshi*, **70**, 935 (1967); *Chem. Commun.*, 36 (1967).
(6) R. Okawara and M. Wada, *Advan. Organometal. Chem.*, **5**, 137 (1967).

oxygen cleavage of β-propiolactone. All results we have obtained in this series of study are summarized in Table I.

TABLE I

REACTION OF β-PROPIOLACTONE WITH VARIOUS GROUP IV ORGANOMETALLIC COMPOUNDS

Compound	Predominant mode of fission	Difference in electronegativity	Second order rate constant,[a] l./mol sec k_{AL}	k_{AC}
$Me_2Sn(NEt_2)_2$	Acyl oxygen	1.2		$>10^{-1}$
Me_3GeNEt_2	Alkyl oxygen[b]	1.2	4.9×10^{-3}	
Me_3SiNEt_2	Alkyl oxygen[b]	1.2	6.1×10^{-4}	
Me_2SnOMe	Acyl oxygen	1.7	2.1×10^{-4}	1.8×10^{-3}
Me_2SnSMe	Alkyl oxygen	0.7	2.1×10^{-6}	3.1×10^{-6}
Me_2SnBr	Alkyl oxygen	1.0	3.0×10^{-6}	
Me_2SnCl	Alkyl oxygen	1.2	7.9×10^{-7}	
$Me_2SiSC_2H_5$	Alkyl oxygen	0.7	7.2×10^{-7}	

[a] Temperature 65.0° in ethylene dichloride. [b] See ref 3-5. [c] K. Itoh, K. Matsuzaki, and Y. Ishii, *J. Chem. Soc. C*, in press.

Study on the Reactivity of Various Trimethylmetal-(IV) Compounds.—For comparing the reactivity between various group IV organometallic compounds toward ring-opening reaction of β-propiolactone, kinetic studies were performed. All reaction was found to fit well to second-order kinetics and the second-order rate constants for alkyl oxygen bond fission (k_{AL}) and those for acyl oxygen bond fission (k_{AC}) were determined. Results are included in Table I. As trimethyltin methoxide and trimethyltin methylsulfide showed dual behavior for the reaction, second-order rate constants for each cleavage were calculated as $k_{AL} = k_{obsd}(I/I + II)$ and $k_{AC} = k_{obsd}(II/I + II)$.

Discussion

In order to explain the preferential mode of fission of β-propiolactone, the principle of hard and soft acid and bases (HSAB)[7,8] attracted our attention, because β-propiolactone owns both "hard" sp^2 carbonyl carbon atom and "soft" sp^3 carbon atom in the same molecule. Nucleophilic reagents such as nitrogen or oxygen are known to behave as "hard bases," whereas sulfur or bromine are considered as "soft bases," when they react as free anions. However, the HSAB principle is not simply applicable to explain the reaction behavior of group IV organometallic compounds, because their bonds are essentially covalent.

Degree of ionization which is influenced by (1) difference in electronegativity and (2) contribution of (p–d)π bonding between metal(IV) and heteroatom(Y) is important in determining both the mode of fission of β-propiolactone and the reactivity of group IV organometallic compounds. The latter effect diminishes in the order as Si > Ge > Sn when these atoms form chemical bonds with nitrogen or oxygen atom.[9] Consequently, bonds such as Sn–N or Sn–O are considered to have high polar character and trimethyltin diethylamide and trimethyltin methoxide act as "hard" nucleophiles, giving the adduct through acyl oxygen cleavage. In other words, the ring-opening reaction of β-propiolactone is charge controlled.[8] The fact that the alkyl oxygen bond fission becomes prevalent for trimethylsilyl- and trimethylgermylamines is ascribed to a change of the reaction from charge controlled to frontier controlled due to the increase of (p–d)π interaction between the metal and nitrogen atoms. The reactivity difference between trimethyltin bromide and chloride (Br > Cl) is compatible with the HSAB principle. However, the reactivity difference between trimethyltin methoxide and methyl sulfide in acyl oxygen cleavage is not consistent with HSAB predictions. This difference might be ascribed to the smaller polar character of Sn–S bond.

It was pointed out that the second-order rate constant for the reaction of β-propiolactone with trimethyltin methoxide was smaller in ethylene dichloride than carbon tetrachloride[1] ($k_2 = 4.8 \times 10^{-3}$ l./mol sec). This trend was quite reversed in the case of alkyl oxygen fission for trimethylsilyl- and trimethylgermylamines.[5] The transition state for the acyl oxygen fission would not be dipolar.

Experimental Section

General Remarks.—Infrared and nmr spectra were recorded with Nippon Bunko IR-S type and a Japan Electron Optics C-60 spectrometer, respectively. All reactions were performed under the atmosphere of argon. Trimethyltin halides were prepared by the well-known disproportionation reactions. Trimethyltin diethylamide,[10] methoxide,[11] and methyl sulfide[12] were obtained as cited and purified by distillation. β-Propiolactone was supplied by Dicel Co. Ltd., and purified by distillation.

Reaction of Trimethyltin Compound with β-Propiolactone.—Trimethyltin compounds (10 mmol) were dissolved in 2.00 ml of ethylene dichloride and were added dropwise to equimolar amounts of β-propiolactone. The reaction mixture was kept at 80° (for Y = $N(C_2H_5)_2$ at 0°). Determination of the relative amounts of I and II was performed by measuring the relative intensities of the corresponding peaks in the nmr chemical shifts which were in the case of trimethyltin methoxide, τ 6.77 for I, and τ 6.42 for II and in the case of trimethyltin methyl sulfide, τ 7.84 for I and τ 6.42 for II.

β-Trimethylstannoxypropion-N,N-diethylamide [II, Y = N-$(C_2H_5)_2$].—The reaction was performed by mixing β-propiolactone with an ethylene dichloride solution of trimethyltin diethylamide in the general condition at 0°. After the removal of solvent, the product was obtained as distillation residue (yield 92%): ir (CCl_4), 1641 cm^{-1} (C=O); nmr (CCl_4) τ 9.69 with satellites (s, 9 H, CH_3Sn), 8.93 and 8.82 (two t, 6 H, CH_3CH_2), 7.68 (t, 2 H, CH_2CO–), 6.72 (q, 4 H, CH_2N), and 6.21 (q, 4 H, CH_2O). *Anal.* Calcd for $C_{10}H_{23}NO_2Sn$: C, 39.00; II, 7.54; Sn, 38.54. Found: C, 38.97; H, 7.42; Sn, 38.67.

Trimethyltin β-Methylthiopropionate (I, Y = SMe).—The reaction mixture obtained under the general reaction conditions for 10 hr was distilled under reduced pressure at 110° (0.8 mm). The product was isolated in 60% yield as a colorless waxy material. Recrystallization was accomplished with acetone and white crystals were obtained: mp 107°; ir ($CHCl_3$) 1657 cm^{-1} (C=O); nmr ($CHCl_3$) τ 9.42 (s, 9 H, with two satellites; $J_{Sn^{117}-H} = 54.7$ and $J_{Sn^{119}-H} = 56.8$ Hz, CH_3Sn), 7.84 (s, 3 H, CH_3S), 7.30 (m of Ab type, 4 H, two methylenes). *Anal.* Calcd for $C_7H_{16}O_2Sn$: C, 29.71; H, 5.71; Sn, 41.98. Found: C, 29.86; H, 5.89; Sn; 42.06.

Trimethyltin β-Bromopropionate (I, Y = Br).—After reaction under the standard condition, the product was isolated by crystallization with *n*-hexane in 85% yield and recrystallization from *n*-hexane: mp 114.0–114.5°; ir ($CHCl_3$) 1657 cm^{-1} (C=O); nmr ($CHCl_3$) τ 9.41 (s, with two satellites; $J_{Sn^{117}-H} = 56.3$ and $J_{Sn^{119}-H} = 58.4$ Hz, 9 H, CH_3Sn), 7.16 (t, 2 H, CH_2CO), and 6.44 (t, 2 H, CH_2Br). *Anal.* Calcd for $C_6H_{13}BrO_2Sn$: C, 22.82; H, 4.15. Found: C, 22.98; H, 4.20.

(7) R. G. Pearson and J. Songstad, *J. Amer. Chem. Soc.*, **89**, 1827 (1967).
(8) G. Klopman, *ibid.*, **90**, 223 (1968).
(9) E. W. Abel, D. A. Armitage, and D. B. Brady, *Trans. Faraday Soc.*, **62**, 3459 (1966).
(10) K. Jones and M. F. Lappert, *J. Chem. Soc.*, 1944 (1965).
(11) J. Lorberth and M.-R. Kula, *Chem. Ber.*, **97**, 3444 (1964).
(12) E. W. Abel and D. B. Brady, *J. Chem. Soc.*, 1192 (1965).

Trimethyltin β-Chloropropionate (I, Y = Cl).—The reaction conditions were the same as the corresponding bromide. Purification of the adduct was made by sublimation of the reaction mixture under reduced pressure. Product was isolated as a white needles in 75% yield: mp 88.5–89.4°; ir ($CHCl_3$) 1662 cm^{-1} (C=O); nmr ($CHCl_3$) τ 9.45 (s, with two satellites; $J_{Sn^{117}-H}$ = 60.2 and $J_{Sn^{119}-H}$ = 62.4 Hz, 9 H, CH_3Sn), 7.36 (t, 2 H, CH_2CO) and 6.36 (t, 2 H, CH_2Cl). *Anal.* Calcd for $C_6H_{13}ClO_2Sn$: C, 26.56; H, 4.84; Cl, 43.30. Found: C, 26.75; H, 4.97, Cl; 43.34.

Kinetic Study.—Trimethylmetal(IV) compounds (1 mmol) were dissolved in 9.00-ml samples of ethylene dichloride and kept at 65 ± 0.5°. β-Propiolactone (1 mmol) was added by means of a syringe and the solution was diluted to 10.00 ml. At a suitable time, a sample was withdrawn by syringe and the remaining amounts of β-propiolactone were determined with the characteristic infrared absorption at 1835 cm^{-1}. Second-order rate constants were calculated from the slope of the plot $1/(\beta - PL)$ *vs.* time. On account of the low reactivity of trimethyltin bromide, chloride, and trimethylsilyl ethyl sulfide, the following method was performed. Metal compound (20 mmol) was dissolved in 4.0 ml of ethylene dichloride and 0.5 mmol of β-propiolactone was added by microsyringe. The total volume was diluted to 5.00 ml and the following measurements were the same as above. The second-order rate constants were estimated from $k_2 = (2.303/t) \log [b(a - x)/a(b - x)]$.

Registry No.—β-Propiolactone, 57-57-8; I (Y = SMe), 18386-59-9; I (Y = Br), 18386-60-2; I (Y = Cl), 18386-61-3; II [Y = $N(C_2H_5)_2$], 13340-30-2.

1,1,2-Triphenylbenzocyclobutene

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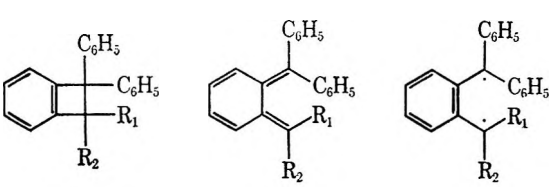
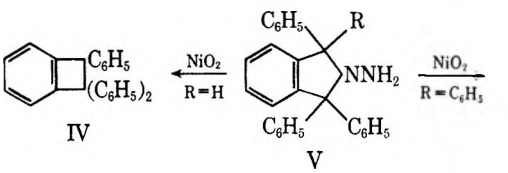
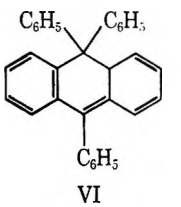
Received April 1, 1968

Following the demonstration[1] of the intermediacy of *o*-quinodimethanes in the reactions of benzocyclobutenes, a reexamination of the synthesis of one of the *gem*-diphenylbenzocyclobutenes was considered of interest in connection with the question, first raised many years ago by Wittig and Leo,[2] of the relationship between cyclic structure I and the corresponding *o*-quinodimethane and diradical structures II and III.



Applying a method which had proved successful in the synthesis of the *cis*- and *trans*-1,2-diphenyl derivatives, namely, oxidation of the corresponding N-aminodihydroisoindoles,[3-5] we examined the synthesis of 1,1,2-triphenyl- and 1,1,2,2-tetraphenylbenzocyclobutene. During the course of these studies, Quinkert[6] and coworkers described a method for the generation of the tetraphenyl derivative (I, $R_1 = R_2 = C_6H_5$) and, in fact, settled the question of the relationship between this labile hydrocarbon and its various isomers. It was demonstrated that I ($R_1 = R_2 = C_6H_5$) is stable at low temperatures but above 0° undergoes isomerization to VI. We also observed the formation of the same yellow hydrocarbon VI on oxidation of V (R = C_6H_5) by means of activated manganese dioxide or nickel peroxide.[7] On the other hand, the corresponding





triphenylbenzocyclobutene (IV), obtained similarly from V (R = H), proved to be sufficiently stable to be isolated without difficulty. In reactions involving prior valence isomerization to II (R_1 = H; $R_2 = C_6H_5$) such as addition to tetracyanoethylene, IV proved to be more reactive than *trans*-1,2-diphenylbenzocyclobutene which, in turn, as shown earlier,[8] is more reactive than the corresponding *cis* isomer. The steric interaction which inhibits valence isomerization of the latter is also operative in the case of IV but is presumably outweighed by the additional conjugative stabilization due to the third phenyl group.

Experimental Section[9]

1,3,3-Triphenylisoindole.—Since the previous description[10] of the synthesis of this compound was unsatisfactory in our hands, the procedure was modified as described below. To a suspension of 205 g of anhydrous aluminum chloride in 380 ml of thiophene-free benzene there was added dropwise over 5 hr with stirring at room temperature a solution of 101 g of crude 1,3,3-trichloroisoindole[10] in 460 ml of benzene. The mixture was stirred for an additional 5 hr and poured into a mixture of 206 ml of concentrated hydrochloric acid and 800 g of chipped ice. The mixture, from which a viscous material had separated, was warmed on a hot plate with stirring until the benzene just began to boil. The mixture was removed from the hot plate and stirring continued at room temperature for 10–12 hr. The green-black solid was filtered and suspended in 880 ml of water and the mixture boiled for 10 min and filtered while hot. After air-drying

(1) For a review, see G. Quinkert, K. Opitz, W-W. Wiersdorf, and M. Finke, *Ann.*, **693**, 44 (1966).
(2) G. Wittig and M. Leo, *Ber.*, **64**, 2395 (1931).
(3) L. A. Carpino, *J. Amer. Chem. Soc.*, **84**, 2196 (1962).
(4) W. Baker, J. F. McOmie, and D. R. Preston, *J. Chem. Soc.*, 2971 (1961).
(5) L. A. Carpino, *Chem. Commun.*, 494 (1966).
(6) G. Quinkert, W-W. Wiersdorff, M. Finke, and K. Opitz, *Tetrahedron Lett.*, 2193 (1966).
(7) K. Nakagawa, R. Konaka, and T. Nakata, *J. Org. Chem.*, **27**, 1597 (1962).
(8) R. Huisgen and H. Seidl, *Tetrahedron Lett.*, 3381 (1964).
(9) Melting and boiling points are uncorrected. Elemental analyses were by Dr. A. Bernhardt, Muhleim (Germany), and Galbraith Laboratories, Knoxville, Tenn. Nmr spectra were taken in deuteriochloroform solution on a Varian A-60 instrument using tetramethylsilane as internal standard. Infrared and ultraviolet spectra were recorded on Perkin-Elmer 237 and 202 instruments, respectively.
(10) W. Theilacker, H. J. Bluhm, W. Heitmann, H. Kalenda, and H. J. Meyer, *Ann.*, **673**, 96 (1964).

for 1 hr the still-wet solid was divided into three portions and each portion extracted with several 300-ml portions of boiling ligroin (bp 88–98°) until only a small amount of black tarry residue (5–10 g) remained insoluble. The filtered ligroin solution (about 1.6 l.) deposited on cooling in a refrigerator a brown-black solid which was recrystallized from ethanol–nitromethane (1:4) to give 92 g (58%) of the isoindole as nearly colorless crystals, mp 146.5–148.5° (lit.[10] mp 144.5°).

1,1,3,3-Tetraphenyldihydroisoindole.—To a solution of phenyllithium freshly prepared from 30 ml of bromobenzene and 4.02 g of lithium in 390 ml of ether there was added in one portion 33 g of 1,3,3-trriphenylisoindole. Very gentle spontaneous refluxing occurred for 3–4 min after which the mixture was refluxed with stirring for 15 hr, cooled in an ice bath and treated with 150 ml of saturated ammonium chloride solution. After stirring at room temperature for 15 min 300 ml of water was added and stirring continued for 2–3 hr. Filtration gave 30 g (74%) of the crude amine, mp 183–185.5° (softening at 179°). This material was pure enough for conversion directly into the nitroso derivative. An analytical sample was obtained by recrystallization from ethanol–nitromethane (1:2) and nitromethane as white flakes: mp 184–185°; δ^{CDCl_3} 3.2 (s, broad, 1 H, NH) and 7.1 (m, 24 H, aromatic).

Anal. Calcd for $C_{32}H_{25}N$: C, 90.74; H, 5.95; N, 3.31. Found: C, 90.35; H, 6.02; N, 3.50.

2-Nitroso-1,1,3,3-tetraphenyldihydroisoindole.—Prepared in 98% yield by a method similar to that used for the triphenyl derivative, the nitroso compound had mp 236–238°; nmr δ^{CDCl_3} 7.3 (m, aromatic).

Anal. Calcd for $C_{32}H_{24}N_2O$: C, 84.93; H, 5.35; N, 6.19. Found: C, 84.70: H, 5.36; N, 6.32.

