VOLUME 39 MAY 3, 1974 NUMBER 9 JOCEAH

THE JOURNAL OF Organic Chemistry

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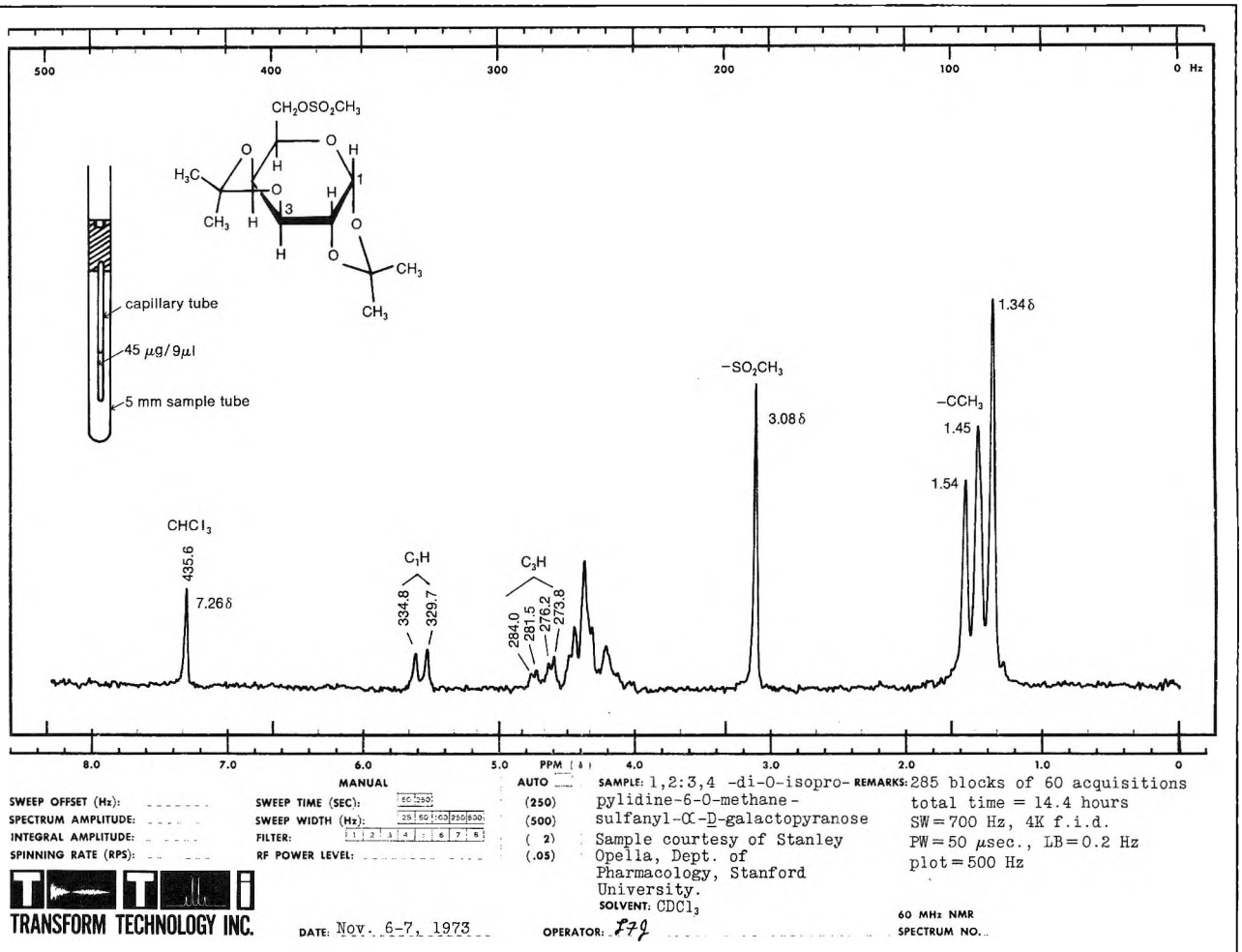

MANUAL AUTO

SWEEP OFFSET (Hz): SWEEP TIME (SEC): (250)
SPECTRUM AMPLITUDE: SWEEP WIDTH (Hz): (500)
INTEGRAL AMPLITUDE: FILTER: (2)
SPINNING RATE (RPS): RF POWER LEVEL: (.05)

SAMPLE: 1,2:3,4 -di-O-isopropylidine-6-O-methane-sulfanyl-α-D-galactopyranose
Sample courtesy of Stanley Opella, Dept. of Pharmacology, Stanford University.
SOLVENT: $CDCl_3$

REMARKS: 285 blocks of 60 acquisitions
total time = 14.4 hours
SW = 700 Hz, 4K f.i.d.
PW = 50 μsec., LB = 0.2 Hz
plot = 500 Hz

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DATE: Nov. 6-7, 1973 OPERATOR: FJ

60 MHz NMR
SPECTRUM NO.

Analysis of very small samples is best done using a microcell approach. Here, 45 micrograms of a compound with molecular weight 338 was contained in a capillary tube of 1.0 mm I.D. The peak at 3.08δ, although weak after one block of acquisitions, served adequately for the peak register method, which effectively cancels long-term field drift. Signal frequencies and chemical shifts were copied from an oscilloscope display of peak positions using an assigned value of 435.6 Hz for the chloroform peak. The spectrum is very well defined, and demonstrates that overnight FT operation with a T-60A/TT-7 system is quite feasible and very useful for microsample analysis.

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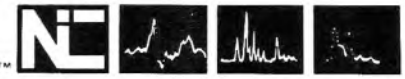

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AUTHOR INDEX

THE JOURNAL OF Organic Chemistry®

VOLUME 39, NUMBER 9

MAY 3, 1974

Reactions Involving Electron Transfer. IV. Reduction of Enones with Chromium(II) Compounds[1a]

Herbert O. House* and Edith Feng Kinloch[1b]

School of Chemistry, Georgia Institute of Technology, Atlanta, Georgia 30332

Received July 16, 1973

Solutions of the Cr(II) complex, $Cr(en)_2(OAc)_2$, in MeOH are capable of reducing simple α,β-unsaturated ketones to the corresponding saturated ketones. With 2-cyclohexenone derivatives **10** and **11** that contain a 3-alkyl substituent, preparatively useful yields of the reduced products may be obtained provided a proton donor (HOAc) and a good hydrogen atom donor (*n*-PrSH or *n*-BuSH) are also present in the reaction mixture. With enones **7**, **12**, and **13** that have only one β-alkyl substituent, the presence of the above additives still does not afford high yields of saturated ketones because of a competing addition of the mercaptan to the enone system. Various types of evidence are offered to support the proposal that these reductions proceed by successive reactions of the enone with 2 equiv of the Cr(II) complex to form the intermediates illustrated in Scheme III.

Solutions containing salts of the chromium(II) ion, either aquated or coordinated with various nitrogen ligands such as ammonia or ethylenediamine, have been used for the reduction of various organic compounds[2] including alkyl and aryl halides,[3b,4] certain α,β-unsaturated carbonyl compounds[3a,5] certain acetylenes,[6] and various unsaturated nitrogen compounds such as oxime acetates,[7a] azides,[7b] and nitro compounds.[7c] In connection with our earlier studies of reductions of α,β-unsaturated carbonyl compounds by processes involving successive electron transfers,[8] we wished to examine various Cr(II) derivatives as potential agents for effecting reductions of this type. Previous studies[5a,c,e,6a,b] had indicated that doubly activated multiple C–C bonds such as that present in compounds of the type RCOCH=CHCOR or RCOC≡CCOR could be reduced with solutions of $CrCl_2$ or $CrSO_4$ in water or aqueous dimethylformamide (DMF). With this reducing agent, $Cr(H_2O)_6^{2+}$, less easily reduced conjugated carbonyl compounds (*e.g.*, RCH=CHCOR) were either recovered unchanged or converted to dihydro dimers $RCOCH_2CH(R)CH(R)CH_2COR$.[5a] Studies with solutions $CrSO_4$ in aqueous NH_3, where the ion $Cr(NH_3)_4(H_2O)_2^{2+}$ was the probable reducing agent, indicated that a more powerful reducing agent was obtained when part of the H_2O ligands surrounding Cr(II) were replaced with NH_3 groups.[5b] This observation, coupled with later studies[3b,4c] demonstrating that the reducing power of Cr(II) toward alkyl and aryl halides was enhanced substantially by the presence of bidentate ligands such as the diamine **1** (en) or the amino alcohol **2**, suggested that complexes of Cr(II) with bidentate or polydentate ligands (*e.g.*, **1**–**6**, Scheme I) may be substantially more effective reducing agents for α,β-unsaturated carbonyl compounds. The present paper reports our investigation of this possibility.

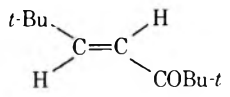
Our initial studies used $Cr(ClO_4)_2$, a reagent that could conveniently be prepared in aqueous solution by reaction of aqueous $HClO_4$ with excess chromium.[3b,4d] Solutions of this reagent in aqueous DMF were ineffective in reducing unsaturated ketones such as **7** and various cyclohexenone derivatives and unchanged enones were recovered.[9] The ability of these solutions to reduce the enone **7** to the ketone **8a** was substantially enhanced by the addition of 2–3 molar equiv of one of the bidentate ligands, **1**, **3**, and **5**; the diamine **1** was especially convenient for this purpose. Previous studies of complexes of Cr(II) salts with the diamine **1** have established that these complexes have the compositions (and probably the stereochemistry) indicated in structure **9**;[4c,10] the tris complex $Cr(en)_3^{2+}$ is normally unstable in solution and decomposes to the bis complex **9** even when excess diamine **1** is present.[10] Thus, the reducing agent employed in our studies can be represented as the bis en complex **9** in which the apical ligands X are relatively labile[11] oxygen ligands such as water, MeOH, DMF, or acetate. Although solutions of the complex **9**, prepared from $Cr(ClO_4)_2$, in aqueous DMF were employed successfully for the reduction of several enones **7**, **10**, and **11** (see Experimental Section), the experimental procedure was complicated by the fact that substantial amounts of the cosolvent, DMF, were often required with the aqueous Cr(II) solution in order to dissolve the enone and separation of the reaction products from large volumes of aqueous DMF was tedious. Consequently, we were prompted to examine use of the dimeric salt, $[Cr(OAc)_2 \cdot H_2O]_2$, which is relatively insoluble in water and can be isolated as a crystalline solid.[12] Although the acetate salt was insoluble in most of the common organic solvents (see Experimental Section), after treatment with 2–3 molar equiv of one of the bidentate ligands **1** or **2** (ligands **3** and **4** were not effective) or 1 molar equiv of the tetradentate ligand **6**, a solution of the corresponding complex was obtained in several solvents, including MeOH, EtOH, *i*-PrOH, *t*-BuOH, and DMF. Among these

Scheme I

$H_2NCH_2CH_2NH_2$ (1) $H_2NCH_2CH_2OH$ (2)

$Me_2NCH_2CH_2NMe_2$ (3) $Me_2NCH_2CH_2OH$ (4)

$Et_2NCH_2CH_2OH$ (5) $H_2NCH_2CH_2NHCH_2CH_2NHCH_2CH_2NH_2$ (6)



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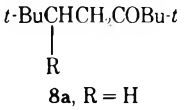
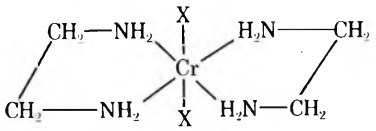
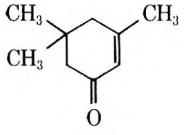


8a, R = H
b, R = D



9a, X = H_2O, MeOH, or DMF
b, X = AcO



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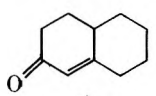

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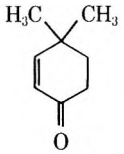

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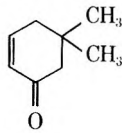

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solvent and ligand combinations, we found the most convenient reagent to be a MeOH solution of the bis diamine complex designated **9b** in this paper; solutions that contained concentrations of the complex **9b** greater than 1 *M* were readily obtained.

Solutions of the Cr(II) complex **9b** in MeOH exhibited a characteristic[4c] absorption maximum at 552 mμ (ε 32) which changed to give maxima at 384 (ε 51) and 520 mμ (ε 69) after air oxidation to form the Cr(III) species. Similar values [Cr(II), λ_{max} 520 mμ (ε 45), and Cr(III), λ_{max} 380 (ε 50) and 520 mμ (ε 54)] were observed for solutions of the complex **9b** in DMF. Addition of the unhindered enone **13** to these solutions of the Cr(II) complex **9b** resulted in the appearance of a new, more intense maximum at 378 mμ (ε ~400) characteristic[4c,5b,11] of a σ alkyl–Cr(III) complex. Similar, although less intense, maxima were observed when solutions of the complex **9b** were treated with the α,β-unsaturated ketones **7**, **10**, and **12**, which possess more steric hindrance to bond formation at the β carbon. This absorption, attributable to an intermediate σ alkyl–Cr(III) complex, persisted for several hours in MeOH solution, but was rapidly discharged when HOAc was added.

The enones **7** and **11** were treated with a solution of the complex $Cr(en)_2(ClO_4)_2$ in a mixture of DMF and D_2O, and the saturated ketone products **8**, **14**, and **15** (Scheme II) were subjected to base-catalyzed exchange to remove any deuterium present at the α carbon. In each case, the saturated ketones contained *ca.* 40% of the products **8b**, **14b**, and **14b** with a single deuterium atom at the β carbon. Since each of these reaction mixtures contained both D^+ and H^+ donors[13] and the kinetic isotope effect favoring the formation of a β-C–H rather than a β-C–D bond is estimated to be *ca.* 4,[2b] these results indicated that at least half (but perhaps not all) of the saturated ketones **8**, **14**, and **15** were formed under these conditions by reaction of an intermediate with a proton donor rather than a hydrogen atom donor.

Solutions of the Cr(II) complex **9b** were examined by polarography and cyclic voltammetry to determine the redox potential for the process $Cr(en)_2(ligand)_2^{2+} \rightleftarrows Cr(en)_2(ligand)_2^{3+} + e$.[14] The solutions of the Cr(II) complex **9b** [and the corresponding Cr(III) complexes obtained by air oxidation] in either MeOH or DMF exhibited behavior characteristic of reversible electron transfer. In DMF solution the half-wave potential was −1.77 V (*vs.* sce) and in MeOH solution the value was −1.09 V (*vs.* sce).[15] Table I lists the polarographic reduction potentials for the various ketones included in this study. In each case the reduction potential is *ca.* 0.5 V less negative in the protic solvent, MeOH, than in DMF. However, in both solvents the ketones reduced have reduction potentials (−1.5 to −1.7 V in MeOH, −2.1 to −2.2 V in DMF) 0.3 to 0.6 V more negative than the redox potential of the $Cr(en)_2^{2+}$–$Cr(en)_2^{3+}$ system (−1.1 V in MeOH, −1.8 V in DMF) and only the very difficultly reduced ketone **20** (−2.4 V in DMF, −1.9 V in MeOH) was recovered unchanged. We believe that this difference between the re-

Scheme II

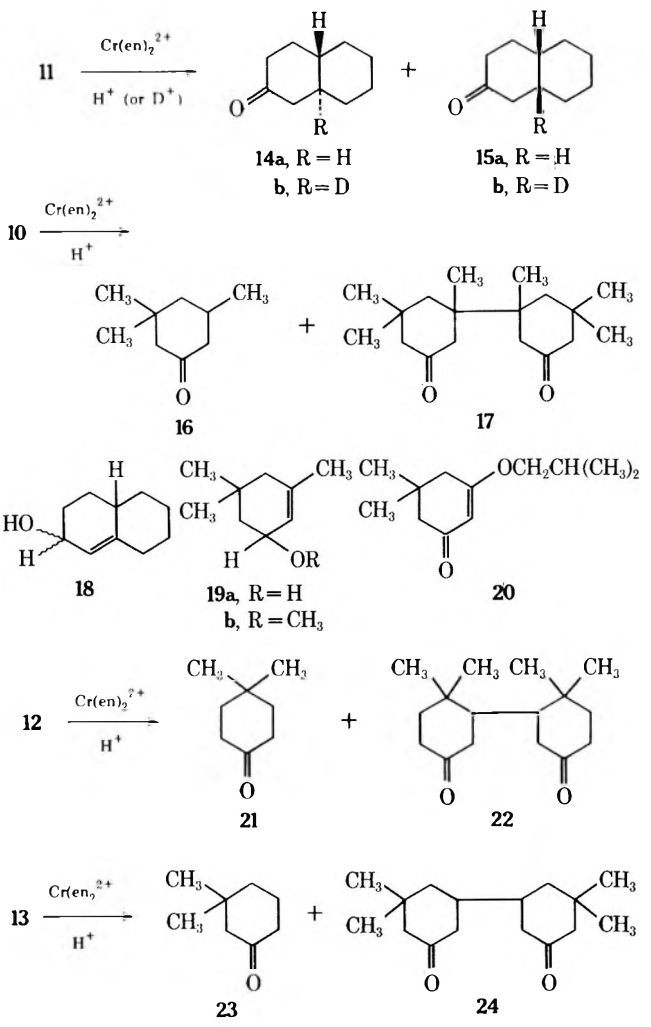
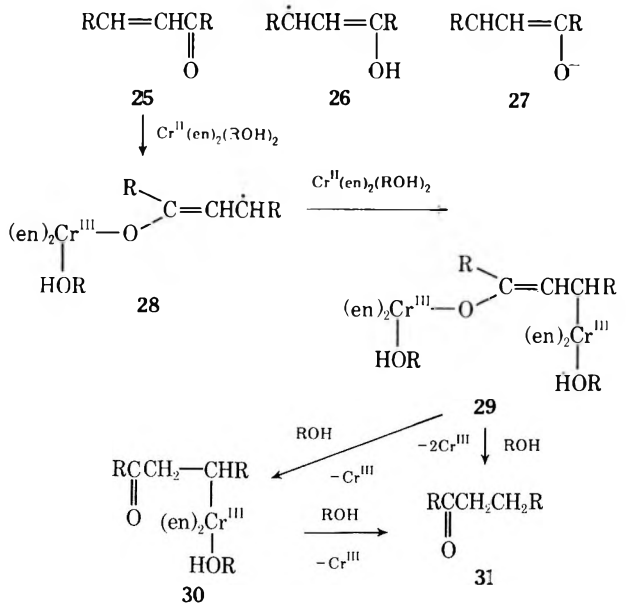


Table I
Polarographic Reduction Potentials of the Enones Studied

Ketone	Reduced with $Cr^{II}(en_2)$	$E_{1/2}$, V *vs.* sce	
		In DMF[a]	In MeOH[a]
7	Yes	−2.22	−1.76
10	Yes	−2.24[b]	−1.65
11	Yes	−2.15	−1.67
12	Yes	−2.1[c]	−1.57
13	Yes	−2.1[c]	−1.56
20	No	−2.43	−1.92

[a] n-$Bu_4N^+BF_4^-$ (0.5 *M*) was employed as the supporting electrolyte. [b] When 0.1 *M* H_2O was present, the $E_{1/2}$ value was −2.19 V. [c] Estimated value; see ref 8c.

Scheme III

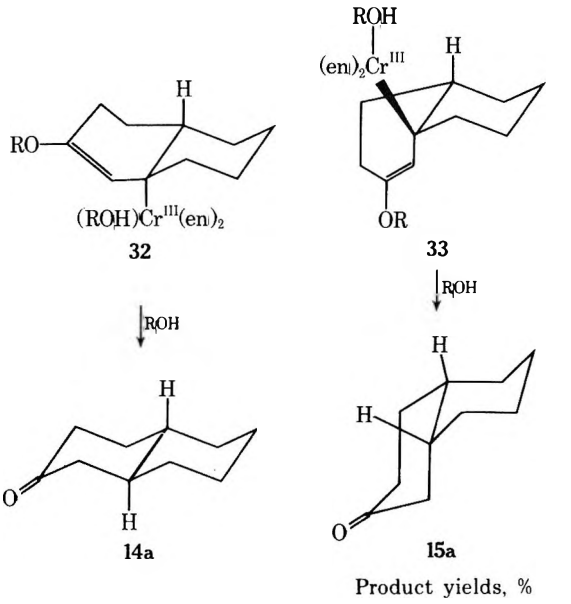


duction potentials (*ca.* 0.5 V or 12 kcal/mol) of the Cr(III) species and the enones (*e.g.*, **25**, Scheme III) is sufficient to exclude the reaction proceding by transfer of only an electron from the Cr(II) species (an outer-sphere electron transfer) to the enone to form directly either the anion radical **27** (as from electrochemical reduction in DMF) or the protonated anion radical **26** (as from electrochemical reduction in MeOH).