2-Amino-1,1,3,3-tetraphenyldihydroisoindole.—Several attempts to use ordinary aluminum amalgam prepared by the method of Vogel[11] failed to give satisfactory results, therefore a more active amalgam was prepared by modification of the method of Hahn and Thieler.[12] A mixture of 20 g of 8-mesh aluminum (Baker and Adamson) and 100 ml of 1.5% sodium hydroxide solution was heated until vigorous gas evolution set in. Reaction was allowed to proceed away from the source of heat until it became sluggish (2–3 min) and the cleaned aluminum washed several times with water by decantation. A second 100 ml of 1.5% sodium hydroxide solution was added followed by immediate addition of 50 ml of a 0.5% solution of mercuric chloride in warm water. The mixture, from which a yellow-orange solid separated, was swirled for 30 sec and then 0.2 g of solid potassium cyanide was added followed by swirling for 1–1.5 min. The orange-brown color disappeared on addition of the cyanide. The amalgam was washed by decantation successively with four to five portions of water, ethanol and ether, and then used at once in the normal manner.[11] Passage of hydrogen chloride gas through the dried ether solution following the usual work-up gave a tacky substance which solidified on continued passage of the gas. Filtration after 1 hr gave 9.5 g of the crude hydrochloride which was washed with ether and suspended in a separatory funnel in a mixture of 300 ml of saturated sodium bicarbonate solution and 150 ml of ether. The solid slowly dissolved on continued shaking. Spontaneous evaporation of the ether layer left a white solid which was recrystallized from nitromethane–ethanol (2:1) to give 6 g (41.3%) of well-formed bulky yellowish needles, mp 150–182°. An analytical sample was obtained by sublimation at 180° (3 mm) followed by recrystallization from nitromethane–ethanol (2:1) to give white flakes: mp 140–170° (forms yellow liquid);[13] δ^{CHCl_3} 2.92 (s, broad, 2 H, NH_2) and 7.1 (s, broad, 24 H, aromatic); uv $\lambda_{max}^{CH_2Cl_2}$ 252 mμ (log ε 3.58), 259 (3.54), 265.5 (3.49) and 271.5 (3.35).

Anal. Calcd for $C_{32}H_{26}N_2$: C, 87.64; H, 5.98; N, 6.39. Found: C, 87.49; H, 6.00; N, 6.66.

The acetyl derivative (from acetic anhydride at room temperature) had mp 280–288° (nitromethane).

Anal. Calcd for $C_{34}H_{28}N_2O$: C, 84.97; H, 5.87; N, 5.83. Found: C, 84.67; H, 5.83; N, 6.13.

2-Nitroso-1,1,3-triphenyldihydroisoindole.—1,1,3-Triphenyldihydroisoindole obtained by $LiAlH_4$ reduction of 1,3,3-triphenylisoindole was treated with $NaNO_2$ in HOAc. Recrystallization (CH_3NO_2) gave 85% of the nitroso compound as yellow crystals: mp 187–188.5°; nmr δ^{CDCl_3} 6.15 (s, 1 H, CH), 7.1 (m, 19 H, aromatic).

Anal. Calcd for $C_{23}H_{20}N_2O$: C, 82.95; H, 5.35; N, 7.44. Found: C, 82.87; H, 5.37; N, 7.40.

2-Amino-1,1,3-triphenyldihydroisoindole Hydrochloride.—Aluminum amalgam[11] reduction of the N-nitroso compound gave the hydrazine isolated as the corresponding hydrochloride, mp 160–210° dec.

Anal. Calcd for $C_{26}H_{23}ClN_2$: C, 78.28; H, 5.81; Cl, 8.89; N, 7.02. Found: C, 78.07; H, 5.96; Cl, 8.73; N, 6.99.

The benzal derivative, obtained in the usual way, was recrystallized from nitromethane-dimethylformamide (5:1) as colorless clumps of crystals, mp 212–213.5°.

Anal. Calcd for $C_{33}H_{26}N_2$: C, 87.97; H, 5.82; N, 6.22. Found: C, 87.58; H, 5.99; N, 6.32.

1,1,2-Triphenylbenzocyclobutene.—To a suspension of 5 g of 1,1,3-triphenyl-2-aminodihydroisoindole hydrochloride in 80 ml of methylene dichloride was added 1.75 ml of triethylamine. The resulting clear solution was treated with 21 g of nickel peroxide[7] added in small portions over a period of about 15 min. The mixture was allowed to stand at room temperature for 30 min with occasional shaking, another 1-g portion of nickel peroxide added and the mixture filtered after a second 30-min period. The oxide was washed well with methylene dichloride and the solvent allowed to evaporate spontaneously from a small beaker. The residual oil on trituration with methanol (seeding, if possible) eventually solidified. Upon evaporation of the methanol the solid was crushed and washed well with water on a filter plate. After air-drying, recrystallization from methanol–nitromethane (1:1) with cooling in a refrigerator gave 3 g (72%) of cream-colored crystals, mp 105.5–108.5°. An analytical sample was obtained by recrystallization from methanol as shiny white flakes: mp 109.5–111°; nmr δ^{CDCl_3} 5.45 (s, 1 H, CH) and 6.8–7.5 (m, 19 H, aromatic); uv $\lambda_{max}^{95\%C_2H_5OH}$ 255 mμ sh (log ε 3.18), 260.5 (3.32), 266 (3.40) and 272.8 (3.33). Except for the intensity differences the ultraviolet curve matched those of *cis*- and *trans*-1,2-diphenylbenzocyclobutene.

Anal. Calcd for $C_{26}H_{20}$: C, 93.94; H, 6.06; mol wt, 332.4. Found: C, 93.99; H, 6.18; mol wt, 307 (osmometric).

α,α,α′-Triphenyl-*o*-xylene. Method A.—Hydrogenolysis of 1.5 g of 1,1,3-triphenylbenzocyclobutene in 150 ml of methanol in the presence of 0.2 g of palladium–carbon (10%) at 55 psi in a Parr apparatus for 20 hr gave 0.75 g (49.6%) of the hydrocarbon, mp 112–116°, after recrystallization from methanol–nitromethane (1:1). An analytical sample, mp 110–111.5°, was obtained by recrystallization from ethanol–nitromethane (10:1): nmr δ^{CDCl_3} 3.85 (s, 2 H, CH_2), 5.61 (s, 1 H, CH) and 7.15 (m, 19 H, aromatic); uv $\lambda_{max}^{95\%C_2H_5OH}$ 244 mμ (log ε 2.69), 250 (2.86), 257 (2.99), 260 (3.02), 262.8 (3.08), 265 sh (2.97) and 269.8 (2.95).

Anal. Calcd for $C_{26}H_{22}$: C, 93.37; H, 6.63. Found: C, 93.38; H, 6.56.

Method B.—A solution of 0.5 g of *o*-benzoyltriphenylmethane,[14] 0.5 g of potassium hydroxide and 0.3 ml of 64% hydrazine in 20 ml of ethylene glycol was refluxed for 1 hr. The condenser was arranged for downward distillation and distillate was removed until the internal temperature reached 199°. After refluxing for an additional 15 hr the solution was poured into 400 ml of water. The mixture was allowed to stand at room temperature for 24 hr during which time the first-precipitated oil crystallized. Filtration gave 0.1 g (21%) of white solid which after recrystallization from ethanol was obtained as tiny white crystals, mp 109–111°. Comparison of infrared spectra demonstrated the identity of this material with the sample prepared by catalytic hydrogenation of 1,1,2-triphenylbenzocyclobutene.

Tetracyanoethylene Adduct of 1,1,2-Triphenylbenzocyclobutene.—A solution of 0.128 g of tetracyanoethylene and 0.332 g of the benzocyclobutene in 25 ml of benzene was allowed to stand at room temperature for 5 hr and the solvent then allowed to evaporate. The resulting oil solidified on trituration with ethanol and recrystallization from ethanol–nitromethane (1:1) gave 0.32 g (69.6%) of the adduct as well-formed crystals, mp 214–216°.

(11) See L. A. Carpino, A. A. Santilli, and R. W. Murray, *J. Amer. Chem. Soc.*, **82**, 2728 (1960).

(12) F. L. Hahn and E. Thieler, *Ber.*, **57**, 671 (1924).

(13) The melting point varied with the rate of heating and always exhibited a wide range no matter how often the compound was recrystallized or sublimed.

(14) C. K. Bradsher and S. T. Webster, *J. Amer. Chem. Soc.*, **79**, 393 (1957).

Anal. Calcd for $C_{32}H_{20}N_4$: C, 83.46; H, 4.38; N, 12.17. Found: C, 82.99; H, 4.49; N, 12.44.

In order to determine the relative reactivities of *cis*-1,2-diphenyl-, *trans*-1,2-diphenyl- and 1,1,2-triphenylbenzocyclobutene toward tetracyanoethylene, 0.2 mmol of each hydrocarbon was dissolved in 1 ml of toluene contained in three separate flasks. To each solution was added 0.1 mmol of tetracyanoethylene and the time required for disappearance of the bright yellow color noted. Times required were as follows (two separate runs): 1,1,2-triphenyl derivative (4–6 min); *trans*-1,2-diphenyl derivative (60–65 min); *cis*-1,2-diphenyl derivative (5–5.5 days).

Sulfur Dioxide Adduct of 1,1,2-Triphenylbenzocyclobutene.—A solution of 0.15 g of the benzocyclobutene in 50 ml of liquid sulfur dioxide was heated in a sealed tube at 90–95° for 15 hr. Evaporation of the solvent gave 0.17 g (94.4%) of the adduct, mp 167–174°. Recrystallization from ethanol–benzene (2:1) gave the sulfone as tiny white crystals: mp 173–175° (gas evolution and yellowing), lit.[15] mp 174–174.5°; nmr δ^{CDCl_3} 5.15 (s, 1 H, CH) and 7.3 (m, 19 H, aromatic); ir λ_{max}^{Nujol} 7.61, 8.81 μ (SO_2). The ultraviolet curve matched that published by Kloosterziel and Backer[15] for 1,1,3-triphenyl-1,3-dihydroisobenzothiophene sulfone.

Registry No.—1,1,3,3-Tetraphenyldihydroisoindole, 18554-09-1; 2-nitroso-1,1,3,3-tetraphenyldihydroisoindole, 18554-10-4; 2-amino-1,1,3,3-tetraphenyldihydroisoindole, 18554-11-5; acetyl derivative of 2-amino-1,1,3,3-tetraphenyldihydroisoindole, 18554-12-6; 2-nitroso-1,1,3-triphenyldihydroisoindole, 18554-13-7; 2-amino-1,1,3-triphenyldihydroisoindole hydrochloride, 18554-14-8; benzal derivative of 2-amino-1,1,3-triphenyldihydroisoindole hydrochloride, 18554-15-9; IV, 18554-16-0; α,α,α'-triphenyl-*o*-xylene, 18554-17-1; tetracyanoethylene adduct of 1,1,2-triphenylbenzocyclobutene, 18598-44-2.

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(15) H. Kloosterziel and H. J. Backer, *Rec. Trav. Chim. Pays-Bas*, **71**, 1235 (1952).

The Solvolysis of Some Substituted Cyclohexyl Methanesulfonates[1]

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In connection with other studies from these laboratories on the effect of polar substituents on the rate of solvolysis of derivatives of substituted cyclohexanols,[2,3] it was desirable to examine the reactivity of some simple cyclohexyl methanesulfonates. Though methanesulfonates have been widely used in carrying out chemical transformations in the steroid and sugar families, relatively few rate measurements have been made with them. Robertson and his coworkers, in their definitive studies of solvent isotope effects, have examined the solvolysis of simple alkyl methanesulfonates.[4] The rate for isopropyl methanesulfonate is about one-half the rate for isopropyl tosylate in water. Cyclopentyl methanesulfonate solvolyzes somewhat more slowly in methanol than does the tosylate,[5] and comparisons of the relative rates of acetolysis of cholestanyl and 4,4-dimethylcholestanyl sulfonates can be made from the reported kinetic measurements of deSousa and Moriarity[6] and of Biellman and Ourisson.[7] The tosylate and methanesulfonate show nearly identical rates.

We have prepared and measured the rate of acetolysis of *cis*- and *trans*-4-*t*-butylcyclohexyl methanesulfonates and of *cis*- and *trans*-4-methylcyclohexyl methanesulfonates. The rate measurements are summarized in Table I, with derived thermodynamic parameters in Table II.

TABLE I

RATES OF ACETOLYSIS OF 4-SUBSTITUTED CYCLOHEXYL METHANESULFONATES

Substituent	Temp, °C	$10^6 k_1$, sec^{-1}	k_{rel} (70°)	k_{OMs}/k_{OTs}[a]
Unsubstituted	50	2.42 ± 0.03		1.23[b]
	70	28.7 ± 0.6	1.16	
	70	28.8 ± 0.6		
trans-4-Methyl	50	1.49 ± 0.88		1.15[c]
	70	19.3 ± 0.3	0.78	
cis-4-Methyl	50	3.88 ± 0.32		1.18[c]
	70	48.8 ± 1.0	1.97	
	70	48.0 ± 3.0	1.94	
trans-4-*t*-Butyl	50	1.91 ± 0.02		1.20[b]
	70	24.8 ± 0.7	1.00	
cis-4-*t*-Butyl	50	7.19 ± 0.25		1.26[b]
	70	75.8 ± 2.2	3.06	

[a] Rate ratio methanesulfonate/tosylate at 75.7°, the only temperature at which data for the 4-methylcyclohexyl tosylates are available. [b] Tosylate data: S. Winstein and N. J. Holness, *J. Amer. Chem. Soc.*, **77**, 5562 (1955). [c] Tosylate data: H. Kwart and T. Takeshita, *ibid.*, **86**, 1161 (1964).

TABLE II

ACTIVATION PARAMETERS

Substituent[a]	$\Delta H^{\ddagger}$, kcal	$\Delta S^{\ddagger}$, eu
trans-4-*t*-Butyl	27.6 ± 0.2	+0.5 ± 0.6
cis-4-*t*-Butyl	25.3 ± 0.4	−3.8 ± 1.1
trans-4-Methyl	27.6 ± 0.4	−0.1 ± 1.2
cis-4-Methyl	27.2 ± 0.7	+0.5 ± 2.2
Unsubstituted	26.6 ± 0.2	−2.1 ± 0.7

[a] Substituent on cyclohexyl methanesulfonate.

These rate measurements may be compared with previously determined rates for the corresponding tosylates, and the data are summarized in the last column in Table I. It is to be noted that the methanesulfonates solvolyze at rates which are very similar to those of the corresponding tosylates. In the present, unhindered cyclohexyl derivatives, the methanesulfonates, solvolyze about 20% faster than the tosylates.

Conformational Analysis.—One of the primary pur-

(1) Supported in part by grants from the National Science Foundation (GP-1572 and GP-6133X).

(2) D. S. Noyce and B. Weinstein, *J. Org. Chem.*, to be submitted.

(3) D. S. Noyce and Byron E. Johnston, *ibid.*, to be submitted.

(4) K. T. Leffek, R. E. Robertson, and S. E. Sugamori, *Can. J. Chem.*, **39**, 1989 (1961); R. E. Heppolette and R. E. Robertson, *ibid.*, **44**, 677 (1966).

(5) F. J. Chloupek and G. Zweifel, *J. Org. Chem.*, **29**, 2092 (1964).

(6) R. M. deSousa and R. M. Moriarity, *ibid.*, **30**, 1509 (1965).

(7) J. F. Biellman and G. Ourisson, *Bull. Soc. Chim. Fr.*, 341 (1962).

poses of the present study was to examine the possibility of carrying out conformational analysis of the equilibrium distribution of conformational isomers in substituted cyclohexyl systems of the type under study. We have examined the infrared spectra of the methanesulfonates, and find that there is a strong band at 931 cm^{-1} for *trans*-4-methylcyclohexyl methanesulfonate, and a doublet at 931 and 941 cm^{-1} for *trans*-4-*t*-butylcyclohexyl methanesulfonate. In the spectrum of *cis*-4-*t*-butylcyclohexyl methanesulfonate a prominent band at 906 cm^{-1} is reproduced in the spectrum of *cis*-4-methylcyclohexyl methanesulfonate, which shows in addition a minor band at 928 cm^{-1}. Assigning the low frequency band to the axial C–O bond, and the high-frequency band to the equatorial C–O bond, and also noting that in the *t*-butyl derivatives the bond intensities are the same within 2%, it is possible to calculate from the observed spectrum of cyclohexyl methanesulfonate a conformational equilibrium. This calculation gives the result that cyclohexyl methanesulfonate is 69% in the equatorial conformation. We have also examined the conformational equilibrium in the case of cyclohexyl methanesulfonate by nmr techniques. Using the peak shift method for the methinyl hydrogen,[8] *A* values in both carbon tetrachloride and acetic acid solvent may be obtained.

Through the kindness of Professor Jensen and his collaborators[9] we have been able to verify these results with low-temperature nmr spectral determination of the *A* value for the methanesulfonate group. The data obtained by these several different methods are summarized in Table III.

TABLE III

A VALUES

Method	Methanesulfonate	Tosylate
Infrared (CCl_4)	0.53 ± 0.10	
Nmr chemical shift in CCl_4	0.48 ± 0.10	0.6[a]
in acetic acid	0.41 ± 0.10	
Low-temperature nmr[b]	0.56 ± 0.03	0.515 ± 0.021

[a] Ref 8. [b] Measurements at 100 MHz kindly carried out by F. R. Jensen, C. H. Bushweller, and B. H. Beck, *J. Amer. Chem. Soc.*, **90**, 344 (1969).

In considering the kinetic method of determining *A* values it is to be noted that the data for the 4-methylcyclohexyl methanesulfonates give a satisfactory answer for the *A* value of the methanesulfonate group using the method of Winstein and Holness,[10] though the *t*-butylcyclohexyl methanesulfonates do not. This is perhaps another manifestation of the suggested small distortion of the cyclohexane ring by the "locking" *t*-butyl group, which has previously been suggested by Kwart and Takeshita.[11]

We would like to suggest that methanesulfonates may be more generally useful than has heretofore been indicated by their utilization in kinetic studies. A further feature which may well increase their utility is the fact that the methanesulfonate is undoubtedly formed from the alcohol by a different mechanism[12,13] than is the tosylate. We have found that the conditions required for the formation of the methanesulfonate are far milder than those required for the formation of tosylates.

Experimental Section[14]

***cis*- and *trans*-4-*t*-Butylcyclohexanol.**—Commercial 4-*t*-butylcyclohexanol (Dow Chemical Co.) was separated as described by Winstein and Holness[10] *via* the acid phthalate to give a sample of pure *trans*-4-*t*-butylcyclohexanol, and by chromatography on neutral grade III Woelm alumina to give a sample of pure *cis*-4-*t*-butylcyclohexanol.

***trans*-4-*t*-Butylcyclohexyl Methanesulfonate.**—Methanesulfonyl chloride (5.12 g) and *trans*-4-*t*-butylcyclohexanol (6.36 g) were combined in dry benzene (75 ml). The solution was stirred vigorously and the temperature was maintained at 5–10° while triethylamine (4.53 g) in benzene (50 ml) was added over a period of 10 min. The solution was immediately filtered to remove the amine hydrochloride, and the clear filtrate was washed with cold 10% HCl and with saturated $NaHCO_3$. The benzene was removed under vacuum, and the remaining solid (8.8 g, 92.5%), mp 72–74°, was crystallized from hexane to give pure *trans*-4-*t*-butylcyclohexyl methanesulfonate, mp 74–75°.

Anal. Calcd for $C_{11}H_{22}O_3S$: C, 56.37; H, 9.46; S, 13.68. Found: C, 56.54; H, 9.27; S, 13.52.

***cis*-4-*t*-Butylcyclohexyl methanesulfonate** was prepared in the same fashion (89% yield, mp 94.0–94.5°).

Anal. Found: C, 56.13; H, 9.27; S, 13.64.

***trans*-4-Methylcyclohexanol** was purified as the 3,5-dinitrobenzoate[15] and ***cis*-4-methylcyclohexanol** was purified as the *p*-nitrobenzoate.[15] ***trans*-4-Methylcyclohexyl methanesulfonate** was prepared as above, and crystallized from benzene, mp 38.5–39.0°.

Anal. Calcd for $C_8H_{16}O_3S$: C, 49.96; H, 8.39; S, 16.67. Found: C, 49.68; H, 8.17; S, 16.48.

Similarly, ***cis*-4-methylcyclohexyl methanesulfonate** was prepared. A liquid at room temperature, this sulfonate ester was purified by low-tempeature (−60°) crystallization from methanol.

Anal. Found: C, 49.81; H, 8.36; S, 16.51.

Cyclohexyl methanesulfonate was prepared in similar fashion. Distillation from a small amount of calcium carbonate, bp 97–98° (0.05 mm), afforded pure material in 76% yield.

Anal. Calcd for $C_7H_{14}O_3S$: C, 47.17; H, 7.92; S, 17.99. Found: C, 47.48; H, 7.89; S, 17.74.

Product Analysis.—The products resulting from the solvolysis of both *cis*- and *trans*-4-*t*-butylcyclohexyl methanesulfonates at 70° in acetic acid solutions contained 0.05 *M* sulfonate, 0.10 *M* sodium acetate and 0.10 *M* acetic anhydride. Analysis was carried out using an Aerograph A-90-P instrument, with a 5-ft 20% Carbowax 20M on 60–80 mesh Chromosorb W column. Comparisons of retention times with those for authentic samples of all products were made, and the thermal conductivities were calibrated. The results obtained are listed in Table IV. Since this work was completed, a very careful study of the solvolysis of the 4-*t*-butylcyclohexyl *p*-toluenesulfonates has been reported by Whiting, *et al.*,[16] and our results show a very close correspondence to those reported (Table 7 of ref 16).

Kinetic Methods.—The kinetics were determined by the usual sealed ampoule technique. Solutions were prepared in purified acetic acid with sulfonate ester approximately 0.05 *M*, with added sodium acetate and acetic anhydride each 0.10 *M*. At

(8) E. L. Eliel and M. H. Gianni, *Tetrahedron Lett.*, 97 (1962).

(9) We wish to express our appreciation to Dr. C. H. Bushweller and Dr. B. H. Beck for providing us with the measurements reported here.

(10) See Table I, footnote *b*.

(11) See Table I, footnote *c*.

(12) J. F. King and T. Durst, *J. Amer. Chem. Soc.*, **86**, 287 (1964).

(13) W. E. Truce, R. W. Campbell, and J. R. Norell, *ibid.*, **86**, 288 (1964).

(14) All melting points are corrected; boiling points are uncorrected. Routine infrared spectra were determined on a Perkin-Elmer Model 237 Infracord; analytical spectra were taken on a Perkin-Elmer Model 421 spectrophotometer. Nmr spectra were determined with a Varian Associates Model A-60 spectrometer. Elemental analyses were determined by the Microanalytical Laboratory, Department of Chemistry, University of California.

(15) L. M. Jackman, A. K. Macbeth, and J. A. Mills, *J. Chem. Soc.*, 1717 (1949).

(16) N. C. G. Campbell, D. M. Muir, R. R. Hill, J. H. Parish, R. M. Southam, and M. C. Whiting, *J. Chem. Soc., B*, 355 (1968).

TABLE IV
PRODUCTS FROM THE ACETOLYSIS OF *t*-BUTYLCYCLOHEXYL METHANESULFONATES

Product	% from *cis*	% from *trans*
4-ene	85.0	75.0
3-ene	0.9	1.5
trans-4-OAc	8.1	0.1
cis-4-OAc	1.2	19.8
trans-3-OAc	4.6	0.3
cis-3-OAc	0.4	1.1

appropriate times aliquots were titrated with standardized perchloric acid in acetic acid to the bromophenol blue end point. Rate constants were calculated by a modified LSKIN2 computer program.[17]

Registry No.—*trans*-4-*t*-Butylcyclohexyl methanesulfonate, 18508-90-2; *cis*-4-*t*-butylcyclohexyl methanesulfonate, 18508-91-3; *trans*-4-methylcyclohexyl methanesulfonate, 18508-92-4; *cis*-4-methylcyclohexyl methanesulfonate, 18508-93-5; cyclohexyl methanesulfonate, 16156-56-2.

(17) D. F. DeTar and C. E. DeTar, Florida State University. We are grateful to Mr. Howell A. Hammond for his assistance in modifying these programs.

A Facile Synthesis of 1,4-Cyclooctadiene

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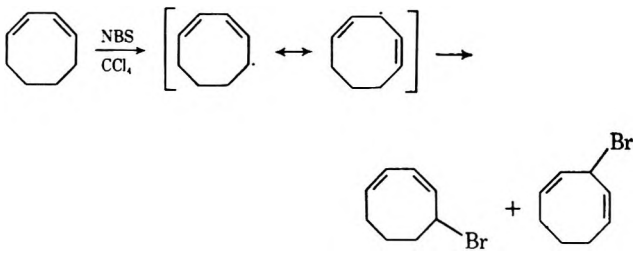
The chemical reactions of both 1,3- and 1,5-cyclooctadiene have been studied in some detail.[1] The chemistry of the corresponding 1,4 isomer, however, has been largely neglected, possibly due to the inaccessibility of this compound.

Although some preparations of 1,4-cyclooctadiene have been reported,[2-6] a facile synthesis which gives a substantial quantity of the pure compound is still lacking. In this paper, we wish to describe a simple synthetic procedure which utilizes a readily available and inexpensive starting material and which affords 1,4-cyclooctadiene of high purity.

The synthesis is based upon the partial rearrangement of 1,3-cyclooctadiene during bromination with N-bromosuccinimide (NBS). Treatment of the bromination product with lithium aluminum hydride affords approximately a 50:50 mixture of 1,3- and 1,4-cyclooctadiene. It therefore appears that the intermediate radical, formed in the NBS reaction, undergoes an allylic rearrangement in the manner illustrated.



On the basis of previous studies made by Jones,[4] we have found that, at room temperature, 1,3-cyclooctadiene is inert to silver nitrate while the 1,4 isomer readily forms a silver nitrate complex. 1,4-Cyclooctadiene can thus be conveniently and selectively separated from the lithium aluminum hydride reduction mixture by extraction with 50% silver nitrate at room temperature. Regeneration of the 1,4-diene from its silver nitrate complex is accomplished by treatment with cold concentrated ammonium hydroxide. Ether extraction of the resultant ammonium hydroxide solution followed by distillation affords pure (>99% by vpc analysis) 1,4-cyclooctadiene.

Experimental Section[7]

Bromination of 1,3-Cyclooctadiene.—To 105.4 g of freshly distilled 1,3-cyclooctadiene[8] in 400 ml of carbon tetrachloride was added 175 g of NBS and 1.25 g of benzoyl peroxide. The mixture was refluxed, with stirring, for 17 hr, then cooled and the succinimide removed by filtration. The filtrate was washed with two 600 ml-portions of 10% $NaHCO_3$ and 600 ml of H_2O and then dried ($MgSO_4$). The solvent was removed under reduced pressure (20 mm) through a Vigreux column. The residue was then distilled through a short-path distillation column to give 97.1 g (53% based on 1,3-cyclooctadiene) of a bromide mixture, bp 25–52° (0.3 mm). The nmr spectrum of the distillate suggested that it was a mixture of 2,4-cyclooctadien-1-yl bromide and 2,7-cyclooctadien-1-yl bromide.

Lithium Aluminum Hydride Reduction of the Bromination Product.—To a suspension of 15 g of lithium aluminum hydride in 250 ml of anhydrous ether was added, dropwise and with stirring, 97.1 g of the bromide mixture in 25 ml of ether. Following complete addition, the solution was refluxed overnight. After cooling, 40 ml of H_2O was cautiously added, dropwise and with stirring, to the externally cooled solution. Sulfuric acid (20%, 100 ml) was then added in a similar manner, followed by 400 ml more of the acid added at room temperature. Stirring was continued until all of the white precipitate, formed on H_2O addition, had dissolved. The aqueous portion was separated and extracted with 250 ml of ether. The latter was added to the original organic layer and the combined extracts were washed with two 400 ml-portions of 10% $NaHCO_3$ and 400 ml of H_2O and dried ($MgSO_4$). The ether was removed by distillation. The crude diene mixture (50.5 g, 90% based on the bromide mixture) was analyzed by vpc (TCEP, 65°) and found to be approximately a 50:50 mixture of two compounds with slightly different retention times. Each compound was isolated by

(1) See, for example, A. C. Cope and P. E. Peterson, *J. Amer. Chem. Soc.*, **81**, 1643 (1959); R. S. H. Liu, *ibid.*, **89**, 112 (1967); I. Haller and R. Srinivasan, *ibid.*, **88**, 5084 (1966).

(2) K. Ziegler and H. Wilms, *Ann. Chem.*, **567**, 1 (1950).

(3) L. E. Craig, R. M. Elofson, and I. J. Ressa, *J. Amer. Chem. Soc.*, **75**, 480 (1953).

(4) W. O. Jones, *J. Chem. Soc.*, 312 (1954).

(5) W. Grimme, *Chem. Ber.*, **98**, 756 (1965).

(6) U. S. Rubber Co., Netherlands Patent 6,607,898 (1966); *Chem. Abstr.*, **67**, 11922 (1967).

(7) Nmr spectra were determined on a Varian A-60 spectrometer. Infrared spectra were recorded on a Perkin-Elmer Model 337 grating infrared spectrophotometer. Gas chromatography was performed on an F & M Model 720 thermal conductivity gas chromatograph using a 4-ft column containing 20% 1,2,3-tris(2-cyanoethoxy)propane (TCEP) on Chromosorb P. Boiling points are uncorrected.

(8) We are grateful to the Columbian Carbon Co. for a generous sample of this compound.

preparative gas chromatography. The ir and nmr spectra of the compound with shorter retention time were identical with those of 1,3-cyclooctadiene. The nmr spectrum (CCl_4) of the second compound showed absorptions centered at τ 4.54 (4 H, multiplet), 7.22 (2 H, multiplet), 7.73 (4 H, multiplet) and 8.58 (2 H, multiplet), while the ir spectrum (neat) exhibited bands at 3000 and 1645 cm^{-1}. Both of these spectra are compatible with those expected for 1,4-cyclooctadiene. In addition, the spectra are idential with those of an authentic sample.[9]

Separation of 1,3- and 1,4-Cyclooctadiene.—To 50.5 g of the diene mixture was added 140 ml of 50% aqueous[10] $AgNO_3$. The mixture was stirred, in the dark, overnight. The silver nitrate complex, a green solid, was isolated by filtration and washed with several small portions of ether which were then added to the filtrate. The complex was further washed with acetone and again with ether and then dried. The filtrate was separated into aqueous and organic portions and the latter reextracted with 100-, 75-, and 75-ml portions of 50% $AgNO_3$. The remaining organic layer, after washing with water, drying ($MgSO_4$) and concentration, gave 22.5 g of 1,3-cyclooctadiene found to be ~98% pure by vpc retention time. Each aqueous $AgNO_3$ extract, including that from the original filtrate, was washed with ether to remove any residual 1,3-cyclooctadiene. To the combined, ether-washed $AgNO_3$ extracts was added, with external cooling and stirring, 250 ml of cold concentrated NH_4OH. After stirring for 15 min, the resultant mixture was extracted with two 500-ml portions of ether. Similarly, the dried solid complex was dissolved in 350 ml of cold, concentrated NH_4OH (a small amount of greyish residue remained insoluble) and carefully extracted with two 300-ml portions of ether (*caution*—vigorous ebullition of bubbles). The ether extracts from the solid complex and the aqueous $AgNO_3$ portions were combined, washed with water, dried ($MgSO_4$) and concentrated by distillation. The residue was further distilled through a microdistillation column to give 13.3 g (13% based upon 1,3-cyclooctadiene used; 16% based upon 1,3-cyclooctadiene consumed) of 1,4-cyclooctadiene (>99% pure by vpc), bp 57–58° (35 mm).

Registry No.—1,4-Cyclooctadiene, 1,073-07-0.

(9) We wish to extend our thanks to Dr. E. Ciganek for kindly supplying us with the spectra of 1,4-cyclooctadiene.

(10) Use of undistilled water was found to cause clouding of the $AgNO_3$ solution due to the formation of AgCl. This may have an adverse affect on the extraction.

The Preparation and Reduction of 2-Methyl-2-nitro-3-benzylthiopropanol[1]

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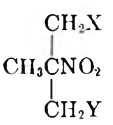
The normal product resulting from the treatment of an aliphatic nitro compound with lithium aluminum hydride is the corresponding amine.[2] However, the reduction of *t*-alkyl nitro compounds can give the corresponding hydroxylamine[3] and the reduction of aliphatic nitro compounds containing a β-hydroxyl group can give cleavage of the carbon–carbon bond between the nitro and hydroxyl group in addition to reduction of the nitro group.[4] In this paper we wish to report the preparation and the lithium aluminum hydride reduction of a *t*-alkyl nitro compound which contains a β-hydroxyl function and to discuss the mechanistic implications of the results.

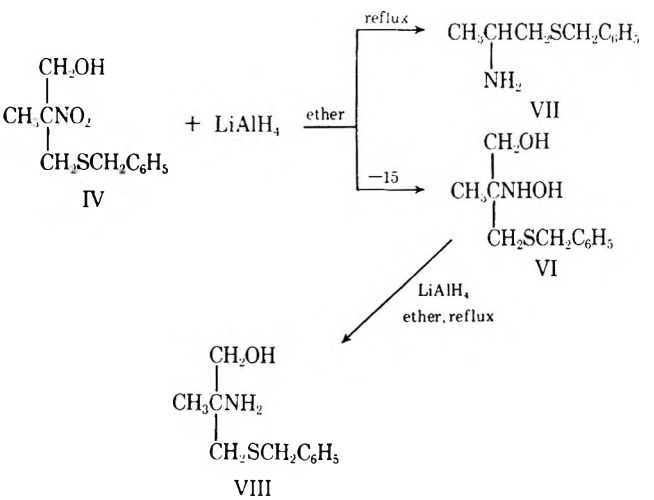
Treatment of 2-methyl-2-nitro-1,3-propanediol (I) with 1 equiv of *p*-toluenesulfonyl chloride in pyridine at 0° gave a 68% yield of monotosylate II. If the reaction was carried out at room temperature using 2 equiv of *p*-toluenesulfonyl chloride, ditosylate III was obtained. The ditosylate could also be prepared by the treatment of II with 1 equiv of *p*-toluenesulfonyl chloride. The reaction of II with sodium benzyl mercaptide gave 57% of 2-methyl-2-nitro-3-benzylthiopropanol (IV). Treatment of IV with *p*-toluenesulfonyl chloride gave tosylate V which was identical with the product obtained by treating III with 1 equiv of sodium benzyl mercaptide. Although the reaction of II and III with sodium benzyl mercaptide proceeded quite smoothly, treatment of II or III with weaker nucelophiles such as thiourea or sodium thiocyanate gave no reaction.



I, X = Y = OH
II, X = OH; Y = 1,4-$CH_3C_6H_4SO_3$
III, X = Y = 1,4-$CH_3C_6H_4SO_3$
IV, X = OH; Y = $C_6H_5CH_2S$
V, X = 1,4-$CH_3C_6H_4SO_3$; Y = $C_6H_5CH_2S$

The reduction of IV with lithium aluminum hydride proved to be quite interesting. The results obtained are summarized in Scheme I. If the reduction was

SCHEME I



carried out in ethyl ether at −15° using the method of inverse addition, a 60% yield of 2-methyl-2-hydroxylamino-3-benzylthiopropanol (VI) was obtained. The structural assignment was based on the elemental analysis, a positive Tollens test and the nmr spectrum which showed a singlet at δ 1.02 ($CH_3C\lessgtr$), an AB quartet at 2.60, J = 13 cps ($-CH_2OH$), an AB quartet

(1) This investigation was supported by the Department of the Army and the U. S. Army Medical Research and Development Command, Contract No. DA-49-193-MD-2164.

(2) N. G. Gaylord, "Reduction with Complex Metal Hydrides," Interscience Publishers, Inc., New York, N. Y., 1956, p 672.

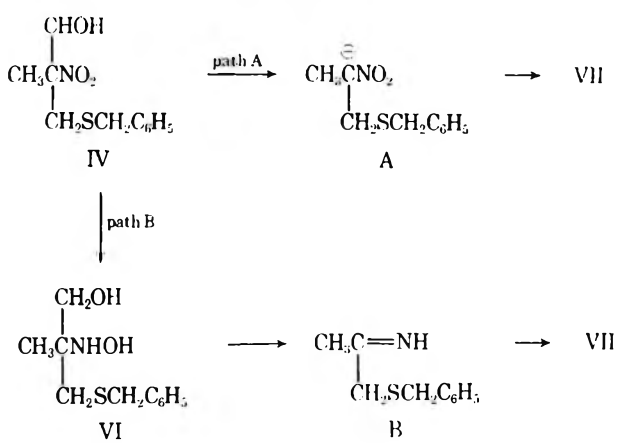
(3) H. J. Barber and E. Lunt, *J. Chem. Soc.*, 1187 (1960).