Instead, it seems most likely that the initial electron transfer involves the enone **25** entering the coordination sphere of the Cr(II) (an inner-sphere electron transfer) as indicated in Scheme III to form the Cr(III) species **28** (where ROH is MeOH or HOAc). This species **28**, an allylic radical, would be expected to react with a second $(en)_2Cr(II)$ ion to form the alkyl-Cr(III) intermediate **29** in a reaction analogous to that observed[2b,4,11] with alkyl radicals and Cr(II) complexes. The further hydrolysis (or alcoholysis) of the intermediate **29** [or the related β-keto alkyl-Cr(III) intermediate **30**] would then yield the reduced product **31**. This reaction path (Scheme III), which is in many respects analogous to the scheme operative in the reduction of alkyl halides with Cr(II) complexes,[2b,4] accounts for the spectroscopically observed alkyl-Cr(III) intermediate, for the formation of β-deuterio ketones **8b**, **14b**, and **15b** in those reactions where part of the proton donor present was replaced with D_2O, and for the ability of the Cr(II) complex to reduce enones with reduction potentials more negative than that of the corresponding Cr(III) complex. The suggested reaction path is also consistent with the data obtained from a kinetic study[6b] of the related reduction of acetylenedicarboxylic acid to fumaric acid with aquated chromium(II) ion. This study[6b] provided kinetic evidence for the reaction of the unsaturated carbonyl compound with 2 mol of the solvated chromium(II) ion to form an organochromium intermediate that hydrolyzed to form the reduced product and chromium(III) ion.

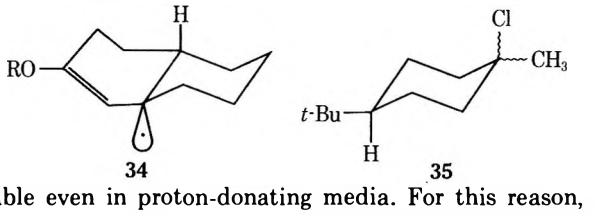
In many respects the reaction pathway suggested in Scheme III also parallels the pathway suggested for the reductions of enones with alkali metals in liquid NH_3 or other solvents[8a,b,16] in that an intermediate enol derivative with an ionic or covalent carbon–metal bond at the β carbon appears to be involved. In this context, the Cr(II) reduction of enones represents a special case of an enone dissolving-metal reduction in which the intermediate **29** (or **30**) possesses a carbon–metal bond that is relatively

Scheme IV



Product yields, %

Reaction conditions	14a	15a
$Cr^{II}(en)_2$, HOAc, MeOH	16	13
$Cr^{II}(en)_2$, MeOH, HOAc, *n*-PrSH	57	11

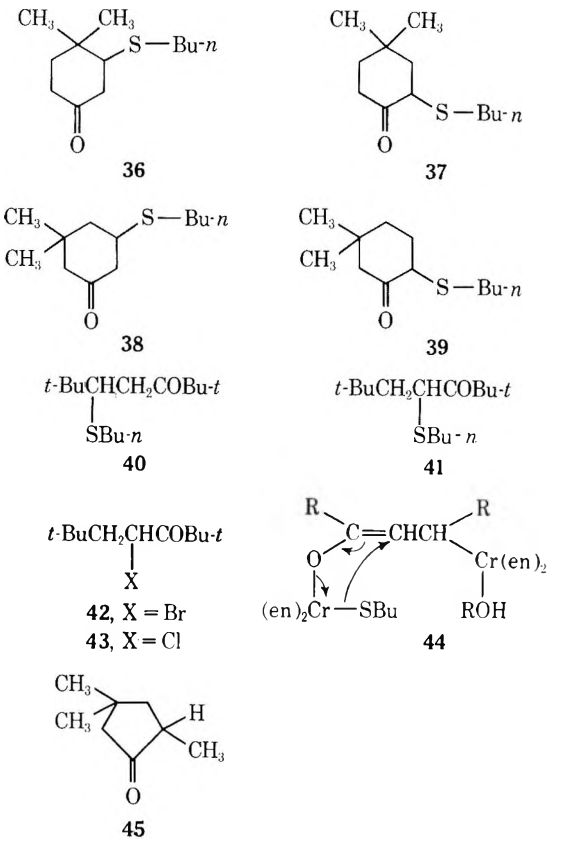


stable even in proton-donating media. For this reason, it was of interest to examine the stereochemistry of the reduction of the octalone **11**, since in typical alkali metal reductions more than 98% of the reduced product is the trans isomer **14a**.[8b,16] However, if relatively stable β-ketoalkyl-Cr(III) intermediates such as **32** and **33** (Scheme IV) are produced, the formation of the intermediate **33** with the bulky Cr(III) group in an equatorial conformation rather than an axial conformation (as in **32**) should be more favorable. Subsequent protonolysis of the carbon–metal bond with retention of configuration should then increase substantially the proportion of the cis ketone **15a** in the reduction product. In fact, the decalone mixture obtained from reduction of the octalone **11** with $Cr^{II}(en_2)$ in MeOH containing HOAc contains 55% of the trans (**14a**) and 45% of the cis (**15a**) ketones.

Although these results support the idea of an intermediate alkyl-Cr(III) intermediate such as **29** or **30** in the reduction sequence, the yields of monomeric reduction products (*e.g.*, **14**, **15**, **16**, **21**, and **23**) from the corresponding enones were often disappointingly low (15–40%; the reduction of enone **7** to **8** in 81% yield was exceptional). In most cases the low yields were the result of two competing side reactions. One side reaction was the competing dimerization of an intermediate radical species (*e.g.*, **28**) to form mixtures of diastereoisomeric dihydro dimers such as **17**, **22**, and **24**. This side reaction, which presumably occurs because the rate of dimerization of the radical **28** is competitive with the trapping of this radical by a second molecule of the Cr(II) complex, is reminiscent of a common side reaction (dimerization of **26**) observed in the electrochemical reduction of enones.[8a,b]

A second, less well-defined competing process involved reaction of the starting enone with the diamine ligand **1** to form one or more basic products that were soluble in

Scheme V



aqueous acid. Although our efforts to isolate and characterize pure substances from these crude basic products were not productive, control experiments in the absence of Cr(II) indicated that a substantial fraction of the unhindered enones (*e.g.*, **12**) was consumed in such competing reactions.

In an effort to overcome these yield-lowering side reactions, we explored the addition to the reaction mixture of various efficient H-atom donors that might serve to intercept the intermediate radical **28**.[4b,c] Among the H-atom donors examined (see Experimental Section), the mercaptans *n*-PrSH and *n*-BuSH proved to be especially effective and completely eliminated the formation of the dihydro dimers **17**, **22**, and **24**. With a reaction mixture composed of 1 molar equiv of the enone, 3–4 molar equiv of the Cr(II) complex **9b**, 3 molar equiv of *n*-BuSH (or *n*-PrSH), and 5 molar equiv of HOAc in MeOH solution, the yields of monomeric, saturated ketonic products were improved substantially in all cases. With the α,β-unsaturated ketones **10** and **11** possessing two β-alkyl substituents, the yields (68–79%) of reduction products **14–16** were sufficient to make this reduction procedure preparatively useful. The change in stereochemical results (85% trans ketone **14a** and 15% cis ketone **15a**) obtained from the reduction of the octalone **11** in the presence of *n*-PrSH suggests that at least part of the increased yield in these cases is attributable to trapping the intermediate *tert*-alkyl radical (*e.g.*, **34**) by an axial H-atom transfer from the mercaptan to form additional trans ketone **14a**. This stereochemical change is analogous to that seen in the reduction of either stereoisomer of the *tert*-alkyl chloride **35** with $(en)_2Cr(ClO_4)_2$ in the presence or absence of *n*-BuSH[4f] in that H-atom transfer to a cyclohexyl radical from an axial direction was favored. Although we were unable to obtain evidence supporting the view, it is possible that part of the increased yield of monomeric reduction products in the presence of mercaptans is attributable to a more rapid reduction by a Cr(II) species with the mercaptan as one of the ligands.

Although the addition of *n*-BuSH also improved the yields of saturated ketones **21** and **23** obtained from the enones **12** and **13**, in each of the Cr(II) reductions of an α,β-unsaturated ketone **7**, **12**, and **13** with a single β-alkyl substituent, a new set of side reactions was observed when *n*-BuSH was added. From each of these reactions, two new thio ether products **36–41** (Scheme V) appeared as by-products. Appropriate control experiments indicated that the β-keto sulfides **36**, **38**, and **40** could arise by at least two likely processes. In the presence of the basic diamine **1** (but not in neutral solution), *n*-BuSH added to each of the enones **7**, **12**, and **13** to form the corresponding β-keto sulfide in a reaction that is very likely a Michael addition of the *n*-BuS^- anion. Each enone also underwent a slow addition of *n*-BuSH to form only the corresponding β-keto sulfide in a free-radical chain reaction[17] catalyzed by azoisobutyronitrile. However, neither of these processes accounts for the formation of the minor α-keto sulfides **37**, **39**, and **41**. An appropriate control experiment also indicated that formation of the α-keto sulfide **41** could not be attributed to addition of *n*-BuSH to the enone **7** in a reaction catalyzed[18] by the Cr(III) species generated by the reduction. It therefore appears that some intermediate formed during the reduction process is responsible for the formation of the α-keto sulfide by-products. One possibility is that illustrated in structure **44**, in which the intermediate chromium enolate serves to transfer a mercaptide group to the α-carbon atom. In any case, the presence of these thio ether by-products clearly makes this procedure [Cr(II) complex + *n*-BuSH] an unattractive method for the reduction of relatively unhindered α,β-unsaturated ketones containing a single β-alkyl substituent.

Finally, we wish to note one other minor by-product, the cyclopentanone **45** (Scheme V), that was observed in the reduction of the enone **13** with the Cr(II) complex **9b** in the absence of *n*-BuSH. This enone reduction with accompanying rearrangement has been observed previously during the reduction of enones with metals in acidic media (*e.g.*, the Clemmensen reduction).[19,20]

Experimental Section[21]

Preparation of the Chromium(II) Reagents. Aqueous solutions of $Cr(ClO_4)_2$ were prepared by stirring excess Cr with aqueous 1.4 *M* $HClO_4$ at 35–40° for 8 hr.[3b,4b] The resulting deep blue solutions were siphoned from the excess Cr and stored under N_2. Aliquots of these solutions were standardized as previously described;[3b,22] the concentration of $Cr(ClO_4)_2$ was 0.490–0.720 *M*. The quantity of Cr(III) salts in these solutions was determined by passing standardized solutions of $Cr(ClO_4)_2$ through a column of amalgamated zinc [a Jones reductor[3a,12] to reduce any Cr(III) to Cr(II)[5]]. Typically, a passage of aqueous 0.720 *M* $Cr(ClO_4)_2$ over zinc amalgam followed by titration indicated the total Cr(II) concentration to be 0.768 *M*, corresponding to 0.048 *M* Cr(III) salts in the stock solution.

The relatively insoluble $Cr(OAc)_2 \cdot H_2O$ was obtained by a modification of previous procedures[12] in which aqueous $Cr(ClO_4)_2$ was treated with boiling aqueous NaOAc in a flask fitted with a coarse sintered glass disk. The mixture was agitated with N_2 passed through the sintered glass disk; then the solid $Cr(OAc)_2 \cdot H_2O$ was collected on the sintered glass and washed successively with three portions of H_2O, two portions of EtOH, and Et_2O, all under N_2. Finally, the sample was dried under reduced pressure and stored under nitrogen. In a typical preparation, the $Cr(OAc)_2 \cdot H_2O$ was obtained as a bright red solid in 94% yield. Although this product dissolved in DMSO to form a purple solution (*ca.* 1 *M*), it was not soluble in preparatively useful concentrations in any of the following solvents: H_2O, MeOH, EtOH, *i*-PrOH, *t*-BuOH, acetone, MeCN, DMF, or HMPA. However, when amounts of the diamine **1** greater than 2 mol/mol $Cr(OAc)_2$ were added, purple solutions of the complex **9b** were obtained in all of the previous solvents except acetone, MeCN, and HMPA.

In MeOH and in *i*-PrOH, it was necessary to add 2.4 molar equiv of the diamine **1** to form 1 *M* solutions of the Cr(II) complex **9b**; in DMF a 3 *M* solution was obtained by the addition of 3.3 molar equiv of the diamine **1**. Complexes soluble in MeOH were not obtained with either of the ligands, the amino alcohol **4** or the diamine **3**. However, a purple solution was obtained from 6.4 mmol of $Cr(OAc)_2$, 3.5 ml of MeOH, and 31 mmol of the amino alcohol **2**. Also, the addition of 66 mmol of aqueous 28% NH_3 to 6.4 mmol of $Cr(OAc)_2$ and 3.5 ml of MeOH afforded a deep blue solution of the corresponding complex.

A solution of the complex **9b** in MeOH exhibited λ_{max} 552 mμ (ε 32) [lit.[4c] in H_2O–DMF λ_{max} 550 mμ (ε 25)]. After exposure to air for 1 hr the resulting $Cr^{III}(en)_2$ solution exhibited maxima at 384 (ε 51) and 520 mμ (ε 69) [lit.[4c] in DMF–H_2O λ_{max} 380 (ε 59) and 510 mμ (ε 75)]. In DMF solution the maximum for the Cr(II) complex **9b** was at 520 mμ (ε 45), and, after air oxidation, the Cr(III) complex had maxima at 380 (ε 50) and 520 mμ (ε 54). A similar solution prepared from $Cr(ClO_4)_2$ and 3 equiv of the diamine **1** in DMF containing 0.5 *M* H_2O exhibited a maximum at 538 mμ (ε 51); after air oxidation to Cr(III) the maxima were at 386 (ε 80) and 534 mμ (ε 93). When a 0.045 *M* solution of this complex **9b** in MeOH was treated with the relatively unhindered ketone **13** (0.022 *M*), a new, more intense absorption appeared with maxima at 378 (ε ~400) and 516 mμ (ε ~130) corresponding to the species $RCr^{III}(en)_2$ [lit.[4c] in DMF–H_2O λ ~400 mμ (ε ~500)]. From a comparable experiment in DMF solution, maxima were observed at 380 (ε ~250) and 536 mμ (ε ~100). In MeOH solution these new peaks slowly disappeared and after several hours the spectrum of the solution corresponded to $Cr^{III}(en)_2$. Comparable spectral changes were observed when $CH_3COCH{=}CH_2$ was added to a solution of the complex **9b** and less intense but related spectral changes were seen upon addition of the complex to the hindered enones **7**, **10**, and **12**. Although the intensities of the new $RCr^{III}(en)_2$ absorptions decayed only over a period of hours in MeOH solution with or without added *n*-BuSH, this absorption was discharged rapidly by the addition of HOAc.

Polarographic Measurements. The measurements of oxidation and reduction potentials by polarography (at a dropping Hg electrode) and by cyclic voltammetry (at a spherical Hg-coated Pt electrode) were obtained with the apparatus and reference electrodes (saturated calomel with intermediate salt bridges containing aqueous 1 *M* $NaNO_3$ and 0.5 *M* $Et_4N^+BF_4^-$ in DMF) described previously.[23] The supporting electrolytes and solvents were either 0.5 *M* n-$Bu_4N^+BF_4^-$ in purified[23] DMF or 0.5 *M* n-$Bu_4N^+BF_4^-$ in purified[24] MeOH. In DMF solution, the $E_{1/2}$ values (*vs.* sce) measured polarographically for the various enones follow: **10** (2.3 m*M*), −2.24 V (αn = 1.2, i_d = 17.4 μA); **11**, −2.15 V;[8c] **7**, −2.22 V;[8] **14**, −2.43 V.[8c] Repetition of this measurement for ketone **10** (2.4×10^{-3} *M*) in DMF containing 0.1 *M* H_2O gave an $E_{1/2}$ value of −2.19 V (αn = 0.9, i_d = 19 μA). The $E_{1/2}$ values (*vs.* sce) determined polarographically in MeOH solution follow: **10** (8.8–10.1 m*M*), −1.65 V (αn = 0.9, i_d = 5.3–6.6 μA); **11** (11.5–15.5 m*M*), −1.67 V (αn = 0.7, i_d = 6.5–11 μA); **7** (4.3–5.6 m*M*), −1.76 V (αn = 0.7, i_d = 2.7–3.5 μA); **13** (4.7–6.4 m*M*), −1.56 V (αn = 0.9, i_d = 3.2–3.4 μA); **12** (2.9–4.6 m*M*), −1.57 V (αn = 0.9, i_d = 1.8–3.1 μA); **14** (7.8–8.3 m*M*), −1.92 V (αn = 0.9, i_d = 5.5–7.6 μA). Thus, the reduction potentials of all these ketones are *ca.* 0.5 V less negative in MeOH than in DMF solution.

Polarographic reduction of a DMF solution containing 0.5 *M* n-Bu_4NBF_4, 4.9 m*M* Cr(II) and Cr(III) species [from $Cr(ClO_4)_2$], and 0.5 *M* H_2O gave $E_{1/2}$ = −1.51 V (*vs.* sce, αn = 0.6, i_d = 13 μA). The irreversible nature of this reduction was indicated by cyclic voltammetry ($E_{1/2} \cong$ −1.60 V) since no oxidation peak was observed. The corresponding polarographic reduction of a DMF solution containing 0.5 *M* n-Bu_4NBF_4, 4.9 m*M* $(en)_2Cr(II)$ and $(en)_2Cr(III)$ species [from $Cr(ClO_4)_2$ and 3 molar equiv of the diamine **1**] and 0.5 *M* H_2O gave $E_{1/2}$ = −1.89 V (*vs.* sce, αn = 1.0, i_d = 11 μA). When the latter measurement was repeated with the mole ratios Cr(II):diamine **1** equal to 1.0, 2.0, and 4.0, the corresponding $E_{1/2}$ values were −1.85, −1.86, and −1.93 V. Solutions of the complex **9b** [6.6 m*M* from $Cr(OAc)_2 \cdot H_2O$ and 3 molar equiv of the diamine **1**] and 0.5 *M* n-Bu_4NBF_4 in MeOH and in DMF were also measured.

In DMF solution a reversible wave [Cr(III) ⇄ Cr(II)] for the complex **9b** was observed at −1.77 V (αn = 0.8, i_d = 2.0 μA) followed by an irreversible wave [presumably Cr(II) → Cr(0)] at −2.13 V (αn = 0.5, i_d = 5.6 μA). The nature and reversibility of the first wave were substantiated by cyclic voltammetry, since the locations of the peak currents, i_{pa} and i_{pc}, were the same with solutions containing (spectrophotometric analysis) the Cr(II) and Cr(III) species and the ratio i_{pc}/i_{pa} did not vary with scan rate. When the DMF solution of the complex **9b** was obtained from 0.027 *M* $Cr(OAc)_2$ and 0.081 *M* diamine **1**, cyclic voltammetry indicated an $E_{1/2}$ value of −1.64 V; a similar measurement with a solution obtained from 0.017 *M* $Cr(OAc)_2$ and 0.81 *M* diamine **1** gave an $E_{1/2}$ value of −1.59 V. The second reduction wave (at −2.13 V) exhibited no current peak on reoxidation and the peak reduction current, i_{pc}, rapidly diminished on repetitive scans. In MeOH solution, a 12 m*M* solution of the Cr(II) complex **9b** exhibited an oxidation wave at *ca.* −1.07 V. These measurements in MeOH were complicated by erratic behavior of the dropping Hg electrode. The $E_{1/2}$ value was better determined by cyclic voltammetry where reversible behavior was observed with solutions containing (spectrophotometric analysis) either complexes of Cr(II) or complexes of Cr(III). With a MeOH solution obtained from 0.026 *M* $Cr(OAc)_2$ and 0.078 *M* diamine **1**, the $E_{1/2}$ value was −1.10 V; when the concentrations were 0.026 *M* $Cr(OAc)_2$ and 0.78 *M* diamine **1**, the $E_{1/2}$ value was −1.17 V.

Reduction of Isophorone (10). A. General Procedure in MeOH Solution. When a suspension of 32.0 g (175 mmol) of $Cr(OAc)_2 \cdot H_2O$ in 100 ml of MeOH was treated with 24.5 g (405 mmol, 2.3 molar equiv) of the diamine **1**, the Cr(II) salt dissolved and the solution (which initially warmed to 55°) was stirred at 50° for 10 min. (If the precaution of stirring this solution for 10 min to complete the formation of the Cr(II) complex **9b** before adding the remaining reactants was not observed, substantial amounts of the subsequently described by-products **19a** and **19b** were present in the final product.) The resulting solution was treated with 13.5 g (16.3 ml, 150 mmol) of *n*-BuSH, cooled to 30°, treated with 15.0 g (250 mmol) of HOAc, and again cooled to 28°. To the resulting purple solution was added, with stirring and external cooling, 7.00 g (51 mmol) of isophorone (**10**) and the reddish-purple reaction mixture was stirred at 25° for 24 hr. The resulting magenta-colored solution was treated with 200 g of ice and 200 ml of H_2O and then acidified to pH 2–3 with aqueous 6 *M* HCl, saturated with NaCl, and extracted with five 75-ml portions of Et_2O. The Et_2O extract was washed successively with aqueous $NaHCO_3$ and H_2O and then dried and concentrated to leave 12.3 g of crude product as a colorless liquid containing (glpc, Carbowax 20 M on Chromosorb P) *n*-BuSH (retention time 1.9 min), the saturated ketone **16** (9.1 min), *n*-BuSSBu-*n* (16.9 min), and a small amount of the starting ketone **10** (19.5 min) as well as several minor unidentified components. Fractional distillation separated 0.61 g of a fraction, bp 25–27° (14 mm), containing (glpc) mainly *n*-BuSH, 5.39 g of the saturated ketone **16**, bp 78–82° (6 mm), $n^{25}D$ 1.4452 [lit.[25] bp 73–74° (14 mm), $n^{20}D$ 1.4461], and 2.70 g of a fraction, bp 75–77° (1.6 mm), containing (glpc) mainly *n*-BuSSBu-*n* accompanied by lesser amounts of ketones **10** and **16**. Redistillation of the latter fraction separated an additional 0.21 g of the saturated ketone **16** (total yield 5.60 g, 79%); this product was identified with an authentic sample by comparison of glpc retention times and ir and nmr spectra. Various related reductions of the enone **10**, summarized in Table II, were performed in which the mode of formation of the complex **9b** was varied and in which no *n*-BuSH was added. When the amount of *n*-BuSH was lowered from the usual 3–5 mol/mol of enone **10** to 1.2 mol of *n*-BuSH/mol of **10**, the yield of the reduction product **16** was lowered to 40%. For glpc analysis (Carbowax 20 M on Chromosorb P), the crude products were mixed with n-$C_{15}H_{32}$ (internal standard) and analyzed on equipment calibrated with known mixtures of authentic samples. In a mixture containing the ether **19b**, the glpc retention times follow: ether **19b** (8.0 min), ketone **16** (13.3 min), *n*-BuSSBu-*n* (24.5 min), and ketone **10** (28.2 min). Collected (glpc) samples of the ketones **10** and **16** were identified with authentic samples by comparison of glpc retention times and ir spectra. A collected (glpc) sample of *n*-BuSSBu-*n* was obtained as a colorless liquid: ir (CCl_4) no peaks in the 3- or 6-μ regions attributable to OH, C=O, or C=C; nmr (CCl_4) δ 2.3–2.8 (4 H, m, CH_2S), 1.1–2.0 (8 H, m, CH_2), and 0.7–1.1 (6 H, m, CH_3); mass spectrum *m/e* (rel intensity) 180 (32), 179 (38), 178 (M^+, 100), 124 (29), 122 (78), 89 (20), 88 (32), 87 (34), 79 (29), 59 (31), 57 (78), 55 (36), 47 (28), 45 (24), 44 (28), 42 (34), and 41 (47). *Anal.* Calcd for $C_8H_{18}S_2$: mol wt, 178.0850. Found: 178.0875.