(4) A. Dornow and M. Gilbrich, *Ann.*, **594**, 177 (1955).

at 3.53 ($-CH_2S-$), a singlet at 3.75 ($-SCH_2Ar$), a broad singlet at 5.55 (OH + NH) and a singlet at 7.31 ppm (aromatic protons). Additional support for this structure results from the reduction of IV to VI with zinc and ammonium chloride, a reagent used specifically for the reduction of nitro groups to hydroxylamino groups.[3] If the reduction of IV with lithium aluminum hydride was carried out in refluxing ethyl ether using the normal mode of addition, very little if any of VI was formed. Instead, 41% of 1-benzylthio-2-propylamine (VII) resulting from the loss of a methylenehydroxy group and reduction of the nitro function was observed. The elemental analysis, the infrared spectrum which showed $-NH_2$ absorption at 3375 cm^{-1} and the absence of hydroxyl absorption, and the nmr spectrum, which showed a doublet at δ 1.03, J = 6 cps (CH_3 of CH_3CH group), a singlet at 1.37 ($-NH_2$), a multiplet at 2.35 (CH_2S), a multiplet at 2.88 (CHN<), a singlet at 3.67 ($-SCH_2Ar$) and a singlet at 7.23 ppm (aromatic protons) are in agreement with this assignment.

The formation of VII under the more stringent conditions could result from the action of lithium aluminum hydride as a strong base on IV to give the resonance stabilized anion A which on further reduction would give VII (Scheme II, path A). Alternatively,

SCHEME II



VII could result from the rearrangement of hydroxylamine VI to an intermediate B which on further reduction would yield VII (path B).[5,6] However, path B can be eliminated since treatment of VI with lithium aluminum hydride in refluxing ether gave a quantitative yield of 2-methyl-2-amino-3-benzylthiopropanol (VIII).[7] The correctness of the structural assignment was shown by the nmr spectrum which showed a singlet at δ 1.03 ($CH_3C<$), a singlet at 2.54 ($-CH_2S-$), a broad singlet at 2.70 (NH_2 and OH), a singlet at 3.33 ($-CH_2O$), a singlet at 3.73 ($-SCH_2Ar$) and a singlet at 7.33 ppm (aromatic protons).

(5) Barber and Lunt[3] have shown that 1-methyleyclohexylhydroxylamine undergoes rearrangement when treated with lithium aluminum hydride.

(6) It is realized that these explanations are oversimplifications since the intermediate reduction products would exist as complex negative ions. However they do give an over-all picture of the results obtained.

(7) 2-Methyl-2-amino-3-benzylthiopropanol was obtained as a viscous liquid and has analyzed as its tosylate salt which could be obtained in 94% yield from the free base.

Experimental Section[8]

Preparation of 2-Methyl-2-nitro-1,3-propanediol Monotosylate (II) and 2-Methyl-2-nitro-1,3-propanediol Ditosylate (III).—To an ice cold, stirred solution of 109 g (0.535 mol) of 2-methyl-2-nitro-1,3-propanediol in as little pyridine as possible was added dropwise 110 g (0.535 mol) of *p*-toluenesulfonyl chloride dissolved in as little pyridine as possible. The reaction mixture was allowed to warm to room temperature and remain for 15 hr. The mixture was then diluted with water and extracted with ether. The ether extracts were washed with a 4% hydrochloric acid solution, washed with water, dried and concentrated to give 132 g of a red-brown oil. The oil was dissolved in a small amount of ethanol and cooled to give 30 g of 2-methyl-2-nitro-1,3-propanediol ditosylate, mp 96–98°.[9] The analytical sample prepared by recrystallization from the same solvent had mp 99.5–100.5°; $\nu_{max}^{CH_2Cl_2}$ 1560 and 1368 (NO_2), and 1180 and 1015 cm^{-1} ($-SO_2O$). The nmr spectrum ($CDCl_3$) showed a singlet at δ 1.56 ($CH_3C<$), a singlet at 2.44 ($ArCH_3$), a singlet at 4.35 ($-CH_2OTos$) and an A_2B_2 pattern for the aromatic protons centered at 7.55 ppm, J = 8 cps.

Anal. Calcd for $C_{18}H_{21}NO_8S_2$: C, 48.29; H, 4.77. Found: C, 48.42; H, 4.81.

The filtrate was concentrated to afford 102 g of an oil. Crystallization from an ether and petroleum ether mixture gave 98 g (68%) of 2-methyl-2-nitro-1,3-propanediol monotosylate, mp 59–61°. The analytical sample prepared by recrystallization from the same solvent had mp 60–62°; $\nu_{max}^{CH_2Cl_2}$ 3600 (OH), 1550 and 1360 (NO_2), and 1275 and 1000 cm^{-1} ($-SO_2O$). The nmr spectrum ($CHCl_3$) showed a singlet at δ 1.55 ($CH_3C<$), a singlet at 2.46 ($ArCH_3$), a singlet at 2.87 (–OH), a singlet at 3.93 ($-CH_2OH$), a singlet at 4.45 ($-CH_2OTos$) and an A_2B_2 pattern at 7.57 ppm for the aromatic protons, J = 8 cps.

Anal. Calcd for $C_{11}H_{15}NO_6S$: C, 45.66; H, 5.23. Found: C, 45.51; N, 5.30.

Treatment of II with *p*-toluenesulfonyl chloride in methylene chloride catalyzed by triethylamine gave a 66% yield of III, mp 99.5–100.5°.

Preparation of 2-Methyl-2-nitro-3-benzylthiopropanol (IV).—To a solution of sodium benzyl mercaptide in 100 ml of absolute ethanol [prepared from 1.15 g (0.065 g-atom) of sodium and 8.1 g (0.065 mol) of benzyl mercaptan] under a dry nitrogen atmosphere was added 18.9 g (0.065 mol) of 2-methyl-2-nitro-1,3-propanediol monotosylate. The stirred reaction mixture was refluxed overnight. The cooled reaction mixture was filtered, and the filtrate was concentrated under vacuum. The residue was dissolved in ether and washed with water. The ether layer was dried (Na_2SO_4) and then concentrated to give 11.5 g of a red-brown oil. This oil was chromatographed on 60 g of Florisil using benzene as the eluent to give 9 g (57%) of 2-methyl-2-nitro-3-benzylthiopropanol as a colorless oil, $\nu_{max}^{CH_2Cl_2}$ 3590 (OH), and 1545 and 1345 cm^{-1} (NO_2). The nmr spectrum ($CDCl_3$) showed a singlet at δ 1.54 ($CH_3C<$), a broad peak at 2.77 (–OH), a singlet at 2.98 ($-CH_2S$), a singlet at 3.70 ($-CH_2OH$), a broad singlet at 3.88 ($-SCH_2Ar$) and a singlet at 4.76 ppm (aromatic protons). This compound could not be crystallized. It was characterized as its tosylate derivative (V) as described in the following experiment.

The Preparation of 2-Methyl-2-nitro-3-benzylthiopropanol Tosylate (V) from 2-Methyl-2-nitro-3-benzylthiopropanol (IV).—A mixture of 5 g (0.02 mol) of 2-methyl-2-nitro-3-benzylthiopropanol, 3.94 g (0.02 mol) of *p*-toluenesulfonyl chloride and 10 ml of pyridine was stirred at room temperature overnight. The reaction mixture was diluted with water and extracted with ether. The ether extracts were washed with 4% hydrochloric acid solution, washed with water, dried ($MgSO_4$) and concentrated under vacuum to give 6.5 g of a red oil. The oil was chromatographed on 100 g of Florisil using a 1:1 mixture of benzene and ethyl acetate as the eluent to give 4.2 g of crystals. Recrystallization of the product from ethanol afforded 3.1 g

(8) Melting points were determined on a Kofler hot-stage microscope using a calibrated thermometer. Nmr spectra were recorded on a Varian Model A-60, using tetramethylsilane as an internal standard. Infrared spectra were measured with a Perkin-Elmer 221 spectrophotometer. Microanalyses were carried out by Micro-Tech Laboratories, Skokie, Ill.

(9) Treatment of 2-methyl-2-nitro-1,3-propanediol with 2 equiv of *p*-toluenesulfonyl chloride in pyridine gave an 87% yield of III.

(42%) of crystals, mp 54.5–56°. The infrared spectrum showed absorption at 1550 and 1365 ($-NO_2$), 1175 and 1005 cm^{-1} ($-SO_2O$) and the absence of hydroxyl absorption. The nmr spectrum ($CHCl_3$) showed a singlet at δ 1.53 (CH_3C), a singlet at 2.40 ($ArCH_3$), a singlet at 2.93 ($-CH_2S$), a singlet at 3.65 ($-CH_2OTos$) a broad singlet at 4.37 ($-SCH_2Ar$), a singlet at 7.25 ($-SCH_2C_6H_5$) and an A_2B_2 pattern centered at 7.54 ppm for the tosylate aromatic proton resonances, J = 8 cps.

Anal. Calcd for $C_{18}H_{21}NO_5S_2$: C, 54.66; H, 5.35. Found: C, 54.47; H, 5.46.

Preparation of 2-Methyl-2-nitro-3-benzylthiopropanol Tosylate (V) from 2-Methyl-2-nitro-1,3-propanediol Ditosylate (III).—To a solution of sodium benzyl mercaptide in 70 ml of absolute ethanol [prepared from 0.69 g (0.03 g-atom) of sodium and 3.72 g (0.03 mol) of benzyl mercaptan] under a dry nitrogen atmosphere was added 13.3 g (0.03 mol) of 2-methyl-2-nitro-1,3-propanediol ditosylate. The stirred reaction mixture was refluxed overnight under a nitrogen atmosphere. The cooled reaction mixture was concentrated, diluted with water and extracted with ether. The ether extracts were dried ($MgSO_4$) and concentrated to give a yellow oil. The oil was chromatograhed on 50 g of Florisil using a 1:1 mixture of benzene and ethyl acetate as the eluent to afford 7.5 g (63%) of 2-methyl-2-nitro-3-benzylthiopropanol tosylate, mp 50–53°. The infrared spectrum of this product was identical with the spectrum of 2-methyl-2-nitro-3-benzylthiopropanol tosylate prepared from 2-methyl-2-nitro-3-benzylthiopropanol. A mixture of the two products melted at 52–54°.

Reduction of 2-Methyl-2-nitro-3-benzylthiopropanol with Lithium Aluminum Hydride in Ethyl Ether at −15°.—To a solution of 6 g (0.025 mol) of IV in 100 ml of ether cooled by an ice–methanol bath (−15°) was added 2.85 g (0.075 mol) of lithium aluminum hydride in 200 ml of ether. The addition was dropwise over a 1-hr period. The excess lithium aluminum hydride was decomposed by the cautious addition of water and then 400 ml of a 20% potassium sodium tartrate solution was added. The organic layer was separated and the aqueous layer extracted with ether. The combined organic layers were dried over anhydrous sodium sulfate. Concentration of the solution afforded 4.34 g of an oil which was crystallized from an ether cyclohexane mixture to give 34. g (60%) of 2-methyl-2-hydroxylamino-3-benzylthiopropanol (VI), mp 77–82°. The analytical sample prepared by further recrystallization from the same solvent mixture had mp 82–83°.

Anal. Calcd for $C_{11}H_{17}O_2NS$: C, 58.13; H, 7.54. Found: C, 58.23; H, 7.61.

Reduction of 2-Methyl-2-nitro-3-benzylthiopropanol with Zinc and Ammonium Chloride.—To a suspension of 0.721 g (0.003 mol) of 2-methyl-2-nitro-3-benzylthiopropanol in 5 ml of water containing 0.161 g (0.003 mol) of ammonium chloride was added 0.392 g (0.006 mol) of zinc powder, and the mixture was stirred vigorously for 4 hr. The aqueous layer was separated by decantation and the remaining residue was washed with methanol. The methanol washings were concentrated to give a cloudy oil which was dissolved in ether and extracted with 5% hydrochloric acid solution. The acid extracts were made alkaline with sodium bicarbonate and extracted with ether. The ether extracts were dried (Na_2SO_4) and concentrated to give 0.250 g of an oil. Crystallization from cyclohexane afforded 0.200 g (30%) of 2-methyl-2-hydroxylamino-3-benzylthiopropanol, mp 78–81°.

Reduction of 2-Methyl-2-nitro-3-benzylthiopropanol with Lithium Aluminum Hydride in Refluxing Ethyl Ether.—A solution of 12 g (0.05 mol) of 2-methyl-2-nitro-3-benzylthiopropanol in 50 ml of ether (dried over sodium metal) was added dropwise to an ice-cooled stirred solution–suspension of 5.7 g (0.15 mol) of lithium aluminum hydride in 200 ml of anhydrous ether. After the addition was completed, the reaction mixture was refluxed for 3 hr. The excess lithium aluminum hydride was decomposed with water and 1 l. of a 20% sodium potassium tartrate solution was added. The ether layer was separated and the remaining aqueous layer was extracted with ether. The organic layers were combined and dried ($MgSO_4$). Concentration of the ether afforded 9.9 g of light yellow liquid. Distillation of the liquid under reduced pressure afforded 3.7 g (41%) of colorless product, bp 95° (0.08 mm), $n^{25}D$ 1.5564. The 1-benzylthio-2-propylamine formed a carbonate salt rapidly on exposure to the atmosphere and was thus analyzed as the hydrochloride salt, mp 149–151°. The nmr spectrum (D_2O) showed a doublet at δ 1.44, CH_3 of ($CH_3^aCH^b$, $J_{a,b}$ = 7 cps), a doublet at 2.81 , $J_{b,c}$ = 7 cps (slightly perturbed due to the nonequivalence of the methylene protons, $-CH_2$ of $CH^bCH_2^cS$), a sextet at 3.57 (CH of $CHCH_2S$ group), a singlet at 3.85 ($-SCH_2Ar$) and a singlet at 7.37 ppm (aromatic protons).

Anal. Calcd for $C_{10}H_{16}ClNS$: C, 55.15; H, 7.41. Found: C, 55.28; H, 7.11.

In a separate experiment the product was isolated in 49% yield as the hydrochloride.

Reduction of 2-Methyl-2-hydroxylamino-3-benzylthiopropanol with Lithium Aluminum Hydride in Refluxing Ethyl Ether.—To a solution–suspension of 0.57 g (0.015 mol) of lithium aluminum hydride in 20 ml of anhydrous ether was added dropwise a solution of 1.14 g (0.005 mol) of VI in 50 ml of ether. After the addition was completed, the mixture was refluxed for 8 hr. The mixture was worked up as in the previous reductions to give 1.07 g of a viscous liquid. This liquid was dissolved in ether and treated with an ethereal solution of *p*-toluenesulfonic acid to give 1.8 g (94%) of 2-methyl-2-amino-3-benzylthiopropanol *p*-toluenesulfonate, mp 133–137°. The analytical sample prepared by recrystallization from an ethanol and ether mixture had mp 134–137°.

Anal. Calcd for $C_{18}H_{25}NS_2O_4$: C, 56.37; H, 6.57; N, 3.65; S, 16.72. Found: C, 56.49; H, 6.58; N, 3.81; S, 16.52.

Registry No.—II, 18386-49-7; III, 18386-50-0; IV, 18386-51-1; V, 18386-52-2; VI, 18354-31-9; VII·HCl, 18354-32-0; VIII·*p*-toluenesulfonate, 18386-53-3.

Acknowledgment.—The author wishes to thank Dr. Monroe E. Wall of this laboratory for his kind encouragement and support of this work and Dr. Richard G. Hiskey, University of North Carolina, for helpful discussions. The author also expresses his appreciation to Mr. William H. Bowers and Mr. H. M. Dickson for assistance in some of the experimental work.

Phenylethynylpentafluorobenzene and Phenylethynylpentachlorobenzene

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During the course of some current studies concerned with the reductive dimerization of arylacetylenes to dilithium reagents[2] and the conversion of arylacetylenes to aryl-substituted cyclobutadiene–cobalt complexes,[3] we developed a need for several diarylacetylenes in which one of the aryl groups was perhalogenated. Very recently, Filler and Heffern[4] have described a multistep, phosphorane-type route to one of these acetylenes, *viz.*, phenylethynylpentafluorobenzene (**1**). Other at-

$ArC{\equiv}CC_6H_5$	$ArC{\equiv}CC{\equiv}CAr$
1, Ar = C_6F_5	**3**, Ar = C_6H_5
2, Ar = C_6Cl_5	**4**, Ar = C_6F_5

(1) National Science Foundation Graduate Trainee, 1965–1968.

(2) M. D. Rausch and L. P. Klemann, *J. Amer. Chem. Soc.*, **89**, 5732 (1967); unpublished studied by these authors.

(3) M. D. Rausch and R. A. Genetti, *ibid.*, **89**, 5502 (1967); F. Higbie, A. Siegel, and M. D. Rausch, unpublished studies.

(4) R. Filler and E. W. Heffern, *J. Org. Chem.*, **32**, 3249 (1967).

tempts[5,6] to form **1** *via* the reaction of phenylethynyllithium and hexafluorobenzene have been reported to be unsatisfactory, due to the ease with which the *p*-fluorine atom in **1** is displaced by additional phenylethynyllithium reagent. It should be mentioned that routes to both bis(pentafluorophenyl)acetylene[4,7,8] and bis(pentachlorophenyl)acetylene[8] have also been described recently.

Earlier studies in our laboratory[9] have shown that the Castro–Stephens procedure[10–12] for the synthesis of diarylacetylenes is applicable to ferrocenyl- and 2-thienylarylacetylenes. In the present note, we describe studies which indicate that this same method represents a convenient route to **1** as well as its chlorinated analog, phenylethynylpentachlorobenzene (**2**).[13]

When iodopentafluorobenzene and phenylethynylcopper(I) were refluxed in pyridine for a period of 10 hr under nitrogen, phenylethynylpentafluorobenzene (**1**) was obtained in 55% yield. A small amount of the oxidative coupling product, diphenylbutadiyne (**3**), was also detected. In general, longer reflux periods resulted in appreciably reduced yields of the desired product, due conceivably to subsequent reactions of **1**.[13] A similar reaction between bromopentafluorobenzene and phenylethynylcopper(I) produced **1** in only 33% yield, and an appreciable amount of diacetylene **3** was formed. These results are in accord with the known halide reactivity series (I > Br > Cl)[12] in reactions of aryl halides with cuprous arylacetylides.

In a reverse manner, a reaction between iodobenzene and pentafluorophenylethynylcopper(I) in refluxing pyridine for 8 hr under nitrogen resulted in the formation of **1** in 74% yield. The oxidative coupling product, perfluorodiphenylbutadiyne (**4**), was not isolated in significant amount from this reaction, although it could readily be prepared by bubbling air through a pyridine solution of ethynylpentafluorobenzene in the presence of cuprous chloride for several hours. Although this alternate route to **1** appears to proceed more smoothly and produces the desired product in higher yield, it is presently handicapped by the limited availability[14] of ethynylpentafluorobenzene.

In several initial reactions involving iodopentachlorobenzene and phenylethynylcopper(I) in refluxing pyridine under nitrogen, the major product was diacetylene **3**, and only low yields of the desired product, phenylethynylpentachlorobenzene (**2**), could be obtained. When extreme care was taken to avoid oxygen from the reaction system by additionally purifying the pyridine *via* a freeze-thaw process, **2** was formed in 49% yield, and only minor amounts of **3** were detected. The conversion of iodopentachlorobenzene into **2** via a concerted displacement process[10–12] is remarkable in view of appreciable steric effects which might be expected to be imposed by the two flanking *o*-chlorine atoms.[15] On the other hand, it has recently been reported that the relative "activating power" of the pentachlorophenyl group in aromatic SN reactions is appreciably greater than for the pentafluorophenyl group, the former being about as activating as an *o*- or a *p*-nitrophenyl group.[16] Such an effect may possibly account for the reactivity of iodopentachlorobenzene in the Castro–Stephens reaction, although a detailed mechanistic study, including steric factors, would seem necessary before any definitive conclusions could be made. As expected, a reaction between hexachlorobenzene and phenylethynylcopper(I) in refluxing pyridine produced only the oxidative coupling product **3**, and none of the desired acetylene **2** could be detected.

Both unsymmetrical acetylenes **1** and **2** exhibit weak absorptions in the 2200–2250-cm^{-1} region, assignable to –C≡C– stretching vibrations, as well as bands characteristic of pentafluorophenyl groups and pentachlorophenyl groups, respectively. Further reactions of these new acetylenes in organic and organometallic systems will be described in subsequent papers.

Experimental Section

Phenylacetylene was purchased from Aldrich Chemical Co. and was converted into its copper(I) salt by the method of Castro and Stephens.[10–12] Pentafluorophenylacetylene and its copper(I) salt were prepared by the method of Coe, Plevey, and Tatlow.[14] Pyridine was reagent grade and was dried over potassium hydroxide and refluxed over barium oxide before use. Bromopentafluorobenzene was purchased from the Imperial Smelting Co., Ltd. Iodopentafluorobenzene, bp 162–164°, was prepared in 48% yield by a modification of the method of Vorozhtsov, *et al.*,[17] from pentafluorophenylmagnesium bromide and iodine in ethyl ether solution. Iodopentachlorobenzene was prepared from a reaction between pentachlorophenyllithium (50 mmol)[18] and iodine (31.7 g, 125 mmol) in ethyl ether at −50°. After the reaction mixture had been allowed to warm to room temperature and treated with saturated sodium thiosulfate solution, the ethyl ether portion was washed with water, dried, and evaporated to produce a pale yellow solid. Recrystallization of the solid from hexane gave 11.2 g of crude product, which was sublimed at 135° (0.3 mm) to afford 9.68 g (52%) of iodopentachlorobenzene in the form of white needles, mp 214–216° (lit.[19] mp 207–208°). Elemental analyses were performed by the Schwarzkopf Microanalytical Laboratory, Woodside, N. Y., and by Mr. Charles Meade of the University of Massachusetts Microanalytical Laboratory.

Reaction of Iodobenzene and Pentafluorophenylethynylcopper(I).—Into a 250-ml, three-necked flask equipped with a magnetic stirring bar, reflux condenser and nitrogen inlet were added iodobenzene (1.0 g, 4.9 mmol), pentafluorophenylethynylcopper(I) (1.0 g, 3.9 mmol) and 50 ml of pyridine. The reaction

(5) M. R. Wiles and A. G. Massey, *Chem. Ind.* (London), 663 (1967); *Tetrahedron Lett.*, 5137 (1967).

(6) P. C. Coe, J. C. Tatlow, and R. C. Terrell, *J. Chem. Soc., C*, 2626 (1967).

(7) J. M. Birchall, F. L. Bowden, R. N. Haszeldine, and A. B. P. Lever, *J. Chem. Soc., A*, 747 (1967).

(8) A. E. Jukes, S. S. Dua, and H. Gilman, *J. Organometal. Chem.*, **12**, P44 (1968).

(9) M. D. Rausch, A. Siegel, and L. P. Klemann, *J. Org. Chem.*, **31**, 2703 (1966).

(10) C. E. Castro and R. D. Stephens, *ibid.*, **28**, 2163 (1963).

(11) R. D. Stephens and C. E. Castro, *ibid.*, **28**, 3313 (1963).

(12) C. E. Castro, E. J. Gaughan, and D. C. Owsley, *ibid.*, **31**, 4071 (1966).

(13) Filler and Heffern[4] have independently investigated the formation of **1** by the Castro–Stephens procedure, using dimethylformamide as the reaction solvent. Their product was obtained in only impure form (20% crude yield), however, and optimum conditions for the synthesis of **1** were not worked out.

(14) P. L. Coe, R. G. Plevey, and J. C. Tatlow, *J. Chem. Soc., C*, 597 (1966).

(15) Mesityl iodide, in contrast, appears largely unreactive under analogous conditions (L. P. Klemann and M. D. Rausch, unpublished observations).

(16) J. Miller and H. W. Yeung, *Aust. J. Chem.*, **20**, 379 (1967).

(17) N. N. Vorozhtsov, Jr., V. A. Barkhash, N. G. Ivanova, S. A. Anichkina, and O. I. Andreevskaya, *Dokl. Akad. Nauk SSSR*, **159**, 125 (1964).

(18) M. D. Rausch, F. E. Tibbetts, and H. B. Gordon, *J. Organometal. Chem.*, **5**, 493 (1966).

(19) M. Istrati, *Bull. Soc. Chim. Fr.*, **5**, 169 (1891).

mixture was heated to reflux with stirring under nitrogen for a period of 8 hr, allowed to cool to room temperature, diluted with water, and the hydrolysate was extracted with ethyl ether. The ether extracts were washed successively with water, 5% hydrochloric acid, 5% sodium hydroxide solution, water, and were dried over magnesium sulfate. The ether was removed and the residue was sublimed at 140° (12 mm) to give 0.77 g (74%) of phenylethynylpentafluorobenzene (1), mp 96.5–98°.[20]

Anal. Calcd for $C_{14}H_5F_5$: C, 62.69; H, 1.89; F, 35.42. Found: C, 62.89; H, 2.04; F, 35.43.

The infrared spectrum (KBr) of 1 exhibited major absorptions at 2230, 1500 (broad), 1440, 1110, 1020, 975 (broad), 740 and 680 cm^{-1}.

Perfluorodiphenylbutadiyne (4).—Ethynylpentafluorobenzene (0.20 g, 1.04 mmol) and cuprous chloride (50 mg) were added to 10 ml of pyridine. Dry air was slowly bubbled through the mixture for 3 hr. The mixture was diluted with water and extracted with ethyl ether. The ether extracts were washed with water, 5% hydrochloric acid, water, and were dried. The ether was evaporated and the resulting residue was sublimed at 140° (16 mm) to afford 181 mg (91%) of perfluorodiphenylbutadiyne, mp 104–105°.

Anal. Calcd for $C_{16}F_{10}$: C, 50.28; F, 49.72. Found: C, 50.14; F, 49.92.

Reaction of Iodopentafluorobenzene and Phenylethynylcopper(I).—Iodopentafluorobenzene (8.0 g, 27 mmol) and phenylethynylcopper(I) (4.9 g, 30 mmol) were refluxed in 150 ml of pyridine for a period of 10 hr under nitrogen. After hydrolysis, washing, and drying in the usual manner, the ether was removed and the residue was fractionally sublimed. At 75° (12 mm), diphenylbutadiyne (3) (1.1 g) sublimed; the mp was 85–86° (lit.[21] mp 88°), and a mixture melting point with an authentic sample was undepressed. The remaining product was sublimed at 140° (12 mm) to produce 4.0 g (55%) of phenylethynylpentafluorobenzene (1), mp 93–94°.[20] Thin layer chromatography indicated contamination by trace amounts of diphenylbutadiyne. An infrared spectrum of the product was identical with a spectrum of the product from the reaction of iodobenzene and pentafluorophenylethynylcopper(I).

Reaction of Bromopentafluorobenzene and Phenylethynylcopper(I).—Bromopentafluorobenzene (5.0 g, 20 mmol) and phenylethynylcopper(I) (3.25 g, 20 mmol) were refluxed in 100 ml of pyridine for a period of 12 hr under nitrogen. After hydrolysis, washing, and drying in the usual manner, evaporation of the solvent left 5.0 g of a tan residue. Thin layer chromatography indicated two components. Accordingly, a 100-mg portion of the residue was subjected to preparative thin layer chromatography on silica gel using pentane as eluent. The bands which separated were extracted with ethyl ether. Evaporation of the solvent containing the component of lower R_f deposited 35 mg of diphenylbutadiyne, mp 85–86°. The solvent containing the band of higher R_f was evaporated to give 35 mg of phenylethynylpentafluorobenzene (1), mp 92–93°; this amount corresponds to a 33% yield of the product in the original reaction.

Reaction of Iodopentachlorobenzene and Phenylethynylcopper(I).—Iodopentachlorobenzene (7.52 g, 20 mmol), phenylethynylcopper(I) (6.58 g, 40 mmol) and 225 ml of dry, degassed (three freeze–thaw cycles) pyridine were refluxed for 21 hr under nitrogen. The reaction mixture was cooled, poured into 500 ml of ice–water, and extracted with 900 ml of dichloromethane. The extracts were washed as described above and were subsequently dried over sodium sulfate. Evaporation gave a brown residue which was washed with 75 ml of cold (−60°) pentane and filtered, leaving 3.93 g of a tan solid. This material was sublimed at 80° (0.1 mm) to remove trace amounts of diphenylbutadiyne. Continued sublimation at 175° (0.1 mm) afforded 3.41 g (49%) of white crystals of phenylethynylpentachlorobenzene (2), mp 218–220°.

Anal. Calcd for $C_{14}H_5Cl_5$: C, 47.98; H, 1.44; Cl, 50.58. Found: C, 48.00; H, 1.47; Cl, 50.53.

The infrared spectrum (KBr) exhibited major absorptions at 2220, 1490, 1460, 1400, 1345, 1300, 1276, 745, 710 and 680 cm^{-1}. A small amount of diphenylbutadiyne was observed in the pentane extract after evaporation.

Registry No.—1, 13509-88-1; 2, 18320-78-0; 4, 18320-79-1.

Acknowledgments.—The authors are indebted to the National Science Foundation and to the Donors of the Petroleum Research Fund, administered by the American Chemical Society, for grants in support of this research.

(20) Wiles and Massey[5] report a melting point for 1 of 93°; Filler and Heffern[4] report mp 108.5–109.5°. The melting point of 1 prepared in our studies varied slightly from run to run, due possibly to the presence of very small amounts of either diacetylene 3 or 4 resulting from an oxidative coupling process.

(21) A. S. Hay, German Patent 1,158,272 (1963); *Chem. Abstr.*, **60**, 7953g (1964).

Optically Active Nuclear Magnetic Resonance Solvents. VIII. Resolution of 2,2,2-Trifluorophenylethanol

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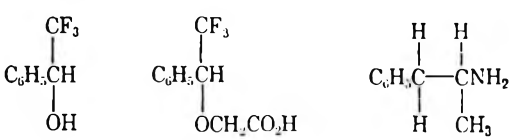
With the reports[1,2] that the optical purities and absolute configurations of a number of amines and sulfoxides may be determined by nmr spectroscopy in optically active 2,2,2-trifluorophenylethanol (1) as solvent, the convenient and efficient resolution herein reported for this carbinol should be of general interest. This carbinol has previously been resolved by Feigl and Mosher[3] through a lengthy series of fractional crystallizations of the diastereomeric 3β-acetoxy-Δ⁵-etienates, an approach which ultimately affords the pure enantiomers, $\alpha^{25}D$ +41.14° and $\alpha^{26}D$ −41.18° (neat, $l = 1$) in low yields.

Typically, alcohols having no other "handles" are converted into acid phthalates or acid succinates, resolved as such, and recovered from the esters after hydrolysis. However, the esters of acidic alcohols generally hydrolyze readily,[4] and this is the result of attempts to resolve the acid phthalate of 1 with optically active bases.[5] This problem has been avoided by converting 1 into a more stable resolvable derivative, 2,2,-2-trifluorophenylethoxyacetic acid (2), prepared from

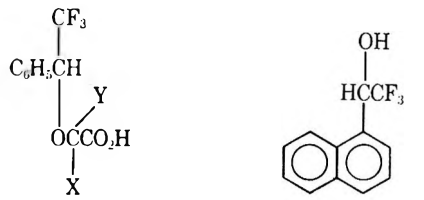


1 2 3

1 and ethyl bromoacetate *via* the Williamson synthesis. One of the diastereomeric salts of 2 and amphetamine (3), both enantiomers of which are readily available,

(1) W. H. Pirkle, T. G. Burlingame, and S. D. Beare, *Tetrahedron Lett.*, in press.
(2) W. H. Pirkle and S. D. Beare, *J. Amer. Chem. Soc.*, **90**, 6250 (1968).
(3) (a) D. M. Feigl and H. S. Mosher, *J. Org. Chem.*, **33**, 4242 (1968).
(4) A. L. Henne and R. L. Pelley, *J. Amer. Chem. Soc.*, **74**, 1426 (1952).
(5) H. S. Mosher, J. E. Stevenot, and D. O. Kimble, *ibid.*, **78**, 4374 (1956).

was found to be highly insoluble. Fractional crystallization is easily accomplished from ethyl acetate, after which the resolved alkoxy acid **2** can be efficiently converted into optically pure **1** by treatment with N-bromosuccinimide and subsequent hydrolysis of the resulting α-bromo ethers **4a–c**.[6] This scheme has also



4a, X = H; Y = Br
b, X = Br; Y = H
c, X = Y = Br

5

been successfully applied to the resolution of 2,2,2-trifluoro-(1-napthyl)ethanol (**5**) and appears attractive for the resolution of other similar alcohols where conventional methods might be expected to fail.

Experimental Section[7]

dl-**2,2,2-Trifluorophenylethanol** (**1**) was prepared in 84% crude yield by the action of methanolic sodium borohydride on trifluoroacetophenone.[8]

2,2,2-Trifluorophenylethoxyacetic Acid (**2**).—To a solution of 92 g of crude **1** (containing *ca.* 23% bromobenzene) in 100 ml of ether was added excess cut sodium at a rate sufficient to maintain gentle reflux. After *ca.* 1.5 hr, alkoxide formation appeared to be complete, whereupon unreacted sodium was removed, 82 g of ethyl bromoacetate was cautiously added, and the mixture was heated to reflux for 2.5 hr. Hydrolysis to the alkoxy acid was accomplished by the addition of 450 ml of 10% sodium hydroxide and heating (steam bath) for 1 hr. The pH was adjusted to 9 by the addition of Dry Ice and the solution was extracted with ether to remove unreacted **1** (*ca.* 10%) and bromobenzene. The aqueous solution was acidified to pH 1 and extracted with ether, yielding the crude acid which was crystallized from 1 l. of petroleum ether (bp 90–120°) to give 68.7 g, mp 105.5–106°. The yield of **2** is 85% based on the amount of unrecovered **1**: ^{1}H nmr (acetone-d_6) δ 4.17 (2 H, AB quartet, $\Delta\nu_{AB}$ = 7.2 Hz, J_{AB} = 16.5 Hz), 5.15 (1 H, quartet, J = 6.8 Hz), 7.45 (5 H, aromatic), and 8.80 ppm (1 H, COOH); ^{19}F nmr (CCl_4) δ 78.2 (doublet, J = 6.8 Hz).

Anal. Calcd for $C_{10}H_9F_3O_3$: C, 51.24; H, 3.87. Found: C, 51.49; H, 4.02.

Resolution of 2 with Amphetamine (**3**).—To a mixture of 56.5 g (0.24 mol) of unrecrystallized **2** (mp 102–104°) and 32.6 g (0.24 mol) of (−)-amphetamine (Aldrich Chemical Co.) was added 200 ml of hot ethyl acetate. The mixture was briefly heated on the steam bath to dissolve all solid, then allowed to stand at room temperature. After 4 hr, the resultant fluffy needles were collected by filtration and washed with cold ethyl acetate to give 22.7 g of salt, mp 149–153°. Two recrystallizations of this material using 12–14 ml of hot ethyl acetate per gram of salt gave 19.4 g (44% of theory) of material which did not change its properties upon further recrystallization: mp 155–156°; $[\alpha]^{25}$D −70.2 ± 1° (*c* 3.22, absolute ethanol).

Anal. Calcd for $C_{19}H_{22}F_3NO_3$: C, 61.78; H, 6.00; N, 3.80. Found: C, 61.65; H, 5.89; N, 3.66.

Concentration of the first crop mother liquors to 150 ml afforded a second crop of crystals, mp 128–130° (16.0 g), which did not significantly change its melting point or rotation upon successive recrystallization from ethyl acetate. This salt is not the other diastereomer but is a mixture of the two diastereomers and is richest in the salt of (+)-**2**.[9] The remaining mother liquors were concentrated at reduced pressure to remove ethyl acetate and then treated with 150 ml of 6 *N* hydrochloric acid to afford, after work-up, 32.7 g (0.14 mol) of partially resolved **2**. Treatment of this material with 18.9 g (0.14 mol) of (+)-**3** in 275 ml of ethyl acetate gave 16.0 g of material, mp 151–154°, which, after one recrystallization, afforded 13.4 g of salt melting at 155–156°; $[\alpha]^{25}$D +69.7 ± 1° (*c* 3.30, absolute ethanol). Purified (+)-amphetamine salt was converted into (+)-**2** with hydrochloric acid, yielding, after work-up, material melting at 87.5–88.5°, $[\alpha]^{24}$D +120 ± 1° (c 3.4 absolute ethanol).

Anal. Calcd for $C_{10}H_9F_3O_3$: C, 51.24; H, 3.87. Found: C, 51.31; H, 3.81.