An authentic sample of *n*-BuSSBu-*n*, prepared in 63% yield by a published procedure,[26] was obtained as a colorless liquid, bp 84–85° (4 mm), $n^{25}D$ 1.4910 [lit.[26] bp 120–123° (25 mm), $n^{20}D$ 1.4926], that was identified with the previously described material by comparison of ir and nmr spectra and glpc retention times.

A collected (glpc) sample of the ether **19b** was obtained as a colorless liquid: ir (CCl_4) 1635 and 1670 cm^{-1} (weak, C=C); nmr

Table II
Reduction of α,β-Unsaturated Ketones with Various Chromium(II) Compounds

Ketone (mmol)	Cr(II) salt (mmol)	Diamine 1, mmol	Additives (mmol)	Solvent (ml)	Reaction time, hr	Reaction temp, °C	Products (yield, %)
10 (51)	$Cr(OAc)_2$ (175)	405	*n*-BuSH (150) + HOAc (250)	MeOH (100)	24	25	*n*-BuSSBu-*n*[a] + **16** (79%)[b]
10 (11)	$Cr(OAc)_2$ (35)	81	*n*-BuSH (30) + HOAc (50)	MeOH (20)	24	25[c]	*n*-BuSSBu-*n*[a] + **16** (84)[a]
10 (25)	$Cr(OAc)_2$ (75)	203	*n*-BuSH (75) + HOAc (125)	MeOH (45)	12	25[d]	*n*-BuSSBu-*n*[a] + **16** (61)[a] + **19b**[a]
10 (87)	$Cr(OAc)_2$ (304)	705	HOAc (435)	MeOH (175)	4	25	**16** (1.2)[a] + **19a**[a] + **19b** (~6)[a] + **17** (2)[b]
10 (22)	$Cr(ClO_4)_2$ (64)	192		DMF (75) + H_2O (150)	3	25	**16** (26)[a] + **17** (5)[b]
11 (21)	$Cr(OAc)_2$ (69)	162	*n*-PrSH (60) + HOAc (90)	MeOH (35)	24	25	*n*-PrSSPr-*n*[a] + **14a** (48)[b] + **15a** (8)[b]
11 (6.7)	$Cr(OAc)_2$ (23)	54	*n*-PrSH (20) + HOAc (33)	MeOH (15)	2	28–35	*n*-PrSSPr-*n*[a] + **14a** (57)[a] + **15a** (11)[a]
11 (2.6)	$Cr(OAc)_2$ (12)	28	HOAc (18)	MeOH (7)	24[e]	0–5	**14a** (16)[a] + **15a** (13)[a] + **18**[a,f]
11 (6.7)	$Cr(ClO_4)_2$ (21)	60		DMF (25) + H_2O (50)	20	25	**14a** (23)[a] + **15a** (19)[a]
7 (18)	$Cr(OAc)_2$ (84)	195	HOAc (90)	MeOH (40)	24	25	**8a** (81)
7 (18)	$Cr(OAc)_2$ (63)	54	*n*-BuSH (54) + HOAc (90)	MeOH (40)	24	25	**8a** (23)[b] + *n*-BuSSBu-*n*[a] + **40**[a] + **41**[a]
7 (1.07)	$Cr(ClO_4)_2$ (2.6)	8.2		DMF (15) + H_2O (5)	0.3	25	**8a** (72)[a]
13 (40)	$Cr(OAc)_2$ (144)	324	HOAc (200)	MeOH (82)	3.5	25	**23** (4)[a] + **24** (3)[b] + **45** (0.4)[a]
13 (24)	$Cr(OAc)_2$ (84)	194	*n*-BuSH (72) + HOAc (120)	MeOH (50)	23	25	*n*-BuSSBu-*n*[a] + **23** (18)[b] + **38**[a] + **39**[a]
20 (20)	$Cr(OAc)_2$ (70)	160	*n*-PrSH (60) + HOAc (100)	MeOH (35)	24	25	**20** (86% recovery)[a]
12 (32)	$Cr(OAc)_2$ (113)	261	HOAc (160)	MeOH (65)	14	25	**21** (20)[b] + **22** (2)[b]
12 (32)	$Cr(OAc)_2$ (113)	261	*n*-BuSH (97) + HOAc (160)	MeOH (65)	23	25	*n*-BuSSBu-*n*[a] + **21** (47)[b] + **36**[a] + **37**[a]

[a] Determined by glpc analysis. [b] Determined by isolation. [c] In this experiment the complex **9b** was formed at temperatures below 25°. [d] In this experiment the reactants were all added rapidly with cooling without allowing an initial 10-min reaction period to form the complex **9b**. [e] This reaction was performed in the dark. [f] The identification of these alcohol by-products **18** is only tentative.

(CCl_4) δ 5.4 (1 H, broad, vinyl CH), 3.5–3.8 (1 H, m, allylic CHO), 3.25 (3 H, s, OCH_3), 1.1–2.0 (7 H, m, CH_2 and allylic CH_3), 0.99 (3 H, s, CH_3), and 0.89 (3 H, s, CH_3); mass spectrum *m/e* (rel intensity 154 (M^+, 20), 139 (100), 107 (35), 99 (32), 84 (35), 83 (35), 58 (35), and 41 (80). *Anal.* Calcd for $C_{10}H_{18}O$: mol wt, 154.1358. Found: 154.1366. Isophorone (**10**) was reduced with $LiAlH_4$ as previously described[27] to yield 94% of the allylic alcohol **19a** as a colorless liquid: bp 93–94° (15 mm); $n^{25}D$ 1.4705 [lit.[27] bp 95–100° (25 mm), $n^{24}D$ 1.4731]; ir (CCl_4) 3600, 3340 (OH), and 1670 cm^{-1} (weak, C=C); nmr (CCl_4) δ 5.4 (1 H, broad, vinyl CH), 4.1 (1 H, broad, allylic CHO), 3.20 (1 H, OH, exchanged with D_2O), 1.1–2.1 (7 H, m, CH_2 and vinyl CH_3), 1.00 (3 H, s, CH_3), and 0.89 (3 H, s, CH_3); mass spectrum *m/e* (rel intensity), 122 (49), 107 (100), 105 (20), 91 (55), 79 (28), 58 (41), 44 (25). and 43 (57). When a solution of 1.00 g of this alcohol **19a** in 15 ml of MeOH was diluted with 200 ml of H_2O, acidified to pH 2 with HCl, and subjected to the previously described isolation procedure used in the Cr(II) reductions, the crude product recovered (0.96 g) corresponded (nmr analysis) to a mixture of the alcohol **19a** and the ether **19b**. The glpc curve of the mixture exhibited two rapidly eluted peaks (presumably dienes from elimination in the injection port) and a peak corresponding in glpc retention time to the ether **19b**.

In an experiment where no *n*-BuSH was added, the crude product was distilled to separate a fraction [bp 56–62° (6 mm)] containing the ketone **16**, the alcohol **19a**, and the ether **19b**. The residue from the distillation was triturated with hexane to separate 152 mg (2%) of a mixture of dihydro dimers **17**, mp 154–162°. Fractional crystallization from EtOH separated 111 mg of the higher melting isomer, mp 163–164.5° (lit.[28] mp 163°), and 10 mg of the lower melting isomer, mp 121–123° (lit.[28] mp 123–124°). Each of these materials was identified with an authentic sample by a mixture melting point determination and by comparison of ir spectra. Authentic samples of the two diastereoisomeric dihydro dimers **17** were obtained by the previously described procedure.[28] The isomer, mp 164–164.5°, had the following spectra properties: ir (CCl_4), 1710 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.2–2.6 (12 H, m, including one resolved AB quartet with J = 14 Hz at *ca.* 1.42 and 1.80, CH_2), 1.09 (12 H, s, CH_3), and 1.04 (6 H, s, CH_3); mass spectrum *m/e* (rel intensity) 139 (100), 125 (30), 83 (53), and 55 (36). The spectral properties of the isomer, mp 120–121°, are ir (CCl_4) 1710 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.2–2.6 (12 H, m, including a resolved AB quartet with J = 14 Hz at *ca.* 1.45 and 1.82, CH_2), and 1.09 (18 H, s, CH_3).

B. General Procedure with DMF and Other Solvents. Although a variety of attempts to reduce various cyclohexenone derivatives with solutions of $Cr(ClO_4)_2$ in aqueous DMF without added nitrogen-containing ligands resulted in no evidence of reduction,[9] these reductions were at least partially successful in the presence of added diamine **1**. For example, a solution of 64 mmol of $Cr(ClO_4)_2$ in 150 ml of H_2O and 75 ml of deoxygenated DMF was treated with 11.5 g (192 mmol) of the diamine **1** and the resulting violet solution was treated with 3.0 g (22 mmol) of isophorone (**10**). After the mixture had been stirred at 25° for 3 hr, it was subjected to the usual isolation procedure to separate 1.32 g of crude product as a pale yellow liquid from which the crystalline dihydro dimer **17** separated. Trituration with hexane separated 0.15 g (5%) of the crude dihydro dimer **17**, mp 159.5–161°. Recrystallization (EtOH) afforded the one epimer of the dihydro dimer **17** as white plates, mp 166.5–167°, identified by comparison of ir and nmr spectra. The mother liquors remaining after separation of the dimer **17** contained (glpc) a mixture of the ketones **10** (7% recovery) and **16** (26% yield) as well as a number of minor unidentified components. A collected (glpc) sample of the ketone **16** was identified with an authentic sample by comparison of glpc retention times and mass spectra. A comparable result was ob-

tained when the reduction of ketone **10** was performed with $Cr(ClO_4)_2$, and the diamine **1** in aqueous THF. An attempt to reduce isophorone (**10**) with a solution of $Cr(OAc)_2$ in DMSO[29] resulted only in recovery of the unchanged ketone **10**. A series of reductions of isophorone (**10**) with the Cr(II) complex **9b** in the solvents DMF, DMSO, HOAc, PhOH, *i*-PrOH, or an *i*-PrOH–HOAc mixture and with the complex formed from $Cr(OAc)_2$ and the triamine **6** in MeOH gave results similar to the previously described reduction in MeOH with no added *n*-BuSH in that low yields (5–10%) of mixtures of reduction products **16** and **17** were obtained. Similar poor yields of reduction products were obtained from reductions of isophorone (**10**) with solutions obtained from $Cr(OAc)_2$ and excess NH_3[5b] either in H_2O or in H_2O–DMSO mixtures.

We explored several hydrogen atom donors other than *n*-BuSH, including H_3PO_2 and $HSCH_2COOH$; H_3PO_2 was without substantial benefit and we were unable to maintain the Cr reagent in solution when $HSCH_2CO_2H$ was added. A series of reductions were performed with solutions of the Cr complex **9b** in *i*-PrOH with 5 mol of *n*-BuSH added/mol of ketone **10** reduced. In the absence of added HOAc, the yield of reduced ketone **16** was in the range of 8–18%. When 5 mol of HOAc/mol of ketone **10** was added without *n*-BuSH, the yield of ketone **16** was 40%. Similar observations were made for reductions performed in EtOH solution, the yield of ketone **16** under optimum conditions (with both *n*-BuSH and HOAc) being 70%. With both solvents, EtOH and *i*-PrOH, the reactions employing 1 *M* solutions of the Cr complex **9b** were frequently complicated by precipitation of a substantial fraction of the Cr complex as a reaction progressed with the result that reduction was incomplete. This difficulty was avoided by the use of MeOH as the reaction solvent.

Reduction of the Octalone 12. A. In MeOH Solution. The crude product, from reduction of 3.00 g (21 mmol) of the octanone **11** with the Cr complex **9b** in MeOH containing HOAc and *n*-PrSH[30] as summarized in Table II, was obtained as a pale yellow liquid containing (glpc, Carbowax 20 M on Chromosorb P) *n*-PrSSPr-*n* (retention time 3.1 min), the trans decalone **14a** (12.0 min), and the cis decalone **15a** (14.5 min). Distillation of this mixture in a short-path still separated 0.21 g of a fraction, bp 79–82° (2.5 mm), containing (glpc) primarily the decalones **14** and **15** with some *n*-PrSSPr-*n*, and 7.61 g (54%) of the decalones **14** and **15**, bp 82–89° (2.5 mm), containing (glpc) 85% of the trans isomer **14a** and 15% of the cis isomer **15a**. Various modifications of this reduction procedure are also summarized in Table II. For the glpc analysis of these compounds, naphthalene was employed as an internal standard and the glpc apparatus was calibrated with known mixtures of authentic samples. On one glpc column (Carbowax 20 M on Chromosorb P) the retention times follow: naphthalene (17.8 min), trans decalone **14a** (22.0 min), cis decalone **15a** (27.7 min), and octalone **11** (34.9 min). On a second glpc column (silicone SE-52 on Chromosorb P) the retention times follow: naphthalene (9.7 min), trans decalone **14a** (17.0 min), cis decalone **15a** (19.7 min), and octalone **11** (27.2 min). Collected (glpc) samples of the cis ketone **15a** ($n^{25}D$ 1.4905) and the trans ketone **14a** ($n^{25}D$ 1.4814) were identified with authentic samples by comparison of glpc retention times and ir and nmr spectra. A collected (glpc) sample of *n*-PrSSPr-*n* was identified with a subsequently described authentic sample by comparison of glpc retention times and ir and mass spectra.

An authentic sample of *n*-PrSSP-*n* was obtained in 53% yield as previously described,[26] and was separated as a colorless liquid: bp 190–191°; $n^{25}D$ 1.4961 [lit.[31] bp 69–70° (10 mm), $n^{20}D$ 1.4940]; ir (CCl_4), no peaks in the 3- or 6-μ regions attributable to OH, C=O, or C=C; nmr (CCl_4) δ 2.63 (4 H, t, J = 7 Hz, CH_2S), 1.69 [4 H, sextet (J = 7 Hz) with additional fine splitting apparent, CH_2], 1.00 (6 H, t, J = 7 Hz, with additional fine splitting, CH_3); mass spectrum *m/e* (rel intensity) 150 (M^+, 30), 108 (25), and 43 (100). *Anal.* Calcd for $C_6H_{14}S_2$: mol wt, 150.0537. Found: 150.0534.

When the octalone **11** was reduced with the Cr(II) complex in the dark and in the absence of added *n*-PrSH (see Table II), the crude product contained, in addition to two rapidly eluted components having the same retention times as the alcohols **18**, the trans decalone **14a** (16% yield), the cis decalone **15a** (13% yield), and the octalone **11** (10% recovery); thus, the mixture of decalones **14** and **15** was composed of 55% **14a** and 45% **15a**. When the same reaction was repeated at 25° without deliberate exclusion of light, the ratio of isomers, 60% **14a** and 40% **15a**, remained about the same but the yields, 7% of **14a** and 5% of **15a**, were lower. When the same reaction was run at −70 to −78° for 12 hr, the crude product again contained (glpc) two rapidly eluted components (retention times 4.3 and 4.8 min) corresponding to the epimeric alcohols **18** as well as the trans ketone **14a** (15.9 min, 5% yield), the cis ketone **15a** (19.6 min, 4% yield), and the enone **11** 35.6 min, 14% recovery).

B. In DMF Solution. As summarized in Table II, reduction of the octalone **11** with the $Cr(ClO_4)_2$–diamine **1** complex in aqueous DMF yielded 23% of the trans isomer **14a** and 19% of the cis isomer **15a**, corresponding to a decalone mixture containing 58% **14a** and 42% **15a**. Collected (glpc) samples of the two decalones **14** and **15** were identified with authentic samples by comparison of the glpc retention times and ir spectra. Repetition of this reaction with added H_3PO_2 or Ph_3SiH as possible hydrogen-atom donors did not significantly improve the yield of the decalones **14** and **15**. When comparable reactions were done in other solvents, the following yields were obtained: THF, 13% **14a** and 10% **15a**; *t*-BuOH, 20% **14a** and 17% **15a**; *i*-PrOH, 24% **14a** and 20% **15a**. Thus, in all of these cases where there was no mercaptan in the reaction mixture, 54–60% of the decalone product was the trans isomer **14a**.

A 0.65 *M* solution of $Cr(ClO_4)_2$ in D_2O was prepared by the previously described reaction of excess Cr with 28.7 g of aqueous 70% $HClO_4$ in 200 ml of D_2O. Following previous procedures a portion of this solution containing 12 mmol of $Cr(ClO_4)_2$ in 20 ml of DMF and 18 ml of D_2O was treated successively with 36 mmol of diamine **1** and 3.81 mmol of the octalone **11** and then stirred at 25° for 8 hr. The crude reaction product (264 mg) contained (glpc) 55% of **14** and 45% of **15**. Collected (glpc) samples of each decalone isomer were passed three times through a glpc column packed with 10% KOH and 10% Carbowax 20 M suspended on Chromosorb P[32] to exchange for hydrogen any deuterium bound to carbons α to the carbonyl group of the decalones **14** and **15**.[33] The resulting cis isomer **15** contained (mass spectral analysis) 60% d_0 species, 39% d_1 species, and 1% d_2 species. The trans isomer **14** contained (mass spectral analysis) 57% d_0 species, 41% d_1 species, and 2% d_2 species.

Reduction of the Ketone 7. A. In MeOH Solution. Table II summarizes the reduction of 3.00 g (18 mmol) of the enone **7** with a MeOH solution of the complex **9b** and HOAc. The crude product (2.63 g) was distilled to separate 2.43 g (81%) of ketone **8a**, bp 87.5–88° (10 mm), $n^{25}D$ 1.4223 (lit.[8a] $n^{25}D$ 1.4217), that was identified with an authentic sample by comparison of ir spectra. None of the corresponding dihydro dimer[8a] was detected (glpc). For analysis of reaction mixtures in this case, cumene was employed as an internal standard. The glpc (Carbowax 20 M on Chromosorb P) retention times follow: cumene, 13.6 min; ketone **8a**, 21.3 min; and ketone **7**, 25.1 min.

A comparable reduction of 3.00 g (18 mmol) of the enone **7**, in the presence of *n*-BuSH (Table II) yielded 3.80 g of a crude product that contained (glpc, Carbowax 20 M on Chromosorb P) *n*-BuSH (retention time 2.0 min), the ketone **8a** (5.2 min), *n*-BuSSBu-*n* (17.0 min), the ketone **41** (32.0 min), and the ketone **40** (36.3 min). Partial distillation of this mixture in a short-path still separated 0.71 g (23%) of the ketone **8a**, identified with an authentic sample by comparison of ir, nmr, and mass spectra. The residue (2.60 g) from this distillation contained (glpc) the two ketones **41** (~45%) and **40** (~55%) but none of the dihydro dimer was detected. Collected (glpc) samples of the ketones **40** and **41** were identified with subsequently described authentic samples by comparison of ir and nmr spectra. As a control experiment, a solution of the enone **7**, the diamine **1**, *n*-BuSH, and HOAc in MeOH was stirred at 25° for 13 hr and then subjected to the usual isolation and analysis. The crude neutral product contained the starting enone **7**, *n*-BuSSBu-*n*, and the β-keto sulfide **40**, but none of the α-keto sulfide **41** was detected. A collected (glpc) sample of the sulfide **40** was identified with a subsequently described sample by comparison of glpc retention times and ir and mass spectra. To be certain that the α-keto sulfide **41** present in the reaction mixtures did not result from a Cr(III)-catalyzed addition of *n*-BuSH to the enone **14**,[18] a solution of 1.5 mmol of the enone **7**, the complex **9b** from 3.0 mmol of $Cr(OAc)_2$ and 8.0 mmol of the diamine **1**, and 7.4 mmol of HOAc in 4 ml of MeOH was stirred at 25° for 9 hr. The resulting solution of reduced ketone **8a** and Cr(III) species was treated with 4.4 mmol of *n*-BuSH, 3.3 mmol of HOAc, 1.5 mmol of enone **7**, and 2 ml of MeOH and then stirred for 13 hr at 25°. After the usual isolation procedure, the crude neutral product contained (glpc) the ketone **8a**, the enone **7**, *n*-BuSSBu-*n*, and the β-keto sulfide **40** but none of the α-keto sulfide **41** was detected.