Conversion of 2,2,2-Trifluorophenylethoxyacetic Acid (**2**) **into 2,2,2-Trifluorophenylethanol** (**1**).—To a solution of 11.5 g (0.05 mol) of (−)-**2** in 100 ml of carbon tetrachloride was added 13.2 g (0.07 mol) of N-bromosuccinimide and the mixture was heated to reflux on the steam bath while being irradiated with a GE sunlamp. After 4 hr, the ^{19}F nmr spectrum of an aliquot showed a trace of starting material and three major doublets 77.22, 77.56, and 77.60 ppm upfield of internal $CFCl_3$, tentatively assigned to the two diastereomeric monobromides **4a** and **b** and the α,α-dibromo derivative, **4c**. The solvent was evaporated, the residue was treated with 100 ml of 10% potassium hydroxide, and active alcohol **1** was collected by steam distillation. The distillate (250 ml) was extracted with ether, dried ($MgSO_4$), and concentrated. Molecular distillation of the residue (2 torr, 40°, cold finger at 0°) gave 6.88 g (80%) of (−)-**1**, identified by its ir and nmr spectra: α^{25}D −40.8° (neat, l = 1) (lit.[2] α^{25}D −41.18° (neat, l = 1). An nmr determination[10] of the optical purity of this carbinol failed to detect the presence of the (+)-enantiomer of **1**.

Registry No.—(+)-**1**, 340-05-6; (−)-amphetamine salt of **2**, 18521-88-5; (+)-**2**, 18521-89-6; (+)-amphetamine salt of **2**, 18521-90-9.

Acknowledgment.—This work was supported by Grant No. GM 14518 from the U. S. Public Health Service and by a U. S. Public Health Service Traineeship to T. G. B.

(6) Crawford has reported the resolution of 1-trifluoromethylethanol *via* the adduct arising from condensation of the alcohol with acrylic acid. Hydrolysis is effected with base by means of the reverse Michael addition [J. W. C. Crawford, *J. Chem. Soc.*, 4280 (1965); *ibid.*, *C*, 2332 (1967)].

(7) Melting points were determined on a Büchi apparatus and are uncorrected. The nmr spectra were determined with a Varian A-56/60 spectrometer and chemical shifts are reported in δ units (parts per million downfield from internal tetramethylsilane or upfield from internal fluorotrichloromethane). Microanalyses were performed by J. Nemeth and his associates.

(8) The trifluoroacetophenone used in this work (Columbia Organic Chemicals, Columbia, S. C.) was shown by glpc to contain 23% bromobenzene. Reported crude yields are corrected for the bromobenzene present.

(9) As a consequence of the formation of this mixture, it is advisable to liberate the partially resolved acid **2** from the mother liquors of the initial crystallization and to proceed with the resolution of this material using the other enantiomer of amphetamine.

(10) (a) W. H. Pirkle, *J. Amer. Chem. Soc.*, **88**, 1837 (1966); (b) W. H. Pirkle and S. D. Beare, *ibid.*, **89**, 5485 (1967).

The Photolysis of Stilbene in the Presence of 2,3-Dihydropyran

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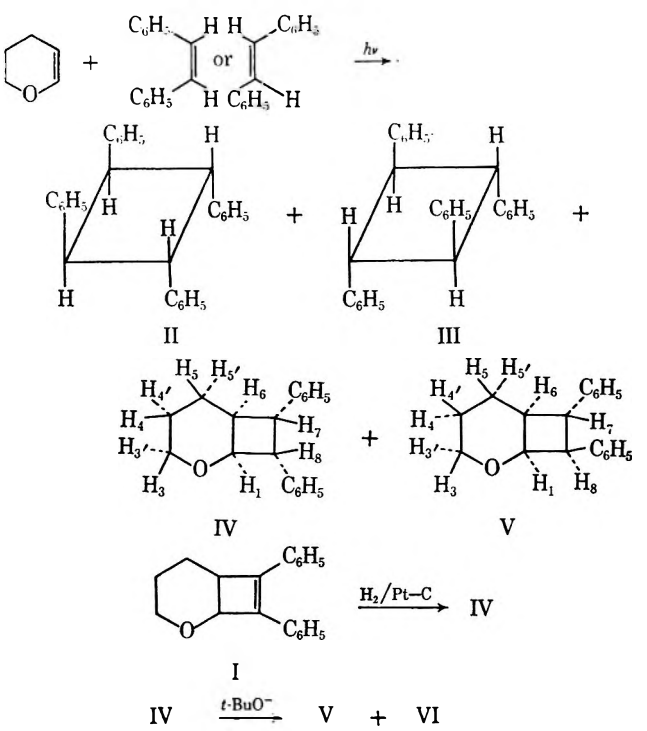
In an earlier paper we reported the photocycloaddition of diphenylacetylene to 2,3-dihydropyran to form

7,8-diphenyl-2-oxabicyclo[4.2.0]oct-7-ene (I).[1] In order to observe the behavior of aryl olefins under similar reaction conditions we photolyzed solutions of *cis*-stilbene and *trans*-stilbene in the presence of 2,3-dihydropyran. The reaction mixtures were irradiated at 2537 Å for 48 hr while exposed to the atmosphere. At the end of this period the stilbene had reacted completely as indicated by glpc analysis. Four products were produced whose yields were virtually independent of stilbene isomer reactant. Two products were identified as *cis,trans,cis*-1,2,3,4-tetraphenylcyclobutane (II) and *trans,trans,trans*-1,2,3,4-tetraphenylcyclobutane[2] (III) (combined yields 24%). The other products were characterized as 7,8-*cis*-*exo*-diphenyl-2-oxabicyclo[4.2.0]octane (IV, 43%) and 7-*exo*-8-*endo*-diphenyl-2-oxabicyclo[4.2.0]octane (V, 23%) (Scheme I).

SCHEME I



The structural assignments of IV and V were supported by the following evidence. High resolution mass spectra established that both products were 1:1 adducts of stilbene and 2,3-dihydropyran. Catalytic hydrogenation (Pt–C) of I afforded one product whose glpc retention time and ir spectrum were identical with those of IV. Compound IV, on treatment with base, gave two products in approximately equal quantities having similar, but not identical, glpc retention times. One of these products (the one with slightly longer retention time) was found to have the identical retention time on two different columns as V. The other product (VI) was not isolated or characterized. These data indicate that IV is a *cis*-diphenylbicyclooctane and V is a *trans*-diphenyl isomer.

The stereochemistry was deduced from their nmr spectra, details of which are given in the Experimental Section. No coupling constants larger than 6.5 cps were found among the cyclobutane protons of IV. Since *cis* couplings for vicinal cyclobutane protons are frequently about 11 cps,[3] it appears unlikely that the cyclobutane protons have an all-*cis* configuration. In addition, the anomolously high chemical shift, *ca.* τ 6.7, for the bridgehead proton adjacent to oxygen (H_1) suggests shielding from the phenyl substituent *cis* to this proton. This is the expected product from the least sterically hindered transition state. We therefore assign the *cis-exo*-diphenyl structure to this compound.

The coupling constants (cycles per second) for the cyclobutane protons of V were found to be the following (approximate values): $J_{1,6} = 11$, $J_{1,8} = 10$, $J_{7,8} = 5$, $J_{6,7} = 3.5$. Spin-tickling experiments demonstrated couplings between all-vicinal protons assigned to the cyclobutane ring. The 7-*exo*-, 8 *endo*-diphenyl structure rests on the assumption that the couplings 10 and 11 cps reflect the *cis* vicinal configuration and the small couplings the *trans* configuration.

Solutions of *cis*- and *trans*-stilbene (0.1 *M*) in dihydropyran exposed to the atmosphere as well as under helium were irradiated in quartz vessels at 2537 Å. In the presence of oxygen the rates of stilbene isomerization were retarded but no corresponding changes in the rates of formation of IV and V were observed. The ratio of IV to V (1.87:1) remained constant throughout all reactions and was independent of the *cis*-stilbene:*trans*-stilbene ratio. Photolysis of a solution of *trans*-stilbene (0.01 *M*) in dihydropyran containing triphenylene (0.05 *M*) at 3500 Å provided evidence for sensitized isomerization of stilbene but no sensitized formation of IV and V.

These results preclude involvement of stilbene triplets in the formation of IV and V. The invariance of product ratio with respect to *cis*-stilbene:*trans*-stilbene ratio also precludes direct reaction of the first excited singlet states of stilbene if one assumes that such reactions are likely to be concerted.

We therefore conclude that formation of IV and V involves the vibrationally excited ground states reached through internal conversion from the first excited singlet states of stilbene. We cannot determine from our data whether these cyclization reactions occur in one or two steps.

Experimental Section

Melting points are uncorrected. Photolyses were conducted in a Rayonet photochemical reactor at 2537 or 3500 Å as indicated. The infrared spectra were obtained on a Beckman IR-4 spectrophotometer. High-resolution mass spectra were obtained on a CEC-21-110 instrument. Glpc was performed with a Barber Coleman Model 5000 gas chromatograph on 6-ft columns packed with 10% Apiezon L on Chromosorb W or 10% SE30 on Chromosorb W. Nmr spectra were taken on a Varian DP-60-1L instrument. The nmr spectra were too complex for accurate analysis. Approximate parameters were used to compute theoretical spectra by means of FREQINT IV[4] until satisfactory agreement was obtained between plots of theoretical spectra using a Calcomp plotter, and the appropriate portions of experimental spectra. The molecules were treated as five spin systems, utilizing parameters for H_1, H_5, H_6, H_7, and H_8.

Reaction of *cis* or *trans*-Stilbene with 3,4-Dihydropyran.—In

(1) H. M. Rosenberg and P. Servé, *J. Org. Chem.*, **33**, 1653 (1968).

(2) See H. Schecter, W. J. Link, and G. V. D. Tiers, *J. Amer. Chem. Soc.*, **85**, 1601 (1963), and references therein.

(3) I. Flemming and D. H. Williams, *Tetrahedron*, **23**, 2747 (1967).

(4) A. A. Bothner-By and C. N-ar-Colin, *J. Amer. Chem. Soc.*, **83**, 231 (1961).

a quartz vessel a solution of stilbene, 7.5 g (0.03 mol), in 200 ml of 3,4-dihydropyran was irradiated at 2537 Å in a Rayonet photochemical reactor for 48 hr. After removal of the unreacted dihydropyran under reduced pressure, the crude reaction mixture was heated with petroleum ether and then cooled. A white crystalline product (2.45 g, 24% based on reacted stilbene) was isolated by filtration and characterized as a mixture of *cis,trans,-cis*-1,2,3,4-tetraphenylcyclobutane (II) and *trans,trans,trans*-1,2,3,4-tetraphenylcyclobutane (III): nmr ($CDCl_3$), τ 2.71, 2.91 (20 H, singlets, aromatic protons), 5.54, 6.33 (4 H, singlets, methine protons).[5] The filtrate was subjected to column chromatography on alumina (80–200 mesh). Elution with benzene–petroleum ether (bp 30–60°) (5:95) gave two products: 7,8-*cis-exo*-diphenyl-2-oxabicyclo[4.2.0]octane (IV) [3.65 g (43.3%); mp 48–50°; parent peak, 264.1495 ($C_{19}H_{20}O$); ir (thin film) 3040 (aromatic CH), 2900 (aliphatic CH), 1610, 1500 (aromatic C=C), 1053 (COC) and 740, 700 cm^{-1} (monosubstituted phenyl); nmr ($CDCl_3$) τ 2.75–2.83 (10 H, multiplet, aromatic protons), 5.75–5.87 (2 H, multiplet, H_7 and H_8), 6.13–6.38 (2 H, multiplet, H_2 and $H_{3'}$) 6.60–6.80 (1 H, multiplet, H_1), 7.10–7.35 (1 H, multiplet, H_6) and 8.36–8.70 (4 H, multiplet, H_4, $H_{4'}$, H_5 and $H_{5'}$), J_{1-6} = 4.5 cps, J_{1-8} = 6.5, J_{6-7} = 6.5, J_{7-8} = 6.5]; 7-*exo*,8-*endo*-diphenyl-2-oxabicyclo[4.2.0]octane (V) [1.92 g (23.6%); mp 36–38°; parent peak, 264.1525 ($C_{19}H_{20}O$); ir (thin film) 3030 (aromatic CH), 2890 (aliphatic CH), 1600, 1490 (aromatic C=C), 1110 (COC) and 750, 740, 700 cm^{-1} (monosubstituted phenyl); nmr ($CDCl_3$) τ 2.72–2.90 (10 H, aromatic protons), 5.7 (1 H, multiplet, H_7), 6.0 (1 H, multiplet, H_1), 6.6 (1 H, multiplet, H_8), 6.20–6.32 (2 H, multiplet, H_2, $H_{3'}$), 7.0 (1 H, multiplet, H_6) and 8.25–8.50 (4 H, multiplet, H_4, $H_{4'}$, H_5, $H_{5'}$), $J_{1,6}$ = 11 cps, $J_{1,8}$ = 10 cps, $J_{7,8}$ = 5 cps, $J_{6,7}$ = 3.5 cps].

The Hydrogenation of 7,8-Diphenyl-2-oxabicyclo[4.2.0]oct-7-ene (I).[1]—In a Paar hydrogenation vessel 0.2 g of 5% Pt on charcoal was added to a solution of I, 1.0 g in 35 ml of absolute ethanol. The solution was then subjected to hydrogenation at 50 lb pressure for 24 hr. The reaction mixture was filtered and evaporated to a volume of 10 ml. The solution was then analyzed by glpc. The chromatogram showed the presence of two peaks with areas in the ratio of 1:4. The retention time of the smaller peak was identical with that of I and the larger peak corresponded to IV. The solvent was removed under vacuum and the products were separated by column chromatography on alumina. The ir spectrum of the reduction product was identical with that of IV.

Isomerization of 7,8-*cis-exo*-Diphenyl-2-oxabicyclo[4.2.0]-octane (IV).—A mixture of 7,8-*cis-exo*-diphenyl-2-oxabicyclo-[4.2.0]octane 0.1 and 0.2 g of potassium *t*-butoxide in 25 ml of ethanol was refluxed for 12 hr. The solvent was evaporated under vacuum and the residue was taken up in ether which was than washed with water and dried over anhydrous $MgSO_4$. The ether solution was analyzed by glpc. The chromatogram showed two new peaks with approximately equal areas. The retention times of one of these components on two different columns was identical with those of V.

Registry No.—*cis*-Stilbene, 645-49-8; *trans*-stilbene, 103-30-0; 2,3-dihydropyran, 110-87-2; IV, 18521-18-1; V, 18521-19-2.

(5) Values reported in ref 2 are the following: τ 2.95 and 5.60 for II and 2.79 and 6.37 for III.

The Hydrogenolysis of Trithiocarbonates

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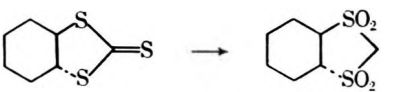
The hydrogenolysis of carbon–sulfur bonds has found extensive use in both structure determination and synthesis.[1] However, relatively little attention has been focused on the hydrogenolysis of trithiocarbonates. Gibson[2] reported an unsuccessful attempt to convert ethylene trithiocarbonate into 1,3-dithiolane, while McSweeney and Wiggins[3] reported the reductive desulfurization of the trithiocarbonate derivatives of carbohydrates with Raney nickel to the corresponding dideoxy compound. In 1960, Iqbab and Owen[4] found cyclic trithiocarbonates, upon treatment with lithium aluminum hydride, undergo smooth reductive fission to vicinal dithiols. More recently, Owen and coworkers[5,6] described the oxidation of *trans*-1,2-cyclohexane trithiocarbonate (I) with excess per acid in



I II

which the thiocarbonyl is converted into a methylene group affording the corresponding methylenedisulfonyl compound II. We now wish to report the results of our studies in which the direct catalytic hydrogenolysis of trithiocarbonates yield the corresponding 1,3 disulfides (see Table I).

TABLE I
CATALYTIC HYDROGENOLYSIS OF TRITHIOCARBONATES

Trithiocarbonate	Reaction conditions: Time, hr	Reaction conditions: Temp, °C	Product: 1,3-Disulfide	Product: Yield, %	Product: Bp, °C (mm)	Product: n_D
I	12	150	V	50	53–55 (0.01)	1.5706 (31°)
III	16	150	IV	88	75 (25)	1.5980 (23°)
VI	12	160	VII	12	70–72 (20)	1.5331 (21°)

Contrary to Gibson's observation[2] we have found hydrogenolysis (2000 psi) of ethylene trithiocarbonate (III) in benzene containing a catalytic amount of mol-

III IV

ybdenum trisulfide at 150° afforded 1,3-dithiolane (IV) as a colorless liquid in 88% yield. The infrared (1415 cm^{-1}) and pmr spectrum [δ 3.83 (singlet, 2 H, $-SCH_2S-$), 3.13 (singlet, 4 H, $-CH_2S-$)] are in complete agreement with IV; both spectra were identical with the spectra of an authentic sample[2] of IV. The reaction is clean with the only other product observed (*via* glpc) being ethylene dimercaptan in ~2% yield. Since current synthetic routes[7] to 1,3-dithiolane suffer from either low yield and/or polymer formation this method offers a

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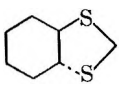
(2) D. T. Gibson, *J. Chem. Soc.*, 12 (1930).
(3) G. P. McSweeney and L. F. Wiggins, *Nature*, **168**, 874 (1951).
(4) S. M. Iqbab and L. N. Owen, *J. Chem. Soc.*, 1030 (1960).
(5) A. K. M. Anisuzzaman and L. N. Owen, *Chem. Commun.*, 16 (1966).
(6) T. J. Adley, A. K. M. Anisuzzaman, and L. N. Owen, *J. Chem. Soc.*, 807 (1967).
(7) E. E. Reid, "Organic Chemistry of Bivalent Sulfur," Vol. III, Chemical Publishing Co., Inc., New York, N. Y., 1958.

direct, high yield synthesis of IV from readily available starting material.

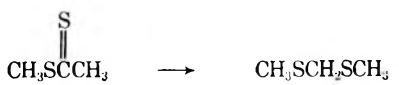
To determine whether this hydrogenolysis reaction was general for a variety of trithiocarbonates, we prepared *trans*-1,2-cyclohexane trithiocarbonate (I) using the method of Culvenor, Davies, and Pausacker.[8] Hydrogenation of I under similar conditions (MoS_3, 160°, 1900 psi) afforded *trans*-methylenedithiocyclohexane (V)[5] in 50% yield. The infrared (1439 cm^{-1}) pmr



V

[δ (CCl_4) 3.78 (singlet, 2 H, $-SCH_2S-$), 2.86 (multiplet, 2 H, >CHS), 1.16–2.36), multiplet (8 H, $-CH_2-$)], and mass spectrum [*m/e* 160 (M^+)] are consistent with our structural assignment.