B. In DMF Solution. A reduction of the enone **7** with the $Cr(ClO_4)_2$–diamine **1** complex in aqueous DMF (Table II) afford-

ed a mixture of the ketone **8a** (72% yield) and the enone **7** (4% recovery). Collected (glpc) samples of ketones **7** and **8a** were identified with authentic samples by comparison of glpc retention times and ir spectra. When a comparable reduction was attempted in the absence of the diamine **1**, 91% of the enone **7** was recovered and no reduced ketone **8a** was detected.[9]

A similar reaction was performed with 0.97 mmol of ketone **7**, 2.6 mmol of $Cr(ClO_4)_2$, 6.57 mmol of *N,N*-diethylethanolamine (**5**), 5 ml of H_2O, and 15 ml of DMF. A green precipitate separated when the amino alcohol **5** was added. After the usual isolation, analysis (glpc) indicated a 96% yield of ketone **8a**. When the reaction was repeated with 1.05 mmol of ketone **7**, 2.60 mmol of $Cr(ClO_4)_2$, 5.7 mmol of *N,N,N',N'*-tetramethylenediamine (**3**), 5 ml of H_2O, and 22 ml of DMF, a brown precipitate was present throughout the reaction. Analysis (glpc) indicated the presence of the saturated ketone **8a** (24% yield) and the starting ketone **7** (71% recovery). In this case it seems likely that reduction is slow because of the insolubility of the Cr(II)-diamine **3** complex. A solution of 12 mmol of $Cr(ClO_4)_2$, 36 mmol of the diamine **1**, and 3.0 mmol of the enone **7** in 10 ml of DMF and 18 ml of D_2O was stirred at 25° for 2.5 hr and then subjected to the usual isolation procedure. Analysis (glpc with added cumene as an internal standard) indicated that the ketone **8** had been formed in 75% yield. The product was passed three times through a column packed with 10% KOH and 10% Carbowax 20 M on Chromosorb P[32] to exchange for hydrogen any deuterium present α to the carbonyl group of the ketone **8**. The resulting ketone **8** contained (mass spectral analysis) 63% d_0 species, 36% d_1 species, and 1% d_2 species.

Preparation of the Ketones 40 and 41. A mixture of 1.00 g (6.0 mmol) of the enone **7**, 5.4 g (60 mmol) of *n*-BuSH, and 0.33 (2 mmol, added in portions during the reaction) of azoisobutyronitrile was stirred at 25° and irradiated with a 150-W incandescent bulb. After a reaction period of 72 hr, analysis (glpc, Carbowax 20 M on Chromosorb P) indicated that all the enone **7** had been consumed and the mixture contained *n*-BuSH (retention time 1.9 min), *n*-BuSSBu-*n* (9.6 min), and the ketone **40** (18.8 min); none of the isomeric ketone **41** was detected. When a neutral MeOH solution of the enone **7** and *n*-BuSH was stirred at 25° without an added radical initiator, none of either ketone **40** or **41** was detected. A collected (glpc) sample of the ketone **40** was obtained as a colorless liquid: $n^{25}D$ 1.4648; ir (CCl_4) 1710 cm^{-1} (C=O); nmr (CCl_4), δ 2.3–3.1 (5 H, m, CH_2CO, CH_2SCH) and 0.8–1.7 [(25 H, m, aliphatic CH including two 9 H singlets at 0.98 and 1.13 (*t*-Bu)]; mass spectrum *m/e* (rel intensity) 258 (M^+, <1), 111 (32), 95 (45), 58 (100), 57 (78), 43 (65), and 41 (26).

Anal. Calcd for $C_{15}H_{30}OS$: C, 69.76; H, 11.70. Found: C, 69.66; H, 11.64.

To a refluxing solution of 3.80 g (17 mmol) of powdered $CuBr_2$ in 18 ml of EtOAc was added a solution of 1.70 g (10 mmol) of the ketone **8a** in 8 ml of $CHCl_3$.[34] This addition was accompanied by separation of a white precipitate (CuBr). After the mixture had been refluxed with stirring for 3 hr, analysis (glpc, Carbowax 20 M on Chromosorb P) indicated the presence of both the ketone **8a** (retention time 3.3 min) and the bromo ketone **42** (8.5 min). An additional 0.67 g (3 mmol) of $CrBr_2$ was added and refluxing and stirring were continued for an additional 1 hr. The reaction mixture was filtered, and the filtrate was decolorized with charcoal, diluted with Et_2O, washed successively with aqueous $NaHCO_3$ and H_2O, dried, and concentrated. The residual liquid was distilled to separate 1.85 g (75%) of the bromo ketone **42** as a colorless liquid: bp 74–75° (3.5 mm); $n^{25}D$ 1.4602; ir (CCl_4) 1715 cm^{-1} C=O); nmr (CCl_4) δ 4.73 (1 H, d of d, J = 7.4 and 4.9 Hz, CHBr), 2.40 (1 H, d of d, J = 15.2 and 7.4 Hz, one of CH_2 protons), 2.12 (1 H, d of d, J = 15.2 and 4.9 Hz, one of CH_2 protons), 1.30 (9 H, s, *t*-Bu), and 0.95 (9 H, s, *t*-Bu); mass spectrum *m/e* (rel intensity), 251 and 249 (M^+, <1), 85 (30), 58 (33), 57 (92), and 43 (100).

Anal. Calcd for $C_{11}H_{21}BrO$: C, 53.02; H, 8.50; Br, 32.07. Found: C, 52.91; H, 8.49, Br, 31.91.

To a warm (80°) solution of 0.64 g (15 mmol) of LiCl and 5.11 g (30 mmol) of $CuCl_2 \cdot H_2O$ in 10 ml of DMF was added 2.00 g (12 mmol) of the ketone **8a**.[35] The resulting solution was heated to 80–90° for 5 hr and then partitioned between H_2O and Et_2O. The ethereal extract was washed with H_2O, dried over anhydrous Na_2SO_4, and concentrated. Distillation separated 1.01 g of a fraction, bp 71–73° (5 mm), containing (glpc, Carbowax 20 M on Chromosorb P) the chloro ketone **43** (retention time 6.5 min) contaminated with a small amount of starting ketone **8a** (3.0 min) and a second fraction, bp 73–74° (5 mm), $n^{25}D$ 1.4420, containing (glpc) the pure chloro ketone **43**: ir (CCl_4) 1720 cm^{-1} (C=O); nmr (CCl_4) δ 4.64 (1 H, d of d, J = 5.6 and 6.8 Hz, CHCl), 1.5–2.4 (2 H, m, CH_2), 1.23 (9 H, s, *t*-Bu), and 0.96 (9 H, s, *t*-Bu); mass spectrum *m/e* (rel intensity), 206 and 204 (M^+, <1), 85 (13), 58 (14), 57 (100), 43 (35), and 41 (13).

Anal. Calcd for $C_{11}H_{21}ClO$: C, 64.53; H, 10.34; Cl, 17.32. Found: C, 64.54; H, 10.33; Cl, 17.25.

To a boiling solution of 0.81 g (9 mmol) of *n*-BuSH and 0.32 g (8 mmol) of NaOH in 7 ml of EtOH was added, dropwise and with stirring, 1.00 g (5 mmol) of the chloro ketone **43**. The resulting mixture, from which a white precipitate separated, was refluxed with stirring for 10 min and then partitioned between saturated aqueous NaCl and Et_2O. The Et_2O solution was dried and concentrated to leave 1.24 g of crude product as a pale yellow liquid containing (glpc, Carbowax 20 M on Chromosorb P) the ketone **41** (retention time 17.2 min) accompanied by minor amounts of the ketone **8a** (3.1 min) and *n*-BuSSBu-*n* (5.2 min). A collected (glpc) sample of the ketone **41** was obtained as a colorless liquid: $n^{25}D$ 1.4642; ir (CCl_4), 1690 cm^{-1} (C=O); nmr (CCl_4) δ 3.66 (1 H, d of d, J = 3.4 and 1.2 Hz, CHS), 1.2–2.6 (17 H, m, CH_2 and *t*-Bu singlet at 1.24), 0.7–1.0 (12 H, CH_3 and *t*-Bu singlet at 0.85); mass spectrum *m/e* (rel intensity) 258 (M^+, 3), 173 (16), 117 (65), 58 (40), 57 (57), and 43 (100).

Anal. Calcd for $C_{15}H_{30}OS$: C, 69.76; H, 11.70; S, 12.41. Found: C, 69.88; H, 11.84; S, 12.31.

Repetition of this reaction with the bromo ketone **42** afforded a crude product containing (glpc, Carbowax 20 M on Chromosorb P) primarily the ketone **8a** (retention time 3.0 min) and *n*-BuSSBu-*n* (9.5 min) accompanied by minor amounts of the starting bromo ketone **42** (8.5 min) and the ketone **41** (16.8 min). Collected (glpc) samples of *n*-BuSSBu-*n* and the ketones **8a** and **41** were identified with authentic samples by comparison of glpc retention times and mass spectra.

Reduction of the Ketone 13. A. Catalytic Hydrogenation. A MeOH solution of the ketone **13** was hydrogenated for 1 hr at 25° and 1 atm H_2 pressure over a 5% Pt/C catalyst to yield 94% of the ketone **23**: bp 74–74.5° (16 mm); $n^{25}D$ 1.4458 [lit.[36] bp 80.5° (30 mm)]; ir (CCl_4) 1710 cm^{-1} (C=O); nmr (CCl_4), δ 1.4–2.4 (8 H, m, CH_2), and 0.98 (6 H, s, CH_3); mass spectrum *m/e* (rel intensity) 126 (M^+, 30), 83 (100), 57 (33), 55 (51), 43 (35), and 41 (23).

B. With the Cr Complex 9b. Reduction of 5.0 g (40 mmol) of the enone **13** with a MeOH solution of Cr complex **9b** and HOAc (Table II) afforded 430 mg of crude neutral product as a yellow oil that was diluted with hexane and cooled to separate 85 mg of the crude solid dihydro dimer **24**. Recrystallization from hexane afforded 68 mg (2.7%) of one epimer of the dihydro dimer **24** as white prisms: mp 144–145°; recrystallization raised the melting point to 144.5–146.5°; ir (CCl_4), 1710 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.3–2.7 (14 H, m, CH and CH_2), 1.12 (6 H, s, CH_3), and 0.92 (6 H, s, CH_3); mass spectrum *m/e* (rel intensity), 250 (M^+, <1), 58 (49), and 43 (100). *Anal.* Calcd for $C_{16}H_{26}O_2$: mol wt, 250.1933. Found: 250.1931.

Anal. Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 76.46; H, 10.41.

A portion of the crude neutral reaction product (mixed with 1-phenyloctane as an internal standard) contained (glpc, Carbowax 20 M on Chromosorb P, apparatus calibrated with known mixtures) ketone **45** (retention time 5.0 min, 0.4% yield), ketone **23** (8.4 min, 4% yield), unchanged enone **13** (11.3 min, 0.9% recovery), and 1-phenyloctane (25.8 min). A collected (glpc) sample of the ketone **23** was identified with an authentic sample by comparison of glpc retention times and ir spectra and a collected (glpc) sample of ketone **45** was identified with an authentic sample by comparison of glpc retention times and mass spectra: *m/e* (rel intensity) 126 (M^+, 83), 111 (28), 83 (100), 69 (80), 57 (32), 56 (72), 55 (55), 42 (51), and 41 (60).

A comparable reduction of 3.00 g (24 mmol) of the enone **13** in the presence of *n*-BuSH (Table II) afforded a crude product containing (glpc, Carbowax 20 M on Chromosorb P) the ketone **23** (retention time 10.0 min) and *n*-BuSSBu-*n* (15.5 min); neither of the ketones **13** nor **45** (4.8 min) was detected in the crude product. Fractional distillation of the crude product separated 0.54 g (18%) of the ketone **23**, bp 64–64.5° (5 mm), $n^{25}D$ 1.4458, that was identified with the previously described sample by comparison of glpc retention times and ir and nmr spectra. The residue (1.42 g) from this distillation contained (glpc, Carbowax 20 M on Chromosorb P) two higher boiling components, a minor component thought to be ketone **39** (*ca.* 3%, retention time 23.2 min), and the ketone **38** (*ca.* 97%, 35.5 min). A collected (glpc) sample of the

minor component **39** had the following mass spectrum: *m/e* (rel intensity) 214 (M^+, 8), 126 (41), 70 (13), 68 (15), 58 (61), 55 (17), 43 (100), and 41 (16). Attempts to collect (glpc) a pure sample of the ketone **38** afforded a mixture (ir and nmr analysis) of the ketone **38** and the unsaturated ketone **13** (from elimination of *n*-BuSH from **38**): ir (CCl_4) 1715 (C=O) and 1680 cm^{-1} (conjugated C=O). Comparison of the ir, nmr, and mass spectra of this collected material with the spectra of the subsequently described authentic ketone **38** provided compelling evidence for the presence of ketone **38** in the reaction mixture.

To obtain an authentic sample of the ketone **38**, a mixture of 2.00 g (16 mmol) of the ketone **13**, 14.40 g (160 mmol) of *n*-BuSH, and 0.82 g (5 mmol) of azoisobutyronitrile was stirred at 25° and irradiated with a 150-W incandescent bulb for 72 hr. The resulting solution was concentrated under reduced pressure and then diluted with hexane and cooled at −78° to precipitate the unchanged azoisobutyronitrile. The supernatant liquid was concentrated and then fractionally distilled to separate 0.52 g of fractions, bp 84–100° (1 mm), $n^{25}D$ 1.4868–1.4895, followed by 0.65 g of the ketone **38**: bp 100–102° (1 mm); $n^{25}D$ 1.4906; ir (CCl_4) 1710 cm^{-1} (C=O); nmr (CCl_4) δ 2.0–3.2 (7 H, m, CH_2COCH_2 and $CHSCH_2$), 1.2–2.0 (6 H, m, CH_2), and 0.8–1.2 (9 H, m, CH_3 groups including singlets at 0.89 and 1.10); mass spectrum *m/e* (rel intensity) 214 (M^+, 37), 125 (85), 83 (35), 69 (70), 58 (54), 56 (20), 55 (52), 43 (100), and 41 (40). *Anal.* Calcd for $C_{12}H_{22}OS$: mol wt, 214.1391. Found: 214.1396.

Anal. Calcd for $C_{12}H_{22}OS$: C, 67.23; H, 10.35; S, 14.96. Found: C, 67.16; H, 10.33; S, 14.87.

Reduction of the Ketone 12. Reduction of 4.00 g (32 mmol) of the enone **12** with a MeOH solution of the Cr complex **9b** and HOAc (Table II) gave a crude neutral product containing (glpc, Carbowax 20 M on Chromosorb P) the ketone **21** (retention time 7.5 min) and a small amount of the starting ketone **12** (9.5 min). Fractional distillation separated 0.80 g (20%) of the ketone **21**, bp 80–81.5° (12 mm) (lit.[36] bp 173–176°), that solidified on standing: mp 41–42° (lit.[36] mp 43–44.5°); ir (CCl_4) 1710 cm^{-1} (C=O); nmr (CCl_4) δ 2.28 (4 H, t, J = 7.5 Hz, CH_2CO), 1.66 (4 H, t, J = 7.5 Hz, CH_2), and 1.10 (6 H, s, CH_3); mass spectrum *m/e* (rel intensity) 126 (M^+, 2), 72 (4), 58 (40), 43 (100), and 42 (6).

The residue from this distillation was triturated with hexane to separate 85 mg (2%) of one epimer of the dihydro dimer **22**, mp 127–133°. Recrystallization from hexane afforded the pure epimer of diketone **22** as white needles: mp 137–138°; ir (CCl_4) 1715 cm^{-1} (C=O); nmr ($CDCl_3$) δ 2.0–2.8 (8 H, m, CH_2CO), 1.2–2.0 (6 H, m, CH_2 and CH), 1.17 (6 H, s, CH_3), and 1.13 (6 H, s, CH_3); mass spectrum *m/e* (rel intensity) 250 (M^+, 24), 179 (17), 126 (45), 125 (100), 97 (25), 83 (72), 70 (54), 69 (46), 57 (22), 56 (48), 55 (77), 53 (23), 43 (31), and 41 (37).

Anal. Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 76.71; H, 10.53.

Repetition of this reaction in the presence of *n*-BuSH (Table II) gave a crude product containing (glpc, Carbowax 20 M on Chromosorb P) *n*-BuSH (retention time 2.0 min), the ketone **21** (8.3 min), a very small amount of the starting ketone **12** (10.5 min) and *n*-BuSSBu-*n* (13.6 min). Fractional distillation of the crude product separated 1.87 g (47%) of the ketone **21**, bp 74–75.5° (10 mm), contaminated (glpc) with *ca.* 5% of *n*-BuSSBu-*n*. The residue (1.56 g) from this distillation contained (glpc, Carbowax 20 M on Chromosorb P) a component believed to be ketone **37** (*ca.* 15%, retention time 30.6 min) and the ketone **36** (*ca.* 85%, 44.5 min). A collected (glpc) sample of the minor component **37** had the following spectral properties: ir (CCl_4) 1710 cm^{-1} (C=O); nmr (CCl_4) δ 1.3–3.7 (13 H, m, CH and CH_2) and 0.9–1.3 (9 H, m, CH_3 including two 3 H singlets at 1.12 and 1.18); mass spectrum *m/e* (rel intensity) 214 (M^+, 7), 127 (40), 75 (30), 63 (48), 60 (16), 43 (100), and 41 (16). Attempts to collect (glpc) the major product afforded a mixture (ir and nmr analysis) of the ketone **36** and the unsaturated ketone **12** (from elimination of *n*-BuSH), ir (CCl_4) 1710 (C=O) and 1685 cm^{-1} (conjugated C=O). Comparison of the ir, nmr, and mass spectra of this collected material with the spectra of the subsequently described authentic sample of the ketone **36** has led us to conclude that the ketone **36** is present in the reaction mixture.

An authentic sample of ketone **36** was obtained by the previously described procedure using 3.00 g (24 mmol) of the ketone **12**, 21.0 g (240 mmol) of *n*-BuSH, and 1.31 g (8 mmol) of azoisobutyronitrile. Fractional distillation of the crude product separated 1.14 g of fractions, bp 45–122° (1.8 mm), and 1.15 g of a fraction, bp 122–126° (1.8 mm), $n^{25}D$ 1.4920, containing (ir analysis) mainly the ketone **36**. Redistillation afforded the pure ketone **36**: bp 114–115° (1.4 mm); $n^{25}D$ 1.4961; ir (CCl_4) 1710 cm^{-1} (C=O); nmr (CCl_4) δ 2.1–2.9 (7 H, m, $CHSCH_2$ and CH_2COCH_2), 1.3–1.9 (6 H, m, CH_2), and 0.9–1.3 (9 H, m, CH_3 including singlets at 1.10 and 1.18); mass spectrum *m/e* (rel intensity) 214 (M^+, 13), 125 (30), 58 (50), and 43 (100). *Anal.* Calcd for $C_{12}H_{22}OS$: mol wt, 214.1391. Found: 214.1396.

Anal. Calcd for $C_{12}H_{22}OS$: C, 67.23; H, 10.35; S, 14.96. Found: 67.04; H, 10.31; S, 14.82.

After a solution of the Cr(II)–NH_3 complex, from 56 mmol of $Cr(OAc)_2$ and 560 mmol of aqueous 28% NH_3, and 16 mmol of the ketone **12** in 44 ml of MeOH had been stirred at 25–30° for 3.5 hr, it was subjected to the usual isolation procedure. Distillation afforded 0.61 g (30%) of a mixture (glpc) of ketones **21** (*ca.* 68%) and **12** (*ca.* 32%). The residue from this distillation was triturated with hexane to separate 0.11 g (5%) of the crude dihydro dimer **22**, mp 128–131°. When this reaction was performed with 56 mmol of $Cr(OAc)_2$, 16 mmol of ketone **12**, and 50 ml of aqueous 28% NH_3, with no added cosolvent (MeOH),[5b] the volatile materials in the crude product (1.12 g) were the ketones **21** (*ca.* 37%) and **12** (*ca.* 63%); 92 mg of the crude dihydro dimer **22**, mp 130–132°, was also isolated.

To learn how rapidly the ketone **12** reacted with the nitrogen-containing ligands in the absence of Cr salts, a solution of 1.24 g (10 mmol) of the ketone **12**, 4.86 g (81 mmol) of the diamine **1**, and 319 mg of 1-phenyloctane (an internal standard) in 20 ml of MeOH was stirred at 25° for 30 min and subjected to the usual isolation procedure. The recovered neutral material contained (glpc, Carbowax 20 M on Chromosorb P) the enone **12** (retention time 6.7 min, 31% recovery) and 1-phenyloctane (12.7 min). When the same experiment was performed with 1.24 g (10 mmol) of the ketone **12**, 15 g of aqueous 28% NH_3, and 1-phenyloctane in 10 ml of MeOH, 45% of the ketone **12** was recovered.

A solution of 520 mmol of the diamine **1**, 190 mmol of *n*-BuSH, 320 mmol of HOAc, and 64 mmol of the enone **12** in 128 ml of MeOH was stirred at 25° for 12 hr and then subjected to the usual isolation procedure. The crude neutral product contained (glpc) the enone **12**, *n*-BuSSBu-*n*, and the β-keto sulfide **36**, but none of the component believed to be the α-keto sulfide **37** was detected. Fractional distillation separated 0.83 g of early fractions, bp 90–132° (3.5 mm), containing the three components noted above and 11.2 g of fractions, bp 132–134.5° (3.5 mm), that contained (glpc and ir analysis) the pure β-keto sulfide **36**.

Registry No.—**7**, 1653-94-7; **8a**, 40239-53-0; **10**, 78-59-1; **11**, 1196-55-0; **12**, 1073-13-8; **13**, 4694-17-1; **14a**, 700-77-6; **15a**, 1579-21-1; **17** isomer A, 50987-69-4; **17** isomer B, 4994-12-1; **19a**, 470-99-5; **19b**, 50987-46-7; **20**, 15466-96-3; **21**, 4255-62-3; **22**, 5020-04-2; **23**, 2979-19-3; **24**, 50987-47-8; **36**, 50987-48-9; **37**, 50987-49-0; **38**, 50987-50-3; **40**, 50987-51-4; **41**, 50987-43-4; **42**, 50987-44-5; **43**, 50987-45-6; **45**, 4694-12-6; *n*-BuSSBu-*n*, 629-45-8; *n*-PrSSPr-*n*, 629-19-6.

References and Notes

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(13) Since the aqueous 70% $HClO_4$ and the diamine **1** used in these reactions were not deuterated, the ratio of D^+ donor:H^+ donor in these reactions was ca. 4:1.
(14) Although it is clear from earlier studies[4c,10] that the Cr(II) species is present as a bis en complex, the Cr(III) species may be present as either $Cr(en)_3^{3+}$ or $Cr(en)_2(ligand)_2^{3+}$, since the bis and tris en complexes of Cr(III) appear to be of comparable stability [see C. L. Rollinson and J. C. Bailar, Jr., *Inorg. Syn.*, **2**, 196, 200 (1946)]. Earlier polarographic studies[10c] of reduction of $Cr(en)_3^{3+}$ in aqueous solution have indicated that electrode process observed is $Cr(en)_3^{3+} + e \rightleftarrows Cr(en)_3^{2+} \rightleftarrows Cr(en)_2(ligand)_2^{2+} + en$. This process exhibited "pseudo-reversible" behavior in alkaline solution at relatively high en concentrations. In our studies starting with preformed $Cr(en)_2(ligand)_2$ and low concentrations of en we believe we are observing only the reversible electron transfer process: $Cr(en)_2(ligand)_2^{2+} \rightleftarrows Cr(en)_2(ligand)_2^{3+} + e$.
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A New Ring Expansion Procedure. VI. The Decomposition of the Magnesium Salts of Some 1-(α-Bromobenzyl)-1-cycloalkanols and Bicycloalkanols

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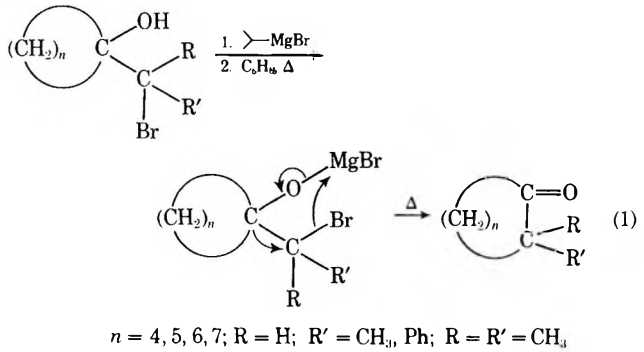
The results of the new ring expansion procedure applied to 2-methylcyclopentanone, 2-methylcyclohexanone, camphor, and bicyclo[2.2.2]octanone-2 are presented and discussed. Particular attention is afforded to the factors affecting product distribution. Each ketone was converted to its corresponding 2-phenyl-substituted ring-enlarged ketone by the decomposition of the magnesium salt from the 1-(α-bromobenzyl)-1-cycloalkanol.

Previously published papers[1] describe a new and relatively simple procedure by which one may achieve a ring enlargement (eq 1). The bromohydrins were prepared from olefins by treatment with aqueous *N*-bromosuccinimide, or ketones by reaction with benzylmagnesium chloride followed by a free-radical bromination.[1] Ring-enlarged ketones of reasonable purity were obtained in overall fair yields.



(1)

$n = 4, 5, 6, 7$; R = H; R′ = CH_3, Ph; R = R′ = CH_3

The studies of Geissman and Akawie[2] have mechanistically classed the rearrangement as a pinacol type involving a migration to an incipient electron-deficient carbon atom produced from an electrophilic attack by magnesium on the halogen atom (eq 1). A high degree of carbonium ion character is involved in the transition state, since they observed that secondary and tertiary halides rearrange regardless of the migrating group but primary halides only rearrange when a good migrating group is involved.

The results of the ring-enlargement procedure applied to 2-methylcyclopentanone, 2-methylcyclohexanone, camphor, and bicyclo[2.2.2]octanone-2 are presented and dis-

cussed. Each ketone was converted to the 2-phenyl-substituted ring-enlarged ketone by the decomposition of the magnesium salt from the 1-(α-bromobenzyl)-1-cycloalkanol.

Results and Discussion

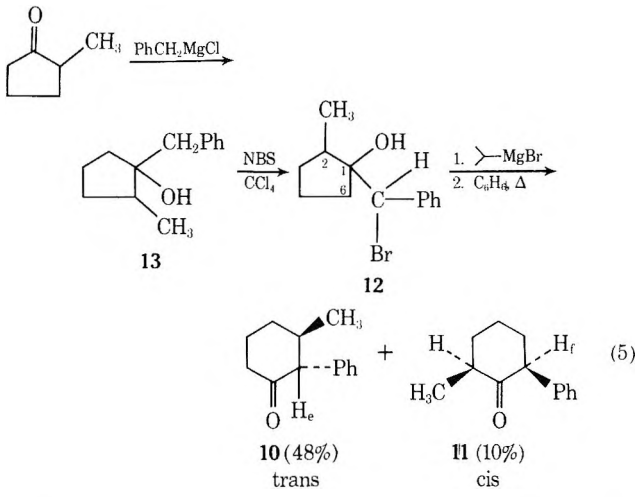
1,8,8-Trimethyl-3-phenyl[3.2.1]bicyclooctanone-2 (3) and 1,8,8-Trimethyl-2-phenyl[3.2.1]bicyclooctanone-3 (4) from Camphor and 3-Phenyl[3.2.2]bicyclononanone-2 (5) and 2-Phenyl[3.2.2]bicyclononanone-3 (6) from Bicyclo[2.2.2]octanone-2. The bromohydrins[3] 2 and 8 were prepared as shown (eq 2 and 3) and the indicated structures were based upon ir and nmr spectra. The conversion of 2 and 8 to their magnesium salts, followed by decomposition, afforded the ketones 3 and 4 in overall 52 and 23% yields, and 5 and 6 in overall yields of 43 and 20%, respectively (based on 1 and 7). The products 3 and 4 were separated by column chromatography, and the structures assigned were based upon elemental analysis, deuterium exchange and the ir and nmr spectra. The nmr signal at τ 6.45, a broad triplet, was ascribed to H_a in 3. The treatment of 3 with trifluoroacetic acid-*d* revealed that only H_a was exchanged.[4] The benzyl hydrogen singlet signal at τ 6.53 was ascribed to H_b in 4. The ketone 4 readily formed the 2,4-dinitrophenylhydrazone derivative, whereas 3 did not even under coercing conditions. These results, explained from steric considerations, were also consistent with the structures assigned for 3 and 4. The products 5 and 6 were separated by fractional crystallization and column chromatography and the structures assigned were based upon elemental analysis and ir and nmr spectra. The benzyl proton in 5 (H_c) appeared as two doublets at τ 6.0 and 6.2, and the benzyl proton in 6 (H_d) appeared as a broad singlet at τ 6.35.

Previous studies have observed that many reaction types involving alkyl migrations to incipient electron-deficient centers (carbon[5] and nitrogen[6]) in the norbornyl system preferred methylene over methine migration and at the same time involved generation of a relatively unstable boat transition state. Our results with camphor (eq 2) and that previously reported with 2-norbornanone[1b] (eq 4) are no exceptions. A new factor to account for the preference for methylene migration was offered by Sauers,[7,8] namely, that because of the eclipsing of the groups on C-2 and C-3 a greater relief of torsional strain accompanies C-2–C-3 bond migration as opposed to C-1–C-2 bond migration, which would entail much less relief of torsional strain, since the groups on C-2 and the bridgehead group at C-1 are disposed at dihedral angles of about 44 and 79°. The justification for the predominance of 3 over 4 may lie then in two favorable features in the transition state for 3 as opposed to 4, namely, a more stable pseudo-chair conformation (while that for 4 would be a boat) and a greater relief of torsional strain accompanying C-2–C-3 bond migration (**3a**, eq 2). The production of the minor product 4 may be ascribed to a somewhat offsetting favorable electronic effect accompanying C-1–C-2 bond migration (tertiary carbon). Similarly, the production of only 9 (eq 4) may be explained by invoking Sauers'[7] new factor.

In the bicyclooctyl system the results also dictate that electronic control is not a primary factor in determining the product distribution (eq 3). However, since, in the bicyclooctyl system the groups on C-2 and C-3 are eclipsed,[9] a greater relief of torsional strain accompanies C-2–C-3 bond migration as opposed to C-1–C-2 bond migration, which would entail much less relief of torsional strain because the groups on C-2 and the hydrogen at C-1 are staggered. Therefore the product distribution (5 and 6) may also be governed by the extent of relief of torsional strain[8] in the respective transition states. The production of 6 may be due to the fact that a twisting in the flexible bicyclooctyl system reduces the magnitude of torsional strain relative to the norbornyl system where no product resulting from C-1–C-2 bond migration was isolated[10,11] (eq 4).

In summary, the product distribution in the bicyclic systems studied here and previously[1b,d,12] appears to be governed primarily by relief of torsional strain[8] with electrical and boat–chair considerations playing a minor role.[1b,d,12]

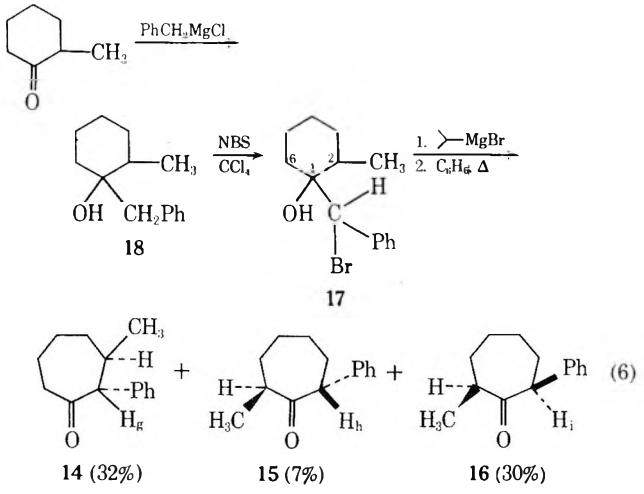
3-Methyl-2-phenylcyclohexanone (10) and 2-Methyl-6-phenylcyclohexanone (11) from 2-Methylcyclopentanone. The bromohydrin[3] 12 was converted to the magnesium salt and decomposed to produce the ketones 10 and 11 in overall 48 and 10% yields, respectively (based upon 13) (eq 5). The ketones[13] 10 and 11 were separated by column chromatography and the structures assigned for 10 and 11 were based upon elemental analysis and ir and nmr spectra. The benzyl hydrogen in 10 (H_e) appeared as a doublet at τ 6.95 and the benzyl hydrogen in 11 (H_f) appeared as a broad quartet at τ 6.50.



(5)

The major product **10** arises from the migration of the more highly substituted bond, which is what one would expect from electronic control of the product distribution in this type of rearrangement.[2] A similar result was obtained from the Tiffeneau–Demjanov ring enlargement of 2-methyl-1-aminomethylcyclopentanol, which yielded 3-methylcyclohexanone.[14] To attribute the product distribution as being solely governed by electronic control seems somewhat naive; undoubtedly conformational and steric considerations play a role.[11]

***trans*-3-Methyl-2-phenylcycloheptanone (14) and *cis*- and *trans*-2-methyl-7-phenylcycloheptanone (16 and 15) from 2-Methylcyclohexanone.** The bromohydrin[3] **17** was prepared as previously described and was converted to the ring-enlarged ketones **14, 15,** and **16** in overall 32, 7, and 30% yields, respectively (based upon **18**) (eq 6). The mix-



(6)

ture of products **14, 15,** and **16** obtained could be only partially separated by column chromatography. That the original mixture contained only **14, 15** and **16** was established from the following: ir spectrum; elemental analysis; the nmr spectrum showed a doublet at τ 6.78 (H_g, **14**) and the methyl group signal as a doublet at τ 9.19; the benzyl hydrogens in **15** and **16** appeared at τ 6.10 (H_h) as a weak, broad multiplet and at τ 6.36 (H_i) as a broad quartet, the methyl groups both appeared as doublets at τ 9.02 and 9.06, respectively; when the mixture was treated with trifluoroacetic acid-*d* at 75° for 24 hr the nmr spectrum showed that only all the signals attributed to the benzyl hydrogens were absent. The relative composition (eq 6) for each ketone was obtained from the nmr spectrum from the value of the ratio of the area for each benzyl hydrogen to one-fifth of the total area for the phenyl hydrogens. The yields so obtained were identical with those obtained from the value of the ratio of the area for each benzyl hydrogen to one-third of the total area for the methyl hydrogens. The yields, when calculated from the nmr integrations with partially separated samples (pure **14** separated) obtained from column chromatography, were in good agreement with the previously obtained values. The ketone **14,** because of its more accessible carbonyl group, could also be separated by the selective conversion to the semicarbazone. The presence of a doublet at τ 6.74 (H_g, **14**) confirmed it to be the semicarbazone of **14.** The cis–trans relationship between **15** and **16** was established from an acid-catalyzed equilibration of the mixture, the nmr spectrum of which revealed that the only change compared to the nmr spectrum of the untreated mixture was an almost complete conversion of **15** to **16.** Both signals for the benzyl proton and methyl protons for **15** vanished while those for **16** became more intense.[15]

The products which result from the migration of the more highly substituted C-1–C-2 bond and the less substituted C-1–C-6 bond are produced in almost equal amounts. This appears to be a characteristic feature of the 2-methylcyclohexyl system: Tchoubar[14] reported obtaining a mixture of 2-methyl- and 3-methylcycloheptanones from the Tiffeneau–Demjanov ring expansion with 2-methyl-1-aminomethylcyclohexanol; Gutsche and Chang[16] reported a mixture of 2-methyl- and 3-methylcycloheptanones in equal amounts from the diazomethane ring expansion of 2-methylcyclohexanone. Our results (eq 6) and those reported[14,16] indicate that the product distribution cannot be solely governed by electrical effects; undoubtedly conformational and steric considerations play a salient role.

In the simple cyclic systems electrical, conformational, and steric considerations play a role with the latter two varying in importance with the particular ring system involved.

Experimental Section[17]

1-(α-Bromobenzyl)-1-cyclo- and -bicycloalkanols were prepared by the dropwise addition of an ether solution of the ketone to benzylmagnesium chloride, after which the mixture was refluxed for 24 hr, except for alcohol **18** which was refluxed for 3 hr. The reaction mixture was decomposed with a saturated NH_4Cl solution and the organic layer was separated, washed with water, and dried ($MgSO_4$). The solvent was removed under vacuum (rotary evaporator) and the residue was distilled.

The alcohol **1** was prepared with 76 g (0.50 mol) of camphor in 100 ml of ether and 75.6 g (0.60 mol) of benzyl chloride, 16 g (0.66 mol) of magnesium, and 300 ml of ether. Distillation[18] yielded 88.4 g (0.36 mol, 73%) of **1**: bp 112–114° (0.3 mm) [lit.[19] bp 162–163° (6 mm)]; ir 3560 cm^{-1}; nmr τ 7.32 (s, $-CH_2Ph$).

The alcohol 13 was prepared with 49.0 g (0.50 mol) of 2-methylcyclopentanone in 100 ml of ether and 75.6 g (0.60 mol) of benzyl chloride, 16 g (0.66 mol) of magnesium, and 300 ml of ether. Distillation yielded 80.0 g (0.43 mol, 84%) of **13**: bp 88–89° (0.75 mm); ir 3525 cm^{-1}.

Anal. Calcd for $C_{13}H_{18}O$: C, 82.05; H, 9.53. Found: C, 81.95; H, 9.66.

The alcohol 18 was prepared with 33.6 g (0.30 mol) of 2-methylcyclohexanone in 80 ml of ether and 50.4 g (0.40 mol) of benzyl chloride, 11 g (0.45 mol) of magnesium, and 250 ml of ether. Distillation produced 49.4 g (0.24 mol, 81%) of **18**: bp 125–126° (2 mm) [lit.[20] bp 115° (0.8 mm)]; ir 3560 cm^{-1}.

The alcohol 7 was synthesized with 9.5 g (0.077 mol) of bicyclo[2.2.2]octanone-2[21] in 25 ml of ether and 12.6 g (0.10 mol) of benzyl chloride, 2.7 g (0.11 mol) of magnesium, and 90 ml of ether. Distillation afforded 15.2 g (0.074 mol, 90%) of **7**: bp 100–104° (0.05 mm); ir 3590 cm^{-1}; nmr τ 7.22 (s, $-CH_2Ph$).

Anal. Calcd for $C_{15}H_{20}O$: C, 83.28; H, 9.32. Found: C, 83. 29; H, 9.23.

1,7,7-Trimethyl-2-(α-bromobenzyl)-2-norbornanol (2). Into a flask was placed 24.4 g (0.10 mol) of **1**, 17.8 g (0.100 mol) of *N*-bromosuccinimide, 1 g of benzoyl peroxide, and 200 ml of CCl_4. The mixture was brought to reflux, at which time a vigorous reaction occurred. When the reaction subsided the mixture was refluxed for an additional 45 min. The mixture was cooled and the

succinimide was removed by suction filtration, after which the solvent was removed under vacuum (rotary evaporator). The residual oil isolated was used directly without purification:[3] ir 3550 cm^{-1}; nmr τ 4.83 [s, -C(**H**)(Br)(Ph)].

1,8,8-Trimethyl-3-phenylbicyclo[3.2.1]octanone-2 (3) and 1,8,8-Trimethyl-2-phenylbicyclo[3.2.1]octanone-3 (4). To an ice-cooled, stirred solution of **2** in 300 ml of anhydrous benzene, a solution of isopropylmagnesium bromide [from 14 g (0.11 mol) of isopropyl bromide, 2.9 g (0.12 mol) of magnesium, and 50 ml of ether] was added dropwise. After the addition the ice bath was removed and the solution was stirred at room temperature for 24 hr and then refluxed for 1 hr. The mixture was cooled and decomposed with a saturated solution of NH_4Cl. The organic layer was separated, washed with a 10% sodium carbonate solution and water, and finally dried ($MgSO_4$). The solvent was removed under reduced pressure (rotary evaporator). The residue was distilled twice, affording 18.0 g (0.075 mol, 75%) of a colorless oil: bp 115–116° (0.10 mm); ir 1710 cm^{-1} (C=O); nmr τ 6.53 [br s, O=CC(**H**)(Ph)], 6.45 [t, O=CC(**H**)(Ph)].

The mixture (**3** and **4**) (1.0 g) was chromatographed (25 g of Woelm acid-washed Alumina, Grade I) using pentane (100 ml), pentane–benzene (75% v/v, 100 ml), benzene (100 ml), and chloroform as eluents. The major product, **3**, was isolated in 70% yield as a waxy solid, mp 64.5–66°, and was equivalent to 12.6 g (0.052 mol, 52%) based upon **1**: ir (CCl_4) 1710 cm^{-1} (C=O); nmr τ 6.45 [t, O=CC(**H**)(Ph)], 2.75–3.20 (br m, phenyl hydrogens), and 9.04 (s, $-CH_3$ all). Two recrystallizations from pentane gave a solid, mp 66–67°.

Anal. Calcd for $C_{17}H_{22}O$: C, 84.25; H, 9.15. Found: C, 84.40; H, 9.19.

Several attempts to prepare the 2,4-DNP were fruitless.

The minor product, **4**, from the chloroform elution was isolated in 30% yield as a waxy solid, mp 70.5–73°, and was equivalent to 5.4 g (0.023 mol, 23%) based upon **1**: ir (CCl_4) 1710 cm^{-1} (C=O); nmr τ 6.53 [s, O=CC(H)(Ph)]. Two recrystallizations (pentane) yielded a solid, mp 78–79.5°.

Anal. Calcd for $C_{17}H_{22}O$: C, 84.25; H, 9.15. Found: C, 84.34; H, 9.12.

The 2,4-DNP of 1,8,8-trimethyl-2-phenylbicyclo[3.2.1]octanone-3, yellow needles (EtOH), had a melting point of 211–212°.