In addition, we have found noncyclic trithiocarbonates can also be converted into the corresponding 1,3-disulfides. Thus dimethyl trithiocarbonate (VI), pre-



VI VII

pared from methyl chloride and sodium trithiocarbonate, was reduced using cobalt sulfide and molybdenum disulfide as catalyst at 2500 psi and 150°. In addition to recovered starting material, 2,4-dithiapentane (VII)[9] [infrared spectrum 1435, 1421 cm^{-1}; δ (neat) 3.65 (singlet, 2 H, $-SCH_2S-$), 2.13 (singlet, 6 H, $-SCH_3$)] was isolated in ~10–15% yield.

Experimental Section

All boiling points are uncorrected. Infrared spectra were recorded with a Perkin-Elmer Infrared or Model 21 spectrophotometer. Pmr spectra were determined at 27° (probe temperature) with a Varian Associates Model A-60A spectrometer using tetramethylsilane (TMS) as an internal standard. For each compound, chemical shifts cited are the centers of the multiplet. Numbers in parentheses refer to the multiplicity of the observed resonance.

Reagents.—Ethylene trithiocarbonate, molybdenum di- and trisulfide, cobalt sulfide and hydrogen (CP grade) were obtained from commercial sources and used without further purification. *trans*-1,2-Cyclohexane trithiocarbonate[8] and dimethyl trithiocarbonate[10] were prepared by known literature methods.

General Procedure.—The experimental conditions for the hydrogenations are recorded in Table II. A typical laboratory procedure for the preparation of 1,3-dithiolane follows.

TABLE II

Compd	Amt, mol	Catalyst (g)	Benzene, ml	H_2, psi
I	0.37	MoS_3 (5)	200	2000
III	0.11	MoS_3 (3)	50	1900
VI	0.36	MoS_2 (5) CoS (5)	100	2500

1,3-Dithiolane.—Ethylene trithiocarbonate (50 g, 0.37 mol) dissolved in 200 ml of benzene and 5.0 g of molybdenum trisulfide were placed in a 300-ml stainless steel autoclave. The autoclave was pressured to 2000 psi with hydrogen and heated to 150° for 12 hr while maintaining a constant hydrogen pressure of 2000 psi. After cooling to 25°, the autoclave was vented through a 20% sodium hydroxide solution; filtration of the clear solution followed by removal of the solvent at 15 mm afforded 37.0 g of 1,3-dithiolane (93% purity). Distillation yielded a malodorous, colorless liquid: bp 75° (25 mm); $n^{23}D$ 1.5980 [lit.[2] bp 61° (11 mm), $n^{15}D$ 1.5975]; infrared 2960, 2919, 1415, 1270, 858, 728, 680 cm^{-1}; pmr (CS_2) δ 3.83 (SCH_2S, 1), 3.13 (CH_2S, 1).

Registry No.—I, 16166-42-0; III, 822-38-8; IV, 4829-04-3; V, 5673-01-8; VI, 2168-84-5; VII, 1618-26-4.

Acknowledgment.—The technical assistance of Mr. Richard Eletto is gratefully acknowledged.

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(9) H. Bohme and R. Marx, *Ber.*, **74**, 1667 (1941).

(10) E. Wertheim, *J. Amer. Chem. Soc.*, **48**, 826 (1926); **53**, 4037 (1931). This compound was kindly provided by Professor N. Remes.

Nitrogen Mustard Reactions by Nuclear Magnetic Resonance Spectroscopy[1]

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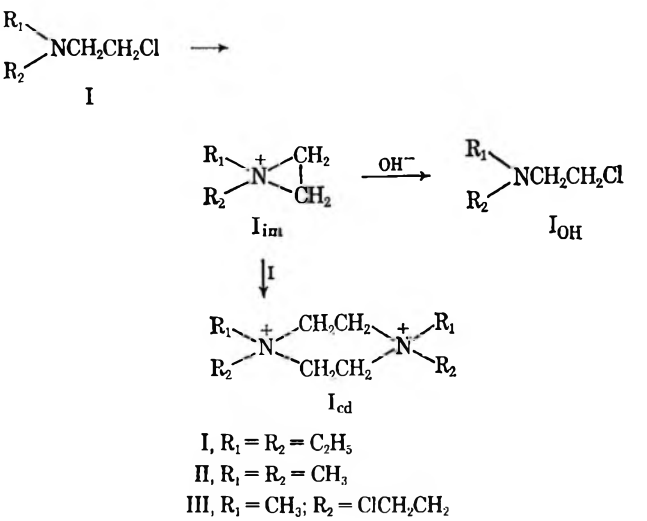
Classical chemical studies have shown that the reactions of many 2-chloroethylamines in aqueous solvent systems proceed through the formation of reactive ethyleneimonium ion intermediates.[3,4]



I, $R_1 = R_2 = C_2H_5$
II, $R_1 = R_2 = CH_3$
III, $R_1 = CH_3$; $R_2 = ClCH_2CH_2$

Levins and Papanastassiou[5] have recently shown that, for a number of primary and secondary 2-haloethylamines and for one tertiary amine, methylbis(2-chloroethyl)amine (HN-2), nmr studies in ^2H_2O can be useful for studying the rate of formation and

(1) Supported in part by U. S. Public Health Service Grant No. Ca-08485.

(2) From the Ph.D. Dissertation of J. R. Sowa, University of Pennsylvania, 1964.

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(4) P. D. Bartlett, S. D. Ross, and C. G. Swain, *J. Amer. Chem. Soc.*, **71**, 1415 (1949).

(5) P. L. Levins and Z. B. Papanastassiou, *ibid.*, **87**, 826 (1965).

disappearance of aziridine and aziridinium intermediates. Before this publication we had also found[2] that nmr studies of solutions of 2-chloroethyl tertiary amines in ^2H_2O fully confirm the presence of the ethylenimonium intermediates and, in fact, serve as simple and useful means of measuring the rate of formation and disappearance of these important reactive intermediates.

In the case of the imonium ions I_{im} and II_{im}, the four hydrogens on the aziridinium ring are equivalent and appear as a singlet. For the case of III_{im}, two aziridinium hydrogens are *cis* to the N-methyl and the other two are *trans*, leading to a weak splitting of these hydrogens to a doublet (J = 2.4 cps). The chemical shifts for the aziridinium methylene hydrogens (δ 3.1–3.3) is upfield from methylenes in the cyclic dimer (4.2–4.4) or protonated bases (3.4–3.7). This is in accord with the normal upfield shift of methylene groups in three-membered rings.

The marked influence of steric hindrance at the nitrogen is indicated by the marked differences in the case of dimer formation from the several mustards. Thus, while II (Table I) cyclizes so readily that the concentration of II_{im} never exceeds 22% and III cyclizes well enough so that the maximum concentration of III_{im} reaches 57% (Table II), for I, conversion into I_{im} is rapid and quantitative, with no detectable formation of the piperazinium dimer (I_{cd}) which we synthesized by an alternate route. Evidently the only reaction which I_{im} in water undergoes is a very slow hydrolysis to the alcohol (I_{OH}).

The data in Tables I, III, and IV are in accord with the hypothesis that the rate of cyclization is related to the base strength, with I > II > III.

TABLE I

CONVERSION OF II (0.1 M), pH 9, 27°, IN D_2O BY NMR SPECTRA

Time, min	% II[a]	% II_{im}	% dimer	k_d[b]
0	79	12.5	8.5	
1	53	19	28	0.25
2	34	21	45	0.23
5	18	22	60	0.20
7	12	22	66	0.22
10	6.7	20	73	
21	5.8	13	81	

[a] $k_1 = 3.25 \times 10^{-3}$ sec^{-1}, based on % II remaining. [b] Rate of dimer formation, k_d[II][II_{im}], in l. mol^{-1} sec^{-1}, was estimated graphically from the slope of a plot of [dimer] *vs.* time.

TABLE II

CONVERSION OF III (1 M), pH 10, 30°, IN WATER AND ALSO IN SODIUM CARBONATE BY NMR SPECTRA

Time, min	% III	% III_{im}	% dimer	k_d[a] × 10[b]
5	72	27		
6	55	36	8.4	8.5
8	49	41	9.6	8.3
10	41	47	11.7	8.6
15	31	52	17	10.3
20	22	57	20	12.8
25	15	57	28	
30	9.4	52	38	
45	3.4	48	47	
60		44	56	
24 hr			100	

[a] Rate of dimer formation = k_d[III][III_{im}], in l. mol^{-1} sec^{-1}, was estimated graphically. The values increase at high conversion, probably owing to more rapid reaction of III_{im} with amino alcohol formed by hydrolysis.

TABLE III

CYCLIZATION OF I (0.09 M), pH 10.5, 0°, IN SODIUM CARBONATE (0.2 M)

Time, min	% I_{im}
15	50[a]
30	84[a]
45	~100
690 (at 32°)[b]	~100

[a] $k \sim 4 \times 10^{-4}$ sec^{-1}. [b] pH 5.

TABLE IV

REACTION OF I_{im} (0.1 M), pH 9, 21°, WITH SODIUM THIOSULFATE (0.1 M)

Time, min	% I_{im}[a]
3	57
6	40
8	31
10	27
15	13.5
19	9.6
22	7.6
35	3.5

[a] k_2 = 0.041 l. mol^{-1} sec^{-1}.

Experimental Section

Cyclization of **diethyl-2-chloroethylamine** (I) to the imonium ion, I_{im}, was readily followed in a Varian Model 4300, HR-60 nmr spectrophotometer using 5-mm-o.d. precision tubes. In ^2H_2O at pH 5, 0.07 M I was protonated and stable, the ion showing a triplet (6 H) at δ' −3.44 (with respect to H_2O in the ^2H_2O) (J = 7 cps), a quadruplet (4 H) at −1.42 (J = 7 cps), a triplet (2 H) at −1.16 (J = 5.6 cps), and a triplet (CH_2Cl) at −0.75 (J = 5.6 cps). When the proton was removed from the nitrogen by adjusting the pH to 10.5, these four absorptions shifted to δ' −3.63, −2.00, −1.80, and −1.10, respectively. Even at 0°, the spectrum at pH 10.5 changed within a few minutes (see Table III), developing absorption characteristics of I_{im} at δ' −3.38 [triplet, J = 6.0 (6 H)], −1.50 [quadruplet, J = 6.0 (4 H)], and −1.69 [singlet (4 H)]. This conversion was essentially complete in 30 min and was unchanged after 20 hr at room temperature at pH 5.0; at pH 10.5, the half-life for the disappearance of I_{im} was 6 hr at 0° and 1.5 hr at 33°. On heating to 100° at pH 5.0, the spectrum of I_{im} changed to a spectrum similar to protonated I, presumably $Et_2N^+HCH_2$-CH_2OH, with a half-life of *ca.* 15 min. A ^2H_2O solution of I (0.1 M) brought to pH 12 by 2 M NaO^{2}H solution, cyclized within a few minutes at 27°, but I_{im} was 40% hydrolyzed to the amino alcohol within 40 min: δ' −3.78 [triplet, J = 7 cps (6 H)], −2.18 [quadruplet, J = 7 cps (4 H)], −1.44 [triplet, J = 7 cps (2 H)], and −1.03 [triplet, J = 7 cps (2 H)].

The nmr spectra of the hydrochloride at pH 5 and pH 7 and of I_{im} at pH 7 and pH 8 in ^2H_2O were checked against sodium trimethylsilylpropanesulfonate; the shifts reported here as δ' should be corrected by adding 4.68 ppm to give values in δ with respect to the trimethylsilyl group of this reference.

Reaction of I_{im} with thiosulfate ion could also be followed by nmr (see Table IV), the Bunte salt of I showing absorption at δ' −3.64 [triplet, J = 7.2 cps (6 H)], −1.93 [quadruplet, J = 7.2 cps (4 H)], and −1.54 [singlet (4 H)].

The **cyclic dimer of I, N,N,N′,N′-tetraethylpiperazinium diiodide** was prepared from N,N′-diethylpiperazine in excess ethyl iodide and recrystallized from methanol: mp <320°.

Anal. Calcd for $C_{12}H_{28}N_2I_2$: C, 31.73; H, 6.21; N, 6.17. Found: C, 31.68; H, 6.19; N, 6.12.

In ^2H_2O this ion showed absorption at δ' −2.47 [triplet, J = 5.0 cps (3 H)], −1.07 [quadruplet, J = 5.0 cps (2 H)],

and −0.96 (2 H). None of this product was observed in any of the reaction conditions above.

Dimethyl-2-chloroethylamine hydrochloride (II HCl) in ^2H_2O (0.1 *M*, pH 5) showed nmr absorption at δ' −1.71 (6 H), −1.10 [triplet, J = 6.0 cps (2 H)], and −0.66 [triplet, J = 6.0 cps (2 H)]. On adjustment of the pH to 9 with sodium bicarbonate, these shifted to δ' −2.34, −1.85, and −0.91, respectively. The singlet for the aziridinium methylenes in II_{im}, δ' −1.51, developed rapidly but was quickly converted to the cyclic dimer, N,N,N′,N′-tetramethylpiperazinium ion, δ' −1.20 (3 H) and −0.64 (2 H). Data on rate of conversion are summarized in Table I.

For the Bunte salt from II, prepared from 0.2 *M* II and 2 *M* sodium thiosulfate in ^2H_2O by heating to 75° for 2.5 hr, nmr absorption was observed as sharp singlets at δ' −1.78 (6 H) and δ' −1.17 (4 H).

For methylbis(2-chloroethyl)amine (III) about 1 *M* in water and also 1 *M* in sodium bicarbonate, nmr spectra showed absorption at δ' −2.67 (3 H), −2.18 [triplet, J = 8.4 cps (4 H)], and −1.25 [triplet, J = 8.4 cps (4 H), CH_2Cl], rapidly developing absorption for III_{im} at δ' −1.74 (3 H) and −1.60 [doublet, J = 2.4 cps (4 H)] and for the cyclic dimer, N,N′-dimethyl-N,N′-bis(2-chloroethyl)piperazinium dichloride (III_{cd}), at δ' −1.30 (singlet, 6 H) and −0.52 (singlet, 8 H). These spectra were useful for following the course of reaction, as summarized in Table II. Our values for nmr chemicals shifts and rates of reaction are not in full agreement with those of Levins and Papanastassiou,[5] perhaps owing to some differences in pH. Our reaction mixtures were buffered by 1 *M* bicarbonate, theirs were "neutralized by a predetermined amount of sodium hydroxide."

Registry No.—I, 100-35-6; cyclic dimer of I, 18386-47-5; II, 107-99-3; III, 51-75-2.

Branched-Chain Sugar Nucleosides. Synthesis of a Purine Nucleoside of 4-*O*-Acetyl-L-arcanose

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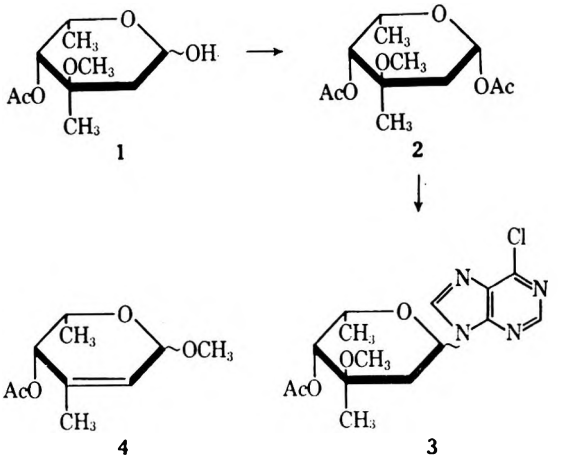
Arcanose is a dideoxy branched-chain sugar which occurs naturally as its 4-*O*-acetyl derivative in lankamycin,[1] a medium-spectrum macrolide antibiotic produced by *Streptomyces violaceoniger*.[2] By a combination of nmr and degradative studies, the 2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-L-*xylo*-hexose structure **1** was proposed for arcanose (Scheme I).[3] This assignment has been corroborated recently by us[4] by the synthesis of the D-enantiomer. We report now the utilization of L-arcanose in the preparation of 6-chloro-9-(4′-*O*-acetyl-2′,6′-dideoxy-3′-*C*-methyl-3′-*O*-methyl-β-L-*xylo*-hexopyranosyl)purine (**3**), the first synthetic nucleoside containing a naturally occurring branched-chain sugar.

SCHEME I



Attempts to obtain a glycosyl chloride derivative of **1** by treatment of its methyl glycoside with methylene chloride saturated with hydrogen chloride were unsuccessful. Although thin layer chromatography (tlc) showed that predominantly one compound had been formed, the nuclear magnetic resonance (nmr) spectrum of the crude product indicated the loss of a methoxyl group and the H-2ax hydrogen, and a downfield shift from τ 8.9 to 8.5 of the signal attributable to the C-3 tertiary methyl group. These data are consistent with the loss of methanol between C-2 and C-3 to give the unsaturated derivative **4**.

Treatment of 4-*O*-acetyl-L-arcanose[4] with acetic anhydride and pyridine gave a syrupy diacetate (**2**), which was assigned the β-L configuration by nmr spectroscopy. Condensation of 1,4-di-*O*-acetyl-2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-β-L-*xylo*-hexopyranose (**2**) with 6-chloropurine was achieved by fusing an intimate mixture of the two compounds in the presence of a trace of *p*-toluenesulfonic acid at 100° for 5 min. Fractionation of the complex mixture of products by preparative tlc on silica gel afforded the pure branched-chain sugar nucleoside **3**. The anomeric configuration has not been established. The ultraviolet absorption, uv max (EtOH) 264 mμ (ε 11,000), is in agreement with a 9-substituted purine.[5]

Experimental Section[6]

1,4-Di-*O*-acetyl-2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-β-L-*xylo*-hexopyranose (2).—A solution of **1** (105 mg) in pyridine (3 ml) and acetic anhydride (2 ml) was kept at ambient temperature overnight. The reaction mixture was poured into water, and the product isolated in the usual manner. Fractionation of the crude product on silica gel (100 × 2 cm column) with 2:3 ethyl acetate–petroleum ether as eluent gave 100 mg (80%) of diacetate **2** as a colorless mobile oil: $[\alpha]_D$ +35° (*c* 1.1, EtOAc); ir (film) 5.75 μ (OAc); nmr ($CDCl_3$) τ 4.1 (one-

(1) (a) W. Keller-Schierlein and G. Roncari, *Helv. Chim. Acta*, **45**, 138 (1962); (b) *ibid.*, **47**, 78 (1964).