Anal. Calcd for $C_{23}H_{26}N_4O_4$: C, 65.38; H, 6.20; N, 13.26. Found: C, 65.28; H, 6.27; N, 13.30.

In another experiment 10 g (0.041 mol) of **3** (41% based upon **1**) was isolated directly from the initial distillate by successive recrystallizations from hexane.

Two 1-g samples of **3** were dissolved in a tenfold excess of trifluoroacetic acid and trifluoroacetic acid-*d*, respectively. The solutions were heated at 50° for 2 hr, neutralized with a 20% solution of sodium carbonate, and extracted with ether, and the ether was dried ($MgSO_4$). The solvent was removed and the products were crystallized from hexane: the nmr spectrum of the sample treated with CF_3CO_2H was identical with the nmr spectrum of untreated **3**; the nmr spectrum of the sample treated with CF_3CO_2D was also identical with that of untreated **3** except that the signals attributed to the benzyl hydrogen were absent.

2-(α-Bromobenzyl)bicyclo[2.2.2]octanol-2 (8) was prepared as described for **2** starting with 6.5 g (0.030 mol) of **7**, 5.7 g (0.030 mol) of *N*-bromosuccinimide, 0.1 g of benzoyl peroxide, and 75 ml of CCl_4. The reaction occurred after a 5-min induction period, after which the mixture was refluxed for 30 min. After removal of the solvent 9.6 g of solid remained: ir 3550 cm^{-1}; nmr τ 4.87 [s, -C(**H**)(Br)(Ph)].

3-Phenylbicyclo[3.2.2]nonanone-2 (5) and 2-Phenylbicyclo[3.2.2]nonanone-3 (6). To the crude product **8**, dissolved in 100 ml of benzene and cooled with an ice bath, 19.8 ml of a 1.52 *M* ethereal solution of isopropylmagnesium bromide[22] was added dropwise. The mixture was stirred for 20 min while in the ice bath, 40 min at room temperature, and 2 hr at reflux, after which it was worked up as before. After the solvent was removed there remained 6.85 g of a waxy, yellow solid. Trituration with pentane gave 1.50 g (0.0073 mol, 24% based upon **7**) of **5**: mp 101–104°; ir (CCl_4) 1710 cm^{-1} (C=O); nmr τ 6.10 [q, O=CC(H)(Ph)]. An analytical sample was prepared by subliming it twice at 90–95° (0.05 mm), mp 108–109.5°.

Anal. Calcd for $C_{15}H_{18}O$: C, 84.07; H, 8.47. Found: C, 84.18; H, 8.52.

Upon cooling the above pentane solution an additional 2.50 g of crystalline product was obtained, which nmr spectral analysis revealed to be a mixture of **5** and **6**. The mixture (2.50 g) was chromatographed (50 g of Woelm acid-washed Alumina, Grade I) using pentane (300 ml), pentane–benzene (75% v/v, 250 ml), pentane–benzene (50% v/v, 200 ml), benzene (200 ml), and chloroform (200 ml) as eluents. In this manner an additional 1.25 g of **5** was obtained resulting in an overall yield of 2.75 g (0.013 mol, 43% based upon **7**). In addition 1.25 g (0.0060 mol) of **6** was obtained (20% based on **7**): mp 48–51°; ir (CCl_4) 1708 cm^{-1} (C=O); nmr τ 6.35 [br s, O=CC(**H**)(Ph)]. An analytical sample of **6** was prepared by two sublimations at 65–70° (0.05 mm), mp 49.5–52°.

Anal. Calcd for $C_{15}H_{18}O$: C, 84.07; H, 8.46. Found: C, 83.93; H, 8.40.

2-Methyl-1-(α-bromobenzyl)-1-cyclopentanol (12) was prepared as described for **2** (0.100 mol of **13** employed). After removal of the solvent a light yellow oil remained: ir 3500 cm^{-1}; nmr τ 4.80 [s, -C(**H**)(Br)(Ph)].

3-Methyl-2-phenylcyclohexanone (10) and 2-Methyl-6-phenylcyclohexanone (11). The ring expansion of **12** was accomplished as for **2** except that the mixture was stirred at room temperature for 1 hr and refluxed for 15 min. The product was distilled twice, yielding 11.0 g (0.058 mol, 58% based upon **13**) of a mixture of **10** and **11**: bp 79–80° (0.05 mm); ir 1715 cm^{-1} (C=O); nmr τ 6.95 [d, O=C-C(**H**)(Ph)], 6.35–6.70 [br q, O=CC(**H**)(Ph)].

The mixture (1.0 g) was chromatographed (25 g of Woelm acid-washed Alumina, Grade I) using pentane (200 ml) and chloroform (200 ml) as eluents. The major product (from $CHCl_3$ eluent) **10** was isolated in 82% yield as a white, waxy solid, equivalent to 9.0 g (0.048 mol, 48% based upon **13**). Recrystallization from pentane gave **10**: mp 49.5–51.5°; ir ($CHCl_3$) 1700 cm^{-1} (C=O); nmr τ 6.95 [d, O=CC(**H**)(Ph)].

Anal. Calcd for $C_{13}H_{16}O$: C, 82.93; H, 8.57. Found: C, 82.73; H, 8.69.

The 2,4-DNP of 2-phenyl-3-methylcyclohexanone had a melting point of 150–151°, orange needles (EtOH).

Anal. Calcd for $C_{19}H_{20}N_4O_4$: C, 61.95; H, 5.47; N, 15.21. Found: C, 62.34; H, 5.47; N, 15.42.

The minor product (from pentane eluent) **11** was isolated in 18% yield as a waxy solid, equivalent to 2.0 g (0.010 mol, 10% based upon **13**). Recrystallization from pentane afforded pure **11**: mp 61–62°; ir ($CHCl_3$) 1690 cm^{-1} (C=O); nmr τ 6.35–6.70 [br q, O=CC(**H**)(Ph)]. The analytical sample melted at 62–62.5° (lit.[23] mp 51–52°).

Anal. Calcd for $C_{13}H_{16}O$: C, 82.93; H, 8.57. Found: C, 82.76; H, 8.77.

2-Methyl-1-(α-bromobenzyl)-1-cyclohexanol (17) was prepared as described for **2** on a 0.100-mol scale except that a vigorous reaction was not observed and the mixture was refluxed for 1 hr. The residual light yellow oil was used directly:[3] ir 3550 cm^{-1}; nmr τ 4.73 [d, -C(**H**)(Br)(Ph)].

***trans*-3-Methyl-2-phenylcycloheptanone (14) and *cis*- and *trans*-2-methyl-7-phenylcycloheptanone (16 and 15).** The ring enlargement was achieved following the procedure described for **2** except that the mixture was refluxed for 45 min and stirred at room temperature for 90 min. Vacuum distillation afforded 13.8 g of a light yellow oil: bp 128–133° (1.5 mm); ir 1720 cm^{-1} (C=O); nmr τ 6.10 (weak, br, benzyl hydrogen), 6.36 (br q, benzyl hydrogen), 6.78 (d, benzyl hydrogen), 9.02 (d, $-CH_3$), 9.06 (d, $-CH_3$), 9.19 (d, $-CH_3$), indicating a mixture of three isomers. An analytical sample of this mixture was prepared by distillation, bp 104–106° (0.15 mm).

Anal. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 82.90; H, 8.83.

The mixture (2.0 g) was chromatographed (100 g of Merck grade alumina) using hexane (250 ml), hexane–benzene (75, 50, and 25% v/v, respectively, 250 ml each), and benzene (500 ml) as eluents. In this manner 0.43 g of **14** was isolated as a colorless oil in the final 500 ml of benzene; the latter was equivalent to 3.0 g (0.015 mol, 15% based upon **17**), nmr τ 6.78 [d, O=CC(**H**)(Ph)]. A mixture (0.61 g) of **16** [nmr τ 6.36, br q, O=CC(**H**)(Ph)] and **15** [nmr τ 6.10, weak, br m, O=CC(**H**)(Ph)], which resisted further separation, was obtained as a colorless oil in the first 600 ml of eluent. The nmr spectrum of this mixture (**15** and **16**) indicated a composition of 0.48 g of **16** and 0.13 g of **15** which was equivalent to 3.3 g (0.016 mol, 16%) of **16** and 0.9 g (0.004 mol, 4%) of **15**, both yields based upon **17**. The yields were based on the ratio of the integration of the benzyl hydrogens to the total integration of the phenyl hydrogens.

The 2,4-DNP of *cis*-2-methyl-7-phenylcycloheptanone **(16)**[14] was prepared directly from the mixture (**15** and **16**), mp 152–153°, orange needles (EtOH).

Anal. Calcd for $C_{20}H_{22}N_4O_4$: C, 62.82; H, 5.80; N, 14.65. Found: C, 62.35; H, 5.88; N, 14.62.

The center portion of the chromatogram contained a mixture of all three components (0.96 g). The ratio of the areas for the ben-

zyl protons in the integration of the nmr spectrum indicated a composition of 0.49 g of **14**, 0.38 g of **16**, and 0.09 g of **15**. The overall yields therefore are 6.4 g (0.032 mol, 32%) of **14**, 6.0 g (0.030 mol, 30%) of **16**, and 1.4 g (0.0070 mol, 7%) of **15**, all based on **17**.

In a separate experiment, 0.30 g (0.0015 mol) of the initial distillate, 0.60 g of sodium acetate, 0.40 g (0.0036 mol) of semicarbazide HCl, 4 ml of water, and 7 ml of ethanol were combined. After standing for 7 days, 0.11 g (0.00043 mol, 28%) of 3-methyl-2-phenylcycloheptanone (**14**) was isolated from the mixture as its semicarbazone: mp 210.5–213°; nmr ($CDCl_3$) τ 6.74 (d, benzyl hydrogen). This represents a 20% yield based on **17**. Two recrystallizations from 42% aqueous ethanol yielded a solid, mp 218.5–219.5°.

Anal. Calcd for $C_{15}H_{21}N_3O$: C, 69.47; H, 8.16; N, 16.20. Found: C, 69.46; H, 7.96; N, 16.08.

Lastly, two 0.1-g aliquots of the initial mixture were combined with a fivefold excess of CF_3CO_2H and CF_3CO_2D, respectively. The samples were heated at 75° for 24 hr and cooled, and their nmr spectra were obtained: nmr (CF_3CO_2H) revealed that the only change in the spectrum[24] of this sample and the spectrum of the untreated initial mixture was a marked decrease in the intensity of the benzyl proton in **15**, τ 6.33, and a marked increase in the intensity of the benzyl proton in **16**, τ 6.55; nmr (CF_3CO_2D) revealed that the only change in the nmr spectrum of this sample and the spectrum of the untreated initial mixture was that signals attributed to the benzyl protons were almost absent. In a second and related experiment 1 g of the initial mixture was treated with 10 g of CF_3CO_2H for 24 hr at 75° and the product was isolated as described for **3**. The results were the same as above:[24] nmr τ 6.10 (br m, benzyl hydrogen of **15**, barely detectable), 6.36 (br q, benzyl hydrogen of **16**), and 6.78 (d, benzyl hydrogen of **14**).

Registry No.—**1**, 50986-74-8; **2**, 51016-54-7; **3**, 50986-99-7; **4**, 50987-00-3; **4** 2,4-DNP, 50987-01-4; **5**, 50986-75-9; **6**, 50986-76-0; **7**, 50986-77-1; **8**, 50986-78-2; **10**, 50987-02-5; **10** 2,4-DNP, 50987-03-6; **11**, 50987-04-7; **12**, 50986-79-3; **13**, 50986-80-6; **14**, 50987-05-8; **14** semicarbazone, 50987-06-9; **15**, 50987-07-0; **16**, 50987-08-1; **16** 2,4-DNP, 50987-09-2; **17**, 50986-81-7; **18**, 50986-82-8; camphor, 76-22-2; benzyl chloride, 100-44-7; 2-methylcyclopentanone, 1120-72-5; 2-methylcyclohexanone, 583-60-8; bicyclo[2.2.2]octanone-2, 2716-23-6; isopropyl bromide, 75-26-3.

References and Notes

(1) (a) A. J. Sisti, *J. Org. Chem.*, **33**, 453 (1968); (b) *Tetrahedron Lett.*, 5327 (1967); (c) *J. Org. Chem.*, **33**, 3953 (1968); (d) *ibid.*, **35**, 2670 (1970); (e) A. J. Sisti and M. Meyers, *ibid.*, **38**, 4431 (1973).

(2) T. A. Geissman and R. I. Akawie, *J. Amer. Chem. Soc.*, **73**, 1993 (1951).

(3) All bromohydrins herein were used directly without purification, since they were relatively unstable.

(4) The product **3** was treated in two experiments with trifluoroacetic acid and trifluoroacetic acid-*d* and the isolated product in each case was identical with **3** from the ring-expansion reaction (eq 2) (except for deuterium exchange which resulted with CF_3CO_2D). Thus the thermodynamically more stable isomer for **3**, and presumably **4**, was isolated directly from the expansion reaction. The structural assignments depicted (eq 2) would appear to be the more stable ones for **3** and **4**.

(5) R. R. Sauers and R. J. Tucker, *J. Org. Chem.*, **28**, 876 (1963).

(6) J. Berson and P. Reynolds-Warnhoff, *J. Amer. Chem. Soc.*, **86**, 595 (1964); J. Berson and D. Willner, *ibid.*, **86**, 609 (1964).

(7) R. R. Sauers and J. A. Beisler, *J. Org. Chem.*, **29**, 210 (1964).

(8) The principle of least motion may be another factor promoting C-2–C-3 bond migration over C-1–C-2 bond migration; more of the carbon atoms in the molecule are in motion and with a greater degree when the C-1–C-2 bond migrates than when the C-2–C-3 bond migrates.

(9) E. L. Eliel in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, p 125.

(10) The nitrous acid deamination of 2-aminomethyl[2.2.2]bicyclooctane has been reported to yield primarily 2-hydroxy[3.2.2]bicyclononane (70%), resulting from C-2–C-3 bond migration, compatible with the observations herein; see K. Alder, H. Krieger, and H. Weiss, *Ber.*, **88**, 144 (1955).

(11) Arguments for the predominance of one of the diastereoisomeric bromohydrins (**2**, **12**) can be presented. From that isomer, conformational and steric considerations for the preferred migration of one bond over the other can be offered (assuming the migrations to be trans and coplanar). Such a detailed mechanistic argument would be too ambitious for the data presented. One, however, cannot overlook these considerations as possible additional factors affecting the product distribution.

(12) A. J. Sisti, G. M. Rusch, and H. K. Sukhon, *J. Org. Chem.*, **36**, 2030 (1971).

(13) It has been demonstrated experimentally with a representative number of ring-enlarged ketones[1b,d,4] that under the reaction conditions the more stable isomers are isolated. The structures assigned for **10** and **11** would appear to be the more stable.

(14) B. Tchoubar, *Bull. Soc. Chim. Fr.*, 160 (1949).

(15) It is assumed that the cis isomer **16** is more stable than the trans isomer **15**. Recent evidence (M. Hanack, "Conformational Theory," Academic Press, New York, N. Y., 1965, pp 151 and 163) indicates that cycloheptanone probably exists in a twist chair conformation and it would seem reasonable that the methyl group in the equatorial position might be more stable, as in 2-methylcyclohexanone; thus the cis isomer **16** (phenyl equatorial) should be the more stable.

(16) C. Gutsche and C. Chang, *J. Amer. Chem. Soc.*, **84**, 2263 (1962).

(17) All melting points are uncorrected. Infrared spectra, all of pure liquid films unless otherwise stated, were determined with a Perkin-Elmer Model 257 Grating Infrared. The nmr spectra, in CCl_4 solutions unless otherwise specified, were determined with a Varian A-60 instrument.

(18) Initially heat was applied to the condenser to prevent the unreacted camphor, which sublimed, from obstructing the condenser. During the distillation of **1** the condenser was cooled in the usual manner.

(19) A. I. Shavrygin, *Zh. Obshch. Khim.*, **21**, 749 (1951).

(20) J. Cook and C. Hewett, *J. Chem. Soc.*, 62 (1936).

(21) Prepared by the oxidation of bicyclo[2.2.2]octanol-2 according to the procedure of Walborsky [A. Youssef, M. Baum, and H. Walborsky, *J. Amer. Chem. Soc.*, **81**, 4709 (1959)]. The alcohol was prepared from bicyclo[2.2.2]oct-5-en-2-yl acetate [J. Hine, J. Brown, L. Zalkow, W. Garden, and M. Hine, *J. Amer. Chem. Soc.*, **77**, 594 (1955)] by conversion to the unsaturated alcohol [H. Goering, R. Greiner, and M. Sloan, *ibid.*, **83**, 1391 (1961)] followed by reduction [K. Mislow and J. Berger, *ibid.*, **84**, 1956 (1962)].

(22) The Grignard was standardized by the procedure of Gilman [H. Gilman, E. Zoliner, and J. Dickey, *J. Amer. Chem. Soc.*, **51**, 1576 (1929)].

(23) R. Ireland and J. Marshall, *J. Org. Chem.*, **27**, 1615 (1962).

(24) The shift in τ values undoubtedly is due to a solvent effect (CCl_4 to CF_3CO_2H), and the values obtained for treated and untreated samples whose spectra were measured in CCl_4 were almost identical.

A New Synthesis of β,γ-Unsaturated Carbonyl Compounds[1]

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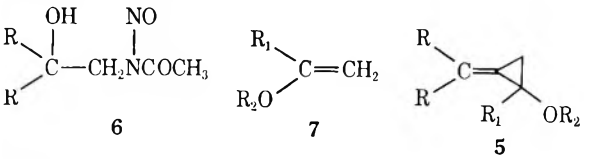
Treatment of 1-alkylidene-2-alkoxycyclopropanes with mercuric acetate in aqueous alcohol, followed by treatment of the vinylmercuric derivative thus produced with hydrogen sulfide, affords γ,γ-disubstituted β,γ-unsaturated carbonyl compounds, free from the corresponding α,β-unsaturated isomers, in high yields.

The ready availability of 1-alkylidene-2-alkoxycyclopropanes, **1**, from addition of alkylidene carbenes to vinyl ethers[3] made a study of the further reactions of this hitherto unavailable class of compounds of interest. In preliminary exploratory work, 1-cyclohexylidene-2-*tert*-butoxycyclopropane, **2**, was shown to yield the dimethyl acetal of 3-cyclohexylidenepropanal, **3**, on treatment with a cation-exchange resin in methanol, and 3-cyclohexylidenepropanal 2,4-dinitrophenylhydrazone, **4**, on treatment with 2,4-dinitrophenylhydrazine reagent.[4] All attempts to isolate 3-cyclohexylidenepropanal after acidic treatment of **2** failed. Because routes to β,γ-unsaturated carbonyl-con-

Table I
Synthesis of 1-Alkylidene-2-alkoxycyclopropanes[a]

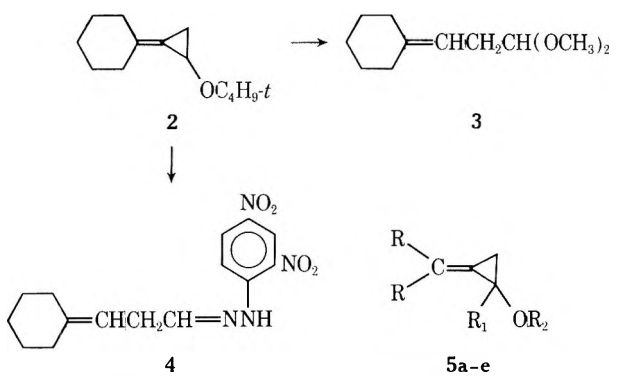


6 7 5

6	7	5[b]	Yield,[c] %
RR = $-(CH_2)_5-$, **6a** (37150-64-4)	$R_1 = R_2 = CH_3$ (116-11-0)	**5a** (51004-16-1)	64[d]
RR = $-(CH_2)_4-$, **6b** (51021-65-9)	$R_1 = R_2 = CH_3$	**5b** (51004-17-2)	66[e]
R = CH_3, **6c** (51021-66-0)	R_1 = Ph; $R_2 = CH_3$ (4747-13-1)	**5c** (51004-18-3)	35[e]
RR = $-(CH_2)_5-$, **6a**	$R_1 = OC_2H_5$; $R_2 = C_2H_5$ (2678-54-8)	**5d** (51004-19-4)	63[f]
RR = $-(CH_2)_5-$, **6a**	R_1 = H; $R_2 = C_2H_5$ (109-92-2)	**5e**[g] (37150-70-2)	80[d]

[a] Registry no. in parentheses under compound. [b] RR are same as R in **6**. [c] Isolated yields of pure material obtained after distillation based on acetylaminomethyl alcohol used—hence overall of 2 steps. See Generalizations in the Experimental Section. [d] Average of several runs. [e] One run. [f] Average of 2 runs. [g] Reference 3.

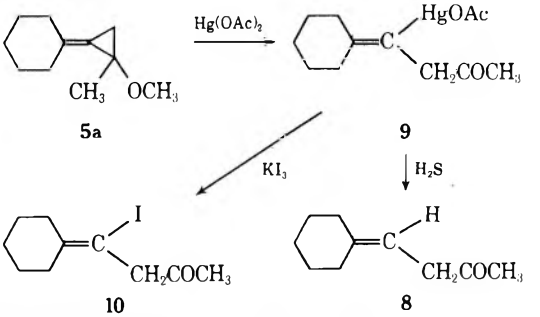
taining compounds free from the α,β-unsaturated isomers are rare, further work with compounds related to **2** seemed desirable. In this paper, the preparation and some reactions of 1-alkylidene 2-substituted 2-alkoxycyclopropanes, **5**, are described.



2 3 4 5a-e

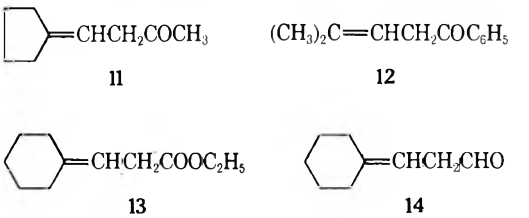
The cyclopropanes, **5**, of interest were prepared by reacting the *N*-nitrosoacetylaminomethyl alcohols, **6**, with excess enol ethers, **7**, by the method described.[3] The yields of **5** decrease as the excess of olefin used decreases. However, the excess olefin can be recovered (see Experimental Section). The compounds prepared and yields thereof are listed in Table I.

Attempts to find acidic conditions suitable for direct conversion of **5a** into 4-cyclohexylidene-2-butanone, **8**, were unsuccessful. However, treatment of **5a** with aqueous alcoholic mercuric acetate presumably afforded an organomercuric acetate, **9**, which was immediately converted into **8** (overall yield 86% based on **5a**) by treatment with hydrogen sulfide. In the case of **5d**, the intermediate mercury compound was also reduced to **13** with sodium borohydride, but there was no advantage over the hydrogen sulfide route. Because of the instability of **9**, evidence as to the structure was sought by treatment with potassium periodide, a reagent known to cause replacement of the mercury in arylmercury[5] and alkylmercury[6] compounds by iodine. The resulting iodo compound, 4-iodo-4-cyclohexylidene-2-butanone, **10**, was also so unstable that a pure sample for analysis could not be obtained. However, pmr, ir, and mass spectral data on crude **10** were sufficiently definitive to leave no doubt as to the structure of **10**. The replacement of vinyl mercury by iodine (to produce **10**) has been accomplished previously[7] and is apparently the first time vinyl mercury has been so replaced. The replacement of vinyl mercury by hydrogen has been accomplished by treatment with concentrated hydrochloric acid.[8]



5a 9 10 8

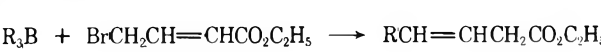
By treatment similar to that described for the synthesis of **8**, compounds **5b-d** were converted into 4-cyclopentylidene-2-butanone, **11** (94%), 3-isopropylidenepropiophenone, **12** (76%), and ethyl 3-cyclohexylidenepropionate, **13** (74%), respectively. However, all attempts to convert **5e**[3] into 3-cyclohexylidenepropanal, **14**, by this procedure yielded multicomponent mixtures from which no pure components were isolated.



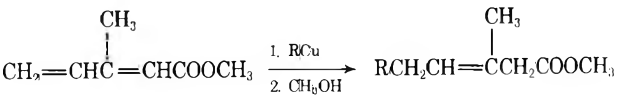
11 12 13 14

Compounds **11**, **12**, and **13** all proved to be entirely β,γ-unsaturated carbonyl-containing compounds. If any α,β-unsaturated isomers were present, they were undetected by glpc (probably ±1%), ir, and pmr (probably ±5%) determinations. Thus, since a new effective route to γ,γ-disubstituted β,γ-unsaturated ketones and esters is at hand, comparison with other methods is of interest.

The addition of trialkylboranes to ethyl 4-bromocrotonate in the presence of potassium 2,6-di-*tert*-butylphenoxide seems to be a general method for producing γ-substituted β,γ-unsaturated esters but has not been applied to the synthesis of β,γ-unsaturated ketones or γ,γ-disubstituted β,γ-unsaturated esters.[9]



The conjugate 1,6 addition of an organocuprous reagent to a conjugated dienoate yields a β,γ-unsaturated ester. This reaction has not yet been extended to ketones.[10]



Other methods for producing β,γ-unsaturated carbonyl compounds contaminated with the corresponding α,β-unsaturated isomers have been recorded.[11-15]

Experimental Section

Generalizations. All melting and boiling points are uncorrected. Melting points were taken with a Thomas-Hoover melting point apparatus. Microanalyses were performed by the M-H-W Laboratories, Garden City, Mich.

Infrared absorption spectra were recorded on a Perkin-Elmer Infracord spectrophotometer. Proton magnetic resonance (pmr) spectra were recorded on a Varian A-60 nmr spectrophotometer, Varian Associates, Palo Alto, Calif.; all samples were dissolved in CCl_4 with tetramethylsilane (TMS) as an internal standard, chemical shifts are reported in δ values (TMS 0.0). All vapor phase chromatographic analyses were performed on a Wilkens Aerograph Model A-700; column (10 ft × ¼ in.): 30% SE-30 on 45/60 a/w Chromosorb A, flow rate 25 ml of helium/min. Vacuum distillations were carried out in a total-reflux partial-take-off column. The boiling points recorded represent the constant boiling material thus obtained. Additional amounts of product were undoubtedly present in lower and higher boiling fractions. The yields in general represent the average of two or more runs after experience with the product had been gained.

2-Methoxy-2-methylcyclohexylidenecyclopropane (5a). To a stirred solution of **6**, prepared as described[3] from 8.55 g (50 mmol) of 1-(*N*-acetylaminomethyl)cyclohexanol[3] and 2.5 g of Aliquat-336[16] in 100 ml of 2-methoxypropene[17] maintained at −10 to −5°, was added dropwise a solution of 2.5 g (60 mmol) of sodium hydroxide in 5 ml of water over 1 hr. The theoretical volume of nitrogen was collected. The reaction mixture was warmed to room temperature for 15 min, diluted with saturated sodium chloride solution, and extracted with ether. The organic layer was filtered through anhydrous sodium sulfate, and the solvent was fractionally distilled at atmospheric pressure with a 10 in. total reflux partial take-off column (hereinafter referred to as a conventional work-up). The residue was chromatographed over 50 g of neutral Woelm alumina with 250 ml of pentane to remove Aliquat-336. The eluate was concentrated by atmospheric fractional distillation as before, and the residue was distilled to afford 5.8 g (64%) of **5a**: bp 99° (13 mm); ir 5.62 μ (C=C); pmr 3.19 (s, 3, OCH_3), 2.2 (m, 4, allylic), 1.58 (m, 6, aliphatic), 1.45 (s, 3, CH_3), and 1.05 (m, 2, cyclopropyl); mass spectrum *m/e* 166.

Anal. Calcd for $C_{11}H_{18}O$: C, 79.5; H, 10.9. Found: C, 79.3; H, 10.9.

An experiment identical with that described above except that the solvent system consisted of 75 ml of pentane and 7.2 g (100 mmol) of 2-methoxypropene afforded 1.7 g (24%) of **5a**, identified by comparison with an authentic sample.

1-(*N*-Acetylaminomethyl)cyclopentanol (15). A mixture of 42.3 g (0.3 mol) of 1-oxa-3-azaspiro[4.4]nonan-2-one[18] and 150 ml of 50% potassium hydroxide was refluxed for 20 min. The cooled mixture was transferred under argon to a separatory funnel. The organic layer was separated, diluted with 200 ml of methanol, and treated dropwise with 30.6 of pure acetic anhydride. After 30 min at reflux the volatile materials were removed on a rotary evaporator, and the residue was recrystallized from benzene–petroleum ether (bp 60–110°) to yield 40.8 g (87%) of **15**: mp 119–120°; ir 2.85 (OH), 3.00 (NH), and 6.01 μ (C=O); pmr (acetone-d_6) 3.52 (m, 2, NH, OH, exchangeable with D_2O), 3.28 (d, 2, CH_2NH), 1.88 (s, 3, $COCH_3$), and 1.57 (broad s, 8, cyclopentyl); mass spectrum *m/e* 157.

Anal. Calcd for $C_8H_{15}NO_2$: C, 61.1; H, 9.6; N, 8.9. Found: C, 60.9; H, 9.8; N, 8.8.

1-(*N*-Nitrosoacetylaminomethyl)cyclopentanol (6b). The nitrosation is carried out exactly as described for **6**[3a] to yield a yellow oil with no NH and a strong carbonyl at 5.75 μ. No further analytical data were obtained on **6b** owing to its thermal instability; the compound must be used immediately or stored in methylene chloride solution for up to 1 week in the freezing compartment of a refrigerator.

2-Methoxy-2-methylcyclopentylidenecyclopropane (5b). In a similar way from 1-(*N*-nitrosoacetylaminomethyl)cyclopentanol prepared from 7.85 g (50 mmol) of **15** there was obtained 5.0 g (66%) of **5b**: bp 85° (13 mm); ir 5.54 μ (C=C); pmr 3.20 (s, 3, OCH_3), 2.32 (m, 4, allylic), 1.71 (m, 4, aliphatic), 1.38 (s, 3, CH_3), and 1.35–0.80 (m, 2, cyclopropyl); mass spectrum *m/e* 152.

Anal. Calcd for $C_{10}H_{16}O$: C, 79.0; H, 10.6. Found: C, 78.8; H, 10.3.

2-Methoxy-2-phenylisopropylidenecyclopropane (5c). In a similar way, from α-methoxystyrene[17] (100 ml) and 6.6 g (50 mmol) of 1-acetylaminomethyl-2-methyl-2-propanol[3a] there was obtained 3.3 g (35%) of **5c**: bp 132° (22 mm); ir 5.67 μ (C=C); pmr 6.97 (s, 3, aromatic), 3.13 (s, 3, OCH_3), 1.80 (s, 6, allylic CH_3), and 1.42 (m, 2, cyclopropyl); mass spectrum *m/e* 188.

Anal. Calcd for $C_{13}H_{15}O$: C, 83.0; H, 8.5. Found: C, 83.1; H, 8.7.

Cyclohexylidenecyclopropanone Diethyl Ketal (5d). Similarly, from **6** and ketene diethyl acetal,[19] there was obtained 6.62 g (63%) of **5d**: bp 88° (2 mm); ir 5.65 μ (C=C); pmr 3.65 (q, J = 7.0 Hz, 4, $-OCH_2CH_3$), 2.28 (m, 4, allylic), 1.58 (m, 6, aliphatic), 1.13 (t, J = 7.0 Hz, 6, $-OCH_2CH_3$), and shoulder on 1.13 (m, 2, cyclopropyl); mass spectrum *m/e* 210.

Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.3; H, 10.5. Found: C, 74.4; H, 10.4.

4-Cyclohexylidene-2-butanone (8). To a stirred solution of 2.0 g of **5a** (12 mmol) in 25 ml of ethanol and 3 ml of water was added a solution of 3.84 g (12 mmol) of mercuric acetate in 20 ml of water. After 5 min, hydrogen sulfide was passed in for 5 min. The resulting black mixture was vacuum filtered through a bed of Celite to remove mercuric sulfide. The product was extracted with ether, and the organic layer was washed successively with water, saturated sodium chloride solution, and filtered through anhydrous sodium sulfate. The solvent was fractionally distilled with a 6 in. total reflux column and the residue distilled to afford 1.57 g (85%) of **8**: bp 120° (20 mm); ir 5.82 μ (C=O); pmr 5.23 (t, J = 7.0 Hz, 1, vinyl), 3.05 (d, 7.0 Hz, 2, $=CHCH_2COCH_3$), 2.10 (m, 4, allylic), 2.03 (s, 3, $COCH_3$), and 1.50 (m, 6, aliphatic); mass spectrum *m/e* 152; uv (C_6H_{12}) λ_{max} 223 nm (ϵ 589).[20] Ozonolysis of a methanolic solution followed by triphenylphosphine reduction[21] afforded cyclohexanone as the only glpc volatile material.

Anal. Calcd for $C_{10}H_{16}O$: C, 79.0; H, 10.5. Found: C, 78.6; H, 10.6.

4-Cyclopentylidene-2-butanone (11). Treatment of **5b** as described above yielded **11** (94%): bp 119° (35 mm); ir 5.82 μ (C=O); pmr 5.38 (t, J = 7.5 Hz, 1, vinyl), 3.0 (d, J = 7.5 Hz, 2, $-CHCH_2COCH_3$), 2.20 (m, 4, allylic), 2.05 (s, 3, $COCH_3$), and 1.62 (m, 4, aliphatic); mass spectrum *m/e* 138.

Anal. Calcd for $C_9H_{14}O$: C, 78.3; H, 10.2. Found: C, 78.5; H, 10.0.

3-Isopropylidenepropiophenone (12). Treatment of **5c** as described above yielded **12** (76%): bp 105° (1 mm); ir 5.91 μ (C=O); pmr 7.82 (m, 2, ortho H), 7.33 (m; 3, meta and para H), 5.35 (t, 1, vinyl), 3.52 (d, 2, $-CHCH_2COPh$), and 1.70 (d, 6, allylic CH_3); mass spectrum *m/e* 174.

Anal. Calcd for $C_{12}H_{14}O$: C, 82.8; H, 8.1. Found: C, 82.6; H, 7.9.

Ethyl 3-Cyclohexylidenepropionate (13). Treatment of **5d** as described above yielded **13** (74%): bp 72° (0.4 mm); ir 5.75 μ (C=O); pmr 5.26 (t, J = 7.0 Hz, 1, vinyl), 4.10 (q, 2, $-OCH_2CH_3$), 2.95 (d, J = 7.0 Hz, 2, $-CHCH_2CO_2Et$), 2.12 (m, 4, allylic), 1.55 (m, 6, aliphatic), and 1.21 (t, 3, $-OCH_2CH_3$); mass spectrum *m/e* 182.

Anal. Calcd for $C_{11}H_{18}O$: C, 72.5; H, 9.9. Found: C, 72.4; H, 9.8.

4-Iodo-4-cyclohexylidene-2-butanone (10). To a solution of 1.0 g (6.0 mmol) of **5a**, 15 ml of methanol, and 2.0 ml of water maintained at 20° was added dropwise over a period of 10 min a solution of 1.92 g (6.0 mmol) of mercuric acetate in 10 ml of water. When the addition was complete, 10 ml of a potassium iodide–iodine solution (*e.g.*, 6 mmol of KI, 8 mmol of I_2) was added dropwise at about 20° over a 20-min period. The black color of the KI/I_2 solution disappeared immediately upon contact with the vinyl mercuric acetate solution. After the addition was complete, a pale orange oil separated. The reaction mixture was extracted thrice with ether. The combined organic portions were worked up in a conventional way, and the solvent was removed under reduced pressure at room temperature to afford 1.5 g (90% from **5a**)

of **10** as a pale orange oil: ir (neat) 5.80 μ sharp (C=O); pmr 3.80 (s, 2, $=ClCH_2COCH_3$), 2.35 (m, 4, allylic), 2.14 (s, 3, $COCH_3$), and 1.58 (m, 6, aliphatic); mass spectrum *m/e* 278, 151 (parent minus I). This oil turned black and became viscous when exposed to air for short periods of time or when heated to 40°. Because of this sensitivity no further analytical data were obtained.

Registry No.—**8**, 21527-61-7; **10**, 51004-20-7; **11**, 51004-21-8; **12**, 36597-09-8; **13**, 18559-89-2; **15**, 51004-22-9; 1-oxa-3-azaspiro[4,4]-nonan-2-one, 19684-59-4.

References and Notes

(1) This work was supported by Grant No. 12445 of the National Science Foundation.
(2) This work formed part of the Ph.D. thesis presented by M. C. V. Z., to The Ohio State University, 1973.
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The Chemistry of Metalated Heterocycles. Dimerization of 2-Lithiomethyl-1,3-thiazoles, -1,3,4-thiadiazoles, and -1,3,4-oxadiazoles

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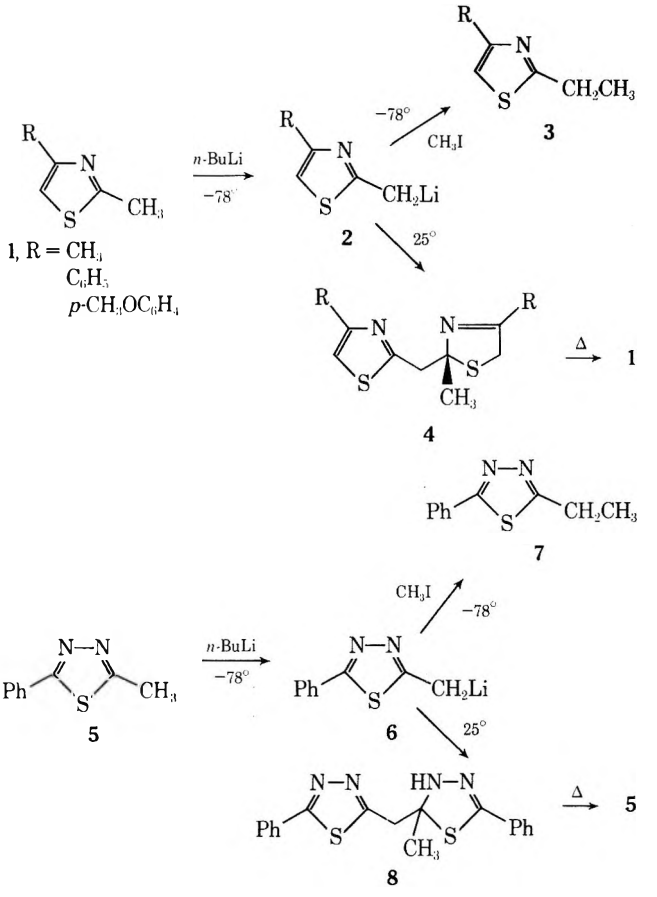
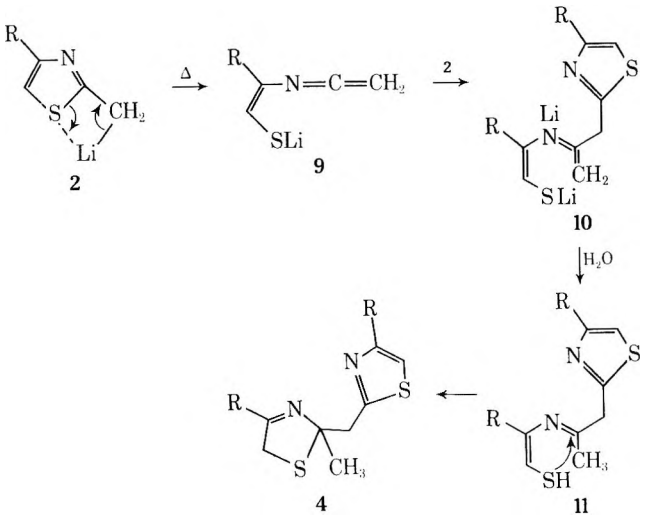
The carbanions derived from 2-methyl-1,3-thiazoles **2** are shown to retain their integrity at low temperatures by C-alkylation with alkyl halides. On the other hand, if these lithiated species are allowed to warm from −78° (their temperature of formation) to ambient temperatures, nucleophilic attack occurs with trace amounts of nonmetalated thiazole **1** producing the dimer **4**. Similar results were obtained when the 2-methyl-1,3,4-thiadiazole **5** (X = S) and the 2-methyl-1,3,4-oxadiazole **5** (X = O) were transformed into their lithio salts. These data tend to nullify the previously suggested mechanism for dimerization involving a ketenimine intermediate.

In a preliminary report[1] the behavior of thiazoles **1** and 1,3,4-thiadiazoles **5** after conversion to their respective lithio salts **2** and **6** was described. It was shown that alkylation of the lithio thiazole with methyl iodide at low temperature produced the expected 2-ethyl derivative whereas allowing **2** to warm to room temperature led to the dimer **4** in 75–90% yield. Similar behavior was noted for the lithio thiadiazole **6**, which produced, after low-temperature alkylation, the 2-ethyl derivative **7** or the dimer **8** upon warming in the absence of methyl iodide. Of further interest was the fact that the dimeric products **4** and **8** readily reversed upon heating (>150°) to the starting heterocycles. This facile dimerization of the lithiated heterocycles and their subsequent reversion to monomers has apparently escaped detection despite the extensive literature pertaining to metalation of heterocycles.[2] The purpose of the present paper is not only to report further details regarding the dimerization of lithio heterocycles but to offer a mechanism for this process.