(2) E. Gaumann, R. Hütter, W. Keller-Schierlein, L. Neipp, V. Prelog, and H. Zähner, *ibid.*, **43**, 601 (1960).

(3) G. Roncari and W. Keller-Schierlein, *ibid.*, **49**, 705 (1966).

(4) G. B. Howarth, W. A. Szarek, and J. K. N. Jones, *Chem. Commun.*, 62 (1968); *Carbohyd. Res.*, **7**, 284 (1968).

(5) E. E. Leutzinger, W. A. Bowles, R. K. Robins, and L. B. Townsend, *J. Amer. Chem. Soc.*, **90**, 127 (1968).

(6) Optical rotations were measured with a Perkin-Elmer Model 141 polarimeter at 20 ± 2°. Infrared spectra were measured on a Beckman-IR5A spectrophotometer. Ultraviolet spectra were measured with a Unicam SP 800B spectrophotometer. Nmr spectra were determined with a Varian A-60 spectrometer; the freshly prepared compounds were examined in chloroform-*d* with tetramethylsilane as the internal standard. Thin layer chromatography was performed using silica gel G and 2:3 ethyl acetate–petroleum ether (bp 60–80°), with indication by sulfuric acid.

proton quartet, $J_{1ax,2ax}$ = 9 Hz, $J_{1ax,2eq}$ = 3 Hz, H-1), 5.26 (one-proton broad singlet, H-4), 5.78 (one-proton octet, $J_{5,6}$ = 6 Hz, $J_{5,4}$ = 1 Hz, H-5), 6.75 (three-proton singlet, C-3 OMe), 7.9, 7.95 (three-proton singlets, C-1 and C-4 OAc's), 8.9 (three-proton singlet, C-3 Me), 8.9 (three-proton doublet, J = 6 Hz, C-5 Me).

Anal. Calcd for $C_{12}H_{20}O_6$: C, 55.5; H, 7.7. Found: C, 55.8; H, 7.9.

6-Chloro-9-(4′-*O*-acetyl-2′,6′-dideoxy-3′-*C*-methyl-3′-*O*-methyl-β-L-*xylo*-hexopyranosyl)purine (3).—An intimate mixture of compound **2** (24 mg), 6-chloropurine (16 mg, 1.1 equiv), and a trace of *p*-toluenesulfonic acid was heated at 100° (oil bath temperature) for 5 min. The dark brown solid residue was extracted with two 10-ml portions of hot ethyl acetate and the extracts were concentrated to a viscous syrup after treatment with carbon. Tlc showed the presence of eight components, the major one having R_f 0.13. Preparative tlc afforded 3.8 mg (12%) of nucleoside **3** as a homogeneous glass: R_f 0.13 (tlc); $[\alpha]_D$ +10° (*c* 0.4, EtOAc), $[\alpha]_{365}$ +50° (*c* 0.4, EtOAc); uv max (EtOH) 208 mμ (ε 13,000), 264 (11,000); ir (film) 5.75 (OAc), 6.3, 6.4, 6.7 μ (purine ring); nmr ($CDCl_3$) τ 1.23, 1.62 (one-proton singlets, H-8 and H-2), 4.15 (one-proton quartet, $J_{1'ax,2'ax}$ = 8 Hz, $J_{1'ax,2'eq}$ = 4.5 Hz, H-1′), 5.05 (one-proton broad singlet, H-4′), 5.70 (one-proton multiplet, H-5′), 6.60 (three-proton singlet, C-3′ OMe), 7.76 (three-proton singlet, C-4′ OAc), 8.74 (three-proton singlet, C-3′ Me), 8.8 (three-proton doublet, J = 6 Hz, C-5′ Me).

Anal. Calcd for $C_{15}H_{19}O_4N_4Cl$: C, 51.0; H, 5.4; N, 15.8. Found: C, 51.3; H, 6.0; N, 15.4.

Registry No.—**2**, 7308-86-3; **3**, 18339-01-0.

Acknowledgments.—The authors thank the National Research Council of Canada for financial support of this research and D. G. Lance for nmr spectral measurements.

The Reactions of 3-Hydroxyflavanone with Carbonyl Reagents

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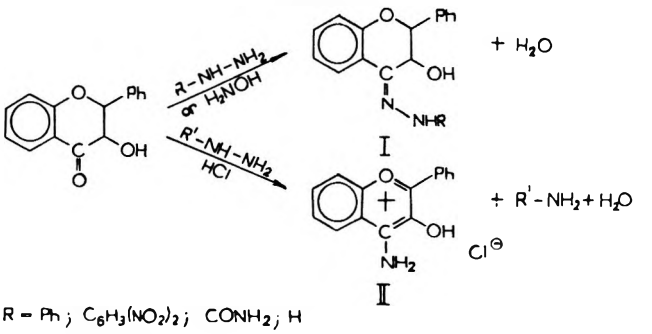
An extension of the study on the carbonyl reactions of flavanone[1] has shown that 3-hydroxyflavanone with *p*-tosylhydrazine gives, by an anomalous reaction, 3-hydroxy-4-aminoflavylium chloride.[2]

The present study is aimed at establishing the conditions leading to the formation of the true carbonyl derivatives I of 3-hydroxyflavanone, or of the flavylium salt II.

Examples from the literature[3] and our additional experiments have revealed that the normal carbonyl derivatives I can be prepared by reacting 3-hydroxyflavanone with hydrazine, a substituted hydrazine, or hydroxylamine.

The use of an acid hydrazide invariably results in the formation of the flavylium salt II (Scheme I).

SCHEME I[a]



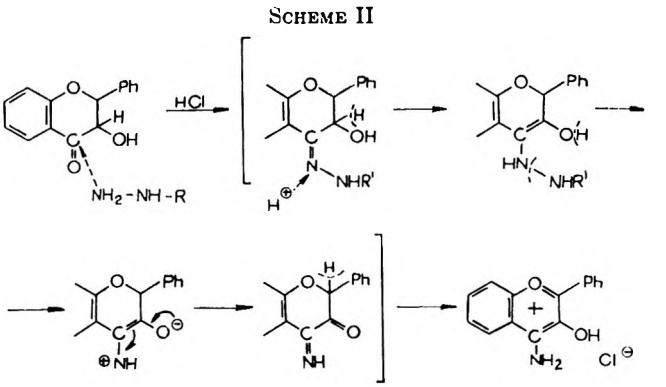
R = Ph; $C_6H_3(NO_2)_2$; $CONH_2$; H

R′ = $SO_2C_6H_4CH_3$; $SO_2C_6H_4Br$; $COC_6H_4NO_2$; COPh; $COCH_3$;

[a] In the case of hydroxylamine NHR stands for OH.

Presumably, I is the primary product of the reaction leading to II; it is the electron-withdrawing character of the substituent attached to the N atom of the carbonyl reagent and the pH of the reaction medium which decide whether I is isolable as such, or eliminates $R'NH_2$ to become converted into II. The yields of II are higher as the electrophilic character of R′ is increased. The role of I as an intermediate is confirmed by conversion of the isolated normal carbonyl derivatives (including the oxime) into the aminocyanidin salt by boiling them in alcoholic hydrochloric acid. For further evidence, 3-hydroxyflavanone tosylhydrazone (I, R = $SO_2C_5H_4CH_3$) was prepared by tosylation in alkaline medium. This compound is converted into II in hot alcoholic HCl, in quantitative yield. It is reasonable to suppose the reaction mechanism given in Scheme II.

SCHEME II



The necessity of the presence of an enolizable 3-OH group is shown by the experimental evidence that while 3-acetoxyflavanone N-monoacetylhydrazone gives mainly 3-hydroxyflavanone on treatment with alcoholic HCl, the 3-hydroxy derivative is converted into II in 63% yield.

A continuation of this work is in progress concerning the carbonyl reactions of C_5-substituted 3-hydroxyflavanones.

Experimental Section

All melting points were determined on a Kofler block and are uncorrected. The compounds were checked for purity by tlc;

(1) F. Kállay, G. Janzsó, and I. Koczor, *Tetrahedron*, **23**, 4317 (1967).
(2) G. Janzsó, F. Kállay, and I. Koczor, *ibid.*, **22**, 2909 (1966).
(3) R. Bognár, M. Rákosi, H. Fletcher, E. M. Philbin, and T. S. Wheeler, *ibid.*, **19**, 391 (1963).

their ir and nmr spectra were recorded as a means of identification or evidence of structure.

3-Hydroxyflavanone 2,4-Dinitrophenylhydrazone [I, R = $C_6H_3(NO_2)_2$].—A solution of 3-hydroxyflavanone (0.5 g, 2.08 mmol) in EtOH (40 ml) was mixed with 2,4-dinitrophenylhydrazine (0.42 g, 2.12 mmol) in EtOH (60 ml). HCl (1 ml) was added, and the red solution was refluxed for 3 hr. The red needles were filtered off after cooling (786 mg, 90.1%), mp 257° (unchanged on recrystallization from dioxane). *Anal.* Calcd for $C_{21}H_{16}O_6N_4$ (420.39): C, 60.0; H, 3.83; O, 22.81; N, 13.34. Found: C, 59.97; H, 4.08; O, 22.57; N, 13.24.

3-Hydroxyflavanone Hydrazone (I, R = H).—A solution of 3-hydroxyflavanone (5.0 g, 0.0208 mol) in pyridine (100 ml) was mixed with a solution of hydrazine monohydrochloride (10 g, 0.146 mol) in 50% aqueous pyridine (100 ml). Standing for 20 hr at room temperature gave a deposit of small yellow crystals (by-product 3-hydroxyflavanone azine), which were removed by filtration, and the mother liquor was poured into ice–water (800 ml). The pale yellow precipitate (4.0 g, mp 138–140°) was dissolved in hot EtOH (80 ml), filtered, and mixed with hot water (85 ml). Cooling gave glistening prisms (3.49 g, 65.9%); mp 147°. *Anal.* Calcd for $C_{15}H_{14}O_2N_2$ (254.29): C, 70.99; H, 5.54; O, 12.56; N, 11.02. Found: C, 70.82; H, 5.68; O, 12.39; N, 11.21.

3-Hydroxyflavanone Azine.—The azine, obtained above as a by-product, could be prepared in good yields by boiling a solution of 3-hydroxyflavanone and hydrazine monohydrochloride in 50% aqueous pyridine for 3 hr, mp 199–200°. *Anal.* Calcd for $C_{30}H_{24}O_4N_2$ (476.53): C, 75.71; H, 5.07; O, 13.45; N, 5.89. Found: C, 75.67; H, 5.11; O, 13.60; N, 5.92.

3-Hydroxyflavanone Benzaldazine.—A solution of the hydrazone in EtOH gave with benzaldehyde pale yellow needles (71.6%), mp 177°. *Anal.* Calcd for $C_{22}H_{18}O_2N_2$ (342.38): C, 77.20; H, 5.28; O, 9.34; N, 8.19. Found: C, 77.17; H, 5.59; O, 9.25; N, 8.12.

3-Acetoxyflavanone Monoacetylhydrazone.—I (R = H) was acetylated with Ac_2O–Py at room temperature, and the product recrystallized from EtOH, yield 70.2%, mp 205–206°. *Anal.* Calcd for $C_{19}H_{18}O_4N_2$ (338.36): C, 67.40; H, 5.36; O, 18.90; N, 8.28. CH_3CO, 25.43. Found: C, 67.86; H, 5.57; O, 18.85; N, 8.54; CH_3CO, 25.43.

Ir analysis showed bands at 1683 (C=O of N-acetyl) and 1720 cm^{-1} (C=O of O-acetyl).

3-Hydroxyflavanone monoacetylhydrazone (I, R = $COCH_3$) was prepared by selective hydrolysis of the former compound. 3-Acetoxyflavanone monoacetylhydrazone (0.5 g) was dissolved in hot 90% aqueous MeOH (100 ml); $KHCO_3$ (0.5 g) was added, and the mixture refluxed for 3 hr. About half of the solvent was evaporated and the residue mixed with hot water (150 ml). Standing at room temperature for 24 hr gave pale yellow plates (320 mg, 73%) which were recrystallized from 96% EtOH to give 208 mg, mp 212°. *Anal.* Calcd for $C_{17}H_{16}O_3N_2$ (296.33): C, 68.99; H, 5.44; O, 16.20; N, 9.45; CH_3CO, 14.53. Found: C, 69.04; H, 5.54; O, 16.69; N, 9.53; CH_3CO, 13.51.

Ir analysis showed a band at 1645 cm^{-1} (C=O of N-acetyl).

3-Hydroxyflavanone Tosylhydrazone (I, R = $SO_2C_6H_4CH_3$).—A suspension of 3-hydroxyflavanone hydrazone (2.0 g, 7.85 mmol) in benzene (360 ml) was mixed with pyridine (1.2 ml, 15.6 mmol) and *p*-toluenesulfonic anhydride (5.1 g, 15.6 mmol; mp 124°). A red solution was obtained which was allowed to stand 1 hr at room temperature. The 3-hydroxyflavanone azine which deposited was removed by filtration, and the benzene solution was extracted with four 100-ml portions of water. The benzene layer was evaporated under reduced pressure to dryness, and the residue rubbed with petroleum ether (bp 30–60°) to give a powder (3.21 g), which was repeatedly recrystallized from EtOH to obtain a white microcrystalline product (602 mg), mp 184° dec. *Anal.* Calcd for $C_{22}H_{20}O_4N_2S$ (408.48): C, 64.75; H, 4.92; O, 15.69; N, 6.66; S, 7.84. Found: C, 64.52; H, 5.21; O, 15.30; N, 6.86; S, 7.99.

3-Hydroxy-4-aminoflavylium Chloride (II). **A. From 3-Hydroxyflavanone Oxime.**—The oxime (200 mg) was refluxed for 5 hr in EtOH (25 ml) containing HCl (0.4 ml). Cooling gave a pale yellow crystalline product (86 mg, 40.3%), mp 258°, which was identical with II prepared by any of the methods described below.

B. From 3-Hydroxyflavanone Monoacetylhydrazone.—I (R = $COCH_3$, 100 mg) in EtOH (25 ml) was refluxed for 5 hr in the presence of HCl (0.5 ml). The solution was diluted with *n*-hexane and chilled to obtain II (57.2 mg, 62.3%), mp 258–260°.

C. From 3-Hydroxyflavanone Tosylhydrazone.—I (R = $SO_2C_6H_4CH_3$, 400 mg) was treated as described in B to obtain II (248 mg, 92%), mp 258–260°.

D. From 3-Hydroxyflavanone and an Acid Hydrazide.—The procedure described[2] for *p*-tosylhydrazine could be applied to the preparation of II using *p*-bromobenzenesulfonylhydrazine, *p*-nitrobenzoylhydrazine, benzoylhydrazine, and monoacetylhydrazine. The yields were between 50 and 70%.

Registry No.—I [R = $C_6H_3(NO_2)_2$], 18500-74-8; I (R = H), 18500-75-9; I (R = $COCH_3$), 18500-76-0; I (R = $SO_2C_6H_4CH_3$), 18500-77-1; II, 4281-27-0; 3-hydroxyflavanone, 1621-55-2; 3-hydroxyflavanone azine, 18500-72-6; 3-hydroxyflavanone benzaldazine, 18500-73-7; 3-acetoxyflavanone monoacetylhydrazone, 18540-93-7.

Acknowledgments.—The authors wish to thank Professor R. Bognár for his interest in this work, Mrs. Gy. Janzsó for the microanalyses, Dr. Miss I. Egyed for the ir analyses, and Mrs. M. Vuich for assistance in the preparative work.

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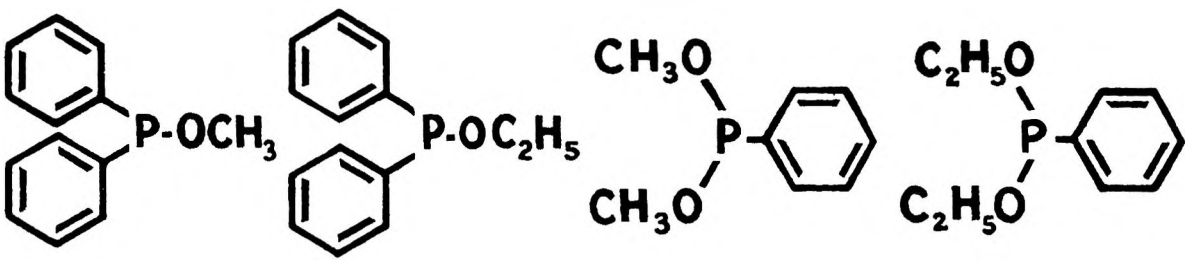
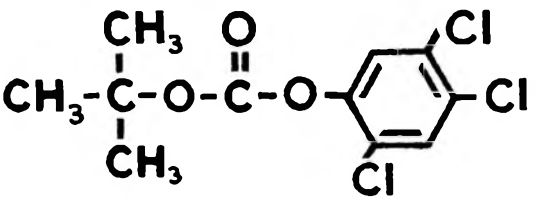


No. 14,949-7	No. 14,948-9	No. 14,947-0	No. 14,946-2
$3.75/g $14./5g	$4./g $15.50/5g	$3.50/g $13./5g	$3.75/g $14./5g
$100./100g	*$100./100g*	*$100./100g*	*$100./100g*

These methyl and ethyl esters of phenylphosphonous and phenylphosphinous acids exhibit excellent donor-acceptor properties when coordinated to transition metals,[1] and lend stability to the low oxidation states of these metals. While triaryl and trialkyl phosphines have been widely used in coordination chemistry,[2,3] very little has been done with mono and dialkoxy phosphines because they were, up to now, unavailable. We believe that many new and challenging compounds can be made by coordinating metals with these phosphines.

(1) B. Chastain, E. Rick, R. Pruett, and H. Gray, J. Am. Chem. Soc., 90, 3994 (1968).
(2) F. Cotton and G. Wilkinson, "Advanced Inorganic Chemistry," 2nd ed., Interscience, 1966.
(3) W. Griffith, "The Chemistry of the Rarer Platinum Metals," Interscience, 1967.

NEW PEPTIDE REAGENT



*

Tert.-butyl 2,4,5-trichlorophenyl carbonate has recently been shown to be a most valuable peptide reagent.[1]

(1) W. Broadbent, J. S. Morley and B. E. Stone, *J. Chem. Soc.*, 2632 (1967).

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