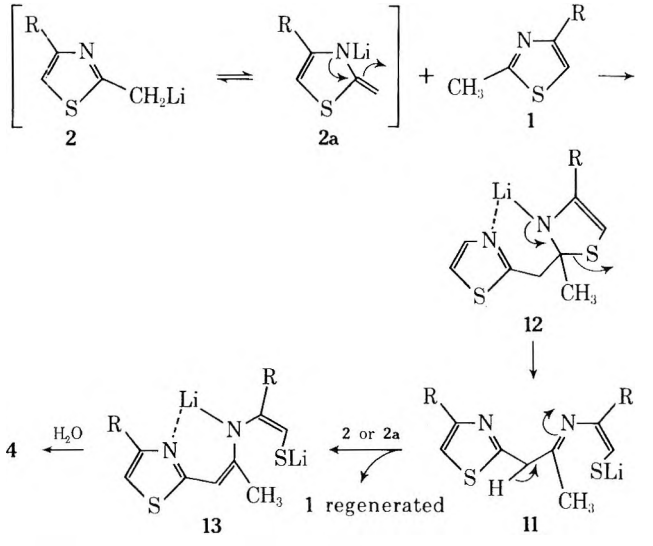


In the case of the thiazole system **1**, the dimer **4** may be envisioned as forming through two different mechanisms (Schemes I and II). The lithio thiazole may rearrange upon warming from −78° to 25° to the thiolithio ketenimine **9**, which is attacked as it is formed by unrearranged lithio thiazole, leading to the adduct **10**. Quenching of the solution would produce the thiol imine **11**, resulting in cyclization to the observed dimer **4**. This pathway, originally suggested for the dimer formation,[1] is based upon the analogous dimerization of oxazine and oxazoline carbanions **14** to their respective dimers **16**,[3a] Proof of the intermediacy of the ketenimine **15** was presented by isolation and characterization of the entrapped O-trimethylsilyl de-

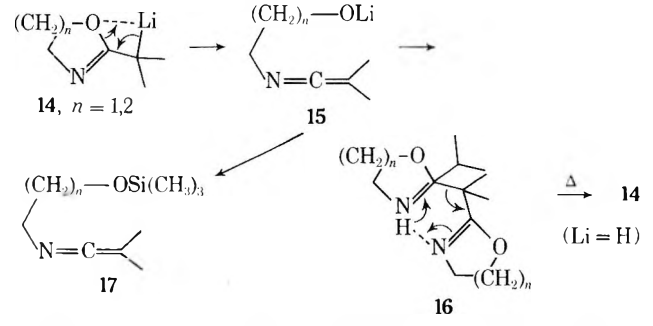
Scheme I



Scheme II

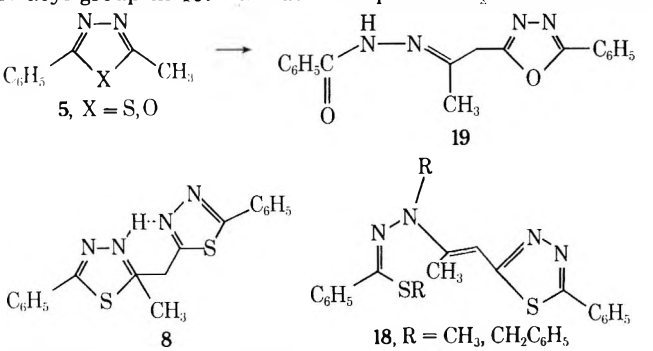


rivatives 17.[3b] In a fashion similar to the thiazole series, 16 also underwent quantitative reversion to 14 on heating.



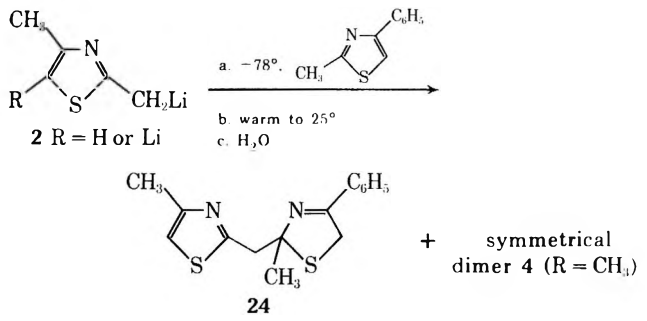
Another feasible pathway leading to the thiazole dimer which does not involve the ketenimine intermediate is outlined in Scheme II.[4] In this route to the dimer, the lithio methylthiazole may add directly to unmetalated thiazole, which need be present in only trace amounts, generating the adduct **12**. Rearrangement to the open-chain imine **11** provides an intermediate whose acidity toward the lithio thiazole **2** should be rather pronounced. Proton abstraction by **2** would give the dilithio intermediate **13** (the tautomer of **10** postulated in Scheme I) and regenerate the 2-methylthiazole **1** for further reaction. Attempts to trap **13** using methyl iodide gave only a complex mixture of products.

Open-chain intermediates were isolated, however, from the related 1,3,4-thiadiazole **5** (X = S) and 1,3,4-oxadiazole **5** (X = O) when their respective lithio salts were allowed to warm from −78° to room temperature. The dimer **8** derived from the thiadiazole was smoothly formed when no external electrophile was added prior to quenching, while the thio imine **18** was isolated if methyl iodide or benzyl bromide was added prior to quenching. The corresponding bicyclic dimer of the oxadiazole **5** (X = O) was not obtained after quenching with water. Rather the open-chain hydrazide **19** was isolated. Presumably, the facile ring–chain tautomerism present in the sulfur heterocycles (leading to **8**) is not as pronounced in the oxygen system owing to the lesser nucleophilic character of the *N*-acyl group in **19**. Various attempts to trap the intermediate ketenimine **9** in Scheme I were uniformly unsuccessful, as was every attempt to detect the strong ketenimine absorption (2000–2100-cm^{-1} region) in the reaction medium. Pursuing the earlier observation in the oxazoline and oxazine series[3] that a tertiary carbanion generated from these systems does not react with ketenimines owing to their bulky nature, the 2-isopropyl thiadiazole **20** was prepared and transformed into its lithio salt **21**. If the ketenimine **22** (R = Li) is indeed an intermediate, the latter should form spontaneously at or near 0° and subsequent alkylation would provide the *S*-methyl ketenimine **22** (R = CH_3). However, addition of methyl iodide to **21** at various temperatures (−78 to 25°) afforded no ketenimine **22** (R = CH_3) but only the 2-*tert*-butylthiadiazole **23** in quantitative yield. It soon became clear that any significant concentration of a ketenimine in the thiadiazole dimerization was rather doubtful and the alternate mechanism (Scheme II) should be considered. In order to test the latter mechanism, a large excess (2.5 equiv) of *n*-butyllithium was added (−78°) to 2,4-dimethylthiazole **1** (R = CH_3) and the solution was allowed to warm to room temperature prior to deuterolysis. After work-up, *only dideuterated thiazole was recovered with no evidence of any dimeric product.* Under these conditions, almost complete dianion formation resulted and the concentration of nonmetalated thiazole was nil.[5] This is in sharp contrast to the earlier experiment wherein 1.0–1.1 equiv of *n*-butyllithium was employed and undoubtedly allowed a small amount of thiazole to escape metalation.



Finally, a crossover experiment involving the dilithio thiazole, generated at −78° with 1.9 equiv of *n*-butyl-

lithium, followed by addition of 2-methyl-4-phenylthiazole at −78°, gave both the unsymmetrical (**24**) and symmetrical (**4**) dimers after the mixture was allowed to rise to ambient. Similar results were obtained using only 0.9 equiv of *n*-butyllithium. One may conclude from these results that 2-lithio thiazoles **2** add to the C=N of nonmetalated thiazoles as the temperature rises to ambient and this process takes place even when the thiazoles are dilithiated.



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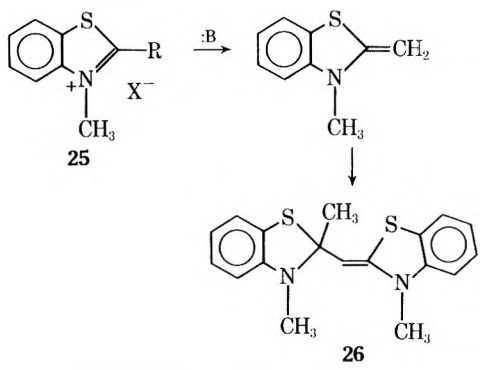
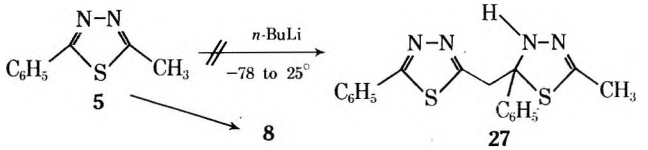
The mechanism depicted in Scheme II has some related precedent. It has been observed[6,7] that benzothiazolium salts **25** (R = CH_3) under basic conditions gave the dimer **26**. It was also noted that the nature of the R group had



25 **26**

an effect upon the ease of dimerization. When R was ethyl[8] or benzyl,[9] **25** did not lead to dimers of the type **26**, but only recovery of the monomeric base. Similar behavior was observed for 2-methyl-5-phenyl-1,3,4-thiadiazole (**5**) when treated with 1.0 equiv of *n*-butyllithium. The dimer derived by carbanion attack at the carbon bearing the methyl group **8** was the only product obtained and none of the dimer **27** was isolated. It would appear, therefore, that the dimerization process is quite sensitive to both steric and electronic factors at the 2 position.



5 **8** **27**

Experimental Section[10]

Metalation and Dimerization of 2,4-Dimethylthiazole (1, R = CH_3). *n*-Butyllithium (8.0 ml, 17.7 mmol) in hexane was added dropwise to a stirred solution (N_2) of 2,4-dimethylthiazole[11a] (2.00 g, 17.7 mmol) in dry tetrahydrofuran (30 ml) at −78°. The resulting wine-colored reaction mixture was stirred at this temperature for 0.5 hr and then allowed to warm to room temperature. This was stirred for a further 8 hr, poured into ice–water (100 ml), and extracted with ether (2 × 150 ml). The combined ether extracts were dried ($MgSO_4$) and evaporated under vacuum to give a light yellow oil. Molecular distillation afforded 1.64 g (82%) of dimer **4** (R = CH_3): bp ~35° (0.02 Torr); ir (NaCl) 1665, 1530, 1465, 1440, 1420 cm^{-1}; nmr ($CDCl_3$) δ 6.77 (s, 1), 3.81 (AB q, *J* = 18 Hz, 2), 3.5 (s, 2, $SCH_2C{=}N$), 2.43 (s, 3), 2.10 (s, 3), 1.80 (s, 3).

Anal. Calcd for $C_{10}H_{14}N_2S_2$: C, 53.06; H, 6.23; N, 12.38. Found: C, 52.79; H, 6.01; N, 12.33.

Metalation and Dimerization of 2-Methyl-4-phenylthiazole (1, R = Ph). *n*-Butyllithium (4.5 ml, 7.1 mmol) in hexane was added dropwise to a stirred solution (N_2) of 2-methyl-4-phenylthiazole[11b] (1.24 g, 7.10 mmol) in dry tetrahydrofuran (30 ml) at −78°. The resulting yellow-colored reaction mixture was allowed to warm to room temperature and stirred for a further 8 hr, at which time it was dark brown in color. Quenching with water and extraction with ether, as described above, gave 1.12 g (90%) of dimer **4** (R = Ph) as a light yellow oil. Crystallization from ether–hexane (−78°) gave an almost colorless solid which melted when warmed to room temperature: nmr ($CDCl_3$) δ 8.0–7.7 (m, 4), 7.6–7.2 (m, 7), 4.30 (AB q, 2), 3.73 (s, 2), 1.91 (s, 3).

Pyrolysis of **4** (R = Ph) (0.95 g) in a molecular distillation apparatus at 150–160° for 0.5 hr, followed by distillation (0.02 Torr), gave 0.91 g (96%) of 2-methyl-4-phenylthiazole.

Metalation and Dimerization of 2-Methyl-4-*p*-methoxyphenylthiazole (1, R = *p*-$CH_3OC_6H_4$). *n*-Butyllithium (4.4 ml, 7.0 mmol) was added dropwise to a stirred solution (N_2) of **1** (R = *p*-$CH_3OC_6H_4$)[12] (1.44 g, 7.00 mmol) in dry tetrahydrofuran (25 ml) at −78°. Quenching with water and work-up as before gave 1.29 g (90%) of dimer **4** (R = *p*-$CH_3OC_6H_4$) as a light yellow oil: nmr ($CDCl_3$) δ 7.33 (A_2B_2, q, 8), 7.17 (s, 1), 4.22 (AB q, 2), 3.80 (s, 6), 3.71 (s, 2), 1.87 (s, 3).

Pyrolysis of **4** (R = *p*-$CH_3OC_6H_4$) (0.88 g) as before and distillation under vacuum (0.02 Torr) gave 0.81 g (92%) of 2-methyl-4-*p*-methoxyphenylthiazole.

Metalation and Dimerization of 2-Methyl-5-phenylthiadiazole (5). A. Quenching with Water. *n*-Butyllithium (3.6 ml, 7.9 mmol) in hexane was added dropwise to a stirred solution (N_2) of 2-methyl-5-phenylthiadiazole[13] (1.40 g, 7.95 mmol) in dry tetrahydrofuran (35 ml) at −78°. Quenching with water (at 25°) and work-up as before gave an orange solid. Recrystallization from acetonitrile–water (15:1 v/v) gave 1.04 g (74%) of dimer **8** as almost white needles: mp 144–145°; ir (KBr) 3310 (NH), 1465, 1455, 1420 cm^{-1}; nmr ($CDCl_3$) δ 8.1–7.9 (m, 2), 7.8–7.3 (m, 8), 6.66 (s, NH, D_2O exchange), 3.73 (AB q, 2), 1.87 (s, 3); mass spectrum (70 eV) *m/e* 352 (M^+, 1).

Anal. Calcd for $C_{18}H_{16}N_4S_2$: C, 61.33; H, 4.58; N, 15.90. Found: C, 61.58; H, 4.74; N, 15.85.

Pyrolysis of dimer **8** (0.58 g) in a sublimation apparatus at 150–170° (0.03 Torr) gave 0.53 g (92%) of 2-methyl-5-phenylthiadiazole.

B. Quenching with Methyl Iodide. The lithio salt was quenched with iodide (1.3 equiv) at 25° and work-up as before gave a yellow solid. Recrystallization from hot acetonitrile gave a 47% yield of dimer **18** (R = CH_3): mp 149–151°; ir (KBr) 1590, 1505, 1435 cm^{-1}; nmr ($CDCl_3$)[14] δ 8.1–7.8 (m, 4), 7.6–7.2 (m, 7), 2.50 (s, 3), 2.37 (s, 3), 2.23 (s, 3); λ_{max} (CH_3CN) 406 nm.

Anal. Calcd for $C_{20}H_{20}N_4S_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 62.95; H, 5.56; N, 14.59.

C. Quenching with Benzyl Bromide. The lithio salt was quenched with benzyl bromide (1.2 equiv) at 25° and work-up as before gave a yellow solid. Recrystallization from hot acetonitrile gave a 38–45% yield of dimer **18** (R = $C_6H_5CH_2$): mp 142–144°; ir (KBr) 1590, 1525, 1495, 1455, 1450, 1435 cm^{-1}; nmr ($CDCl_3$)[14] δ 8.1–7.8 (m, 4), 7.6–7.1 (m, 17), 4.10 (s, 2), 4.01 (s, 2), 2.43 (s, 3); λ_{max} (CH_3CN) 407 nm.

Anal. Calcd for $C_{32}H_{28}N_4S_2$: C, 72.18; H, 5.30; N, 10.53. Found: C, 72.35; H, 5.36; N, 10.71.

Metalation and Dimerization of 2-Methyl-5-phenyloxadiazole. *n*-Butyllithium (2.9 ml, 6.45 mmol) was added dropwise to a stirred solution of 2-methyl-5-phenyloxadiazole[15] (1.03 g, 6.44 mmol) in dry tetrahydrofuran (20 ml) at −78°. The resulting wine-colored reaction mixture was stirred for 0.5 hr (−78°) and then allowed to warm to room temperature. This was stirred for a further 8 hr, poured into ice–water (100 ml), and extracted with ether (2 × 150 ml). The combined ether extracts were dried ($MgSO_4$) and evaporated under vacuum to give a colorless, oily solid. Upon the addition of anhydrous ether (*ca.* 20 ml), a white, crystalline solid separated and was quickly filtered. Recrystallization from acetonitrile–carbon tetrachloride (1:1 v/v) gave 0.36 g (34%) of dimer **19**: mp 135–137°; ir (KBr) 3240 (NH), 1635 (CO), 1530, 1510, 1480 cm^{-1}; nmr ($CDCl_3$) δ 9.12 (s, NH, D_2O exchange, 1), 8.2–7.7 (m, 4), 7.7–7.3 (m, 6), 4.1 (s, 2), 2.1 (s, 3); mass spectrum (70 eV) *m/e* 320 (M^+, 12).

Metalation and Methylation of 2-Isopropyl-5-phenylthiadiazole (20). *n*-Butyllithium (2.2 ml, 5.0 mmol) in hexane was added dropwise to a stirred solution (N_2) of 2-isopropyl-5-phenylthiadiazole[16] (1.02 g, 5.0 mmol) in dry tetrahydrofuran (30 ml) at −78°. The resulting wine-colored reaction mixture was then allowed to warm to room temperature. This was stirred for 8 hr, and methyl

iodide (0.90 g, 6.3 mmol) was added dropwise. This was stirred for a further 1 hr, poured into ice-water (100 ml), and extracted with ether (2 × 150 ml). The combined ether extracts were dried ($MgSO_4$) and evaporated under vacuum to give a light yellow oil. Molecular distillation gave 0.98 g (90%) of 2-*tert*-butyl-5-phenylthiadiazole (23): ir (NaCl) 1470, 1460, 1430 cm^{-1}; nmr ($CDCl_3$) δ 8.1–7.8 (m, 2), 7.6–7.3 (m, 3), 1.44 (s, 9).

Anal. Calcd for $C_{12}H_{14}N_2S$: C, 66.04; H, 6.47. Found: C, 66.07; H, 6.61.

Attempted Dimerization of 2,4-Dimethylthiazole with Excess Base. *n*-Butyllithium (11.1 ml, 25.0 mmol) in hexane was added dropwise to a stirred solution (N_2) of 2,4-dimethylthiazole (1.12 g, 10.0 mmol) in dry tetrahydrofuran (25 ml) at −78°. The resulting wine-colored reaction mixture was allowed to warm to room temperature and stirred for 8 hr. Quenching with deuterium oxide and extraction with ether followed by molecular distillation gave 0.96 g (84%) of 2-deuteriomethyl-5-deuterio-4-methylthiazole: nmr ($CDCl_3$) δ 6.66 (s, 0.1 H), 2.63 (t, 1:1:1, CH_2D), 2.40 (s, 3).

Formation of Mixed Dimer 24. *n*-Butyllithium (3.2 ml, 7.3 mmol) in hexane was added dropwise to a stirred solution (N_2) of 2,4-dimethylthiazole (0.92 g, 8.1 mmol) in dry tetrahydrofuran (30 ml) at −78°. The resulting wine-colored reaction mixture was stirred for 1 hr at −78° and then a solution of 2-methyl-4-phenylthiazole (1.42 g, 8.1 mmol) in dry tetrahydrofuran (10 ml) was added. This was allowed to warm to room temperature, quenched with ice-water (100 ml) 8 hr later, and extracted with ether (2 × 150 ml). The combined ether extracts were dried ($MgSO_4$) and evaporated under vacuum to give a yellow oil. Molecular distillation at an oil bath temperature of 105° (0.08 Torr) gave dimer 4 (R = CH_3) (36%) and 2-methyl-4-phenylthiazole (79%). Further distillation at an oil-bath temperature of 145–150° (0.08 Torr) gave mixed dimer 24 (19%) as a viscous oil: ir (NaCl) 1635, 1530, 1495, 1450 cm^{-1}; nmr ($CDCl_3$) δ 8.05–7.75 (m, 2), 7.60–7.35 (m, 3), 6.77 (s, 1), 4.33 (AB q, 2), 3.77 (s, 2), 2.43 (s, 3), 1.80 (s, 3).

A repeat experiment using 1.90 equiv of *n*-butyllithium to form the dilithiothiazole, followed by the addition of 2-methyl-4-phenylthiazole and work-up as above, gave the symmetrical dimer 4 (32%) and the mixed dimer 24 (11%) along with starting material (82%).

Acknowledgment. The authors wish to express their gratitude to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the National Science Foundation for financial support of this work.

Registry No.—1 (R = CH_3), 541-58-2; 1 (R = C_6H_5), 1826-16-0; 1 (R = *p*-$CH_3OC_6H_4$), 50834-78-1; 4 (R = CH_3), 41898-76-4; 4 (R = C_6H_5), 50834-81-6; 4 (R = *p*-$CH_3OC_6H_4$), 50834-82-7; 5 (X = S), 1456-72-0; 5 (X = O), 4046-03-1; 8, 50883-40-4; 18 (R = CH_3), 41898-82-2; 18 (R = $CH_2C_6H_5$), 50834-83-8; 19, 41898-84-4; 20, 50834-84-9; 23, 50834-85-0; 24, 50834-86-1.

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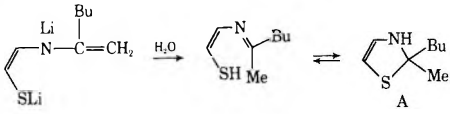
(4) We wish to thank Professor S. Hunig, Wurzburg, for his comments and suggestions pertaining to this scheme.
(5) The possibility of the excess *n*-butyllithium reacting with the proposed ketenimine intermediates **9** or **22** was ruled out on two counts: (a) the high recovery (85%) of starting 2,4-dimethylthiazole and (b) products derived from such a reaction would lead to butylated thiazolines A which were sought but not found.



A

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(10) All boiling points and melting points are uncorrected.
(11) (a) Aldrich Chemical Co., Milwaukee, Wis. (b) G. Vernin, J. P. Aune, H. J. M. Don, and J. Metzger, *Bull. Soc. Chim. Fr.*, 4523 (1967).
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(16) Prepared by successive metalation–methylation (at −78°) of 2-methyl-5-phenylthiadiazole.

The Chemistry of Metalated Heterocycles. The Site of Metalation of 2-Methyl-4-Substituted 1,3-Thiazoles. Electronic, Steric, and Isotope Effects

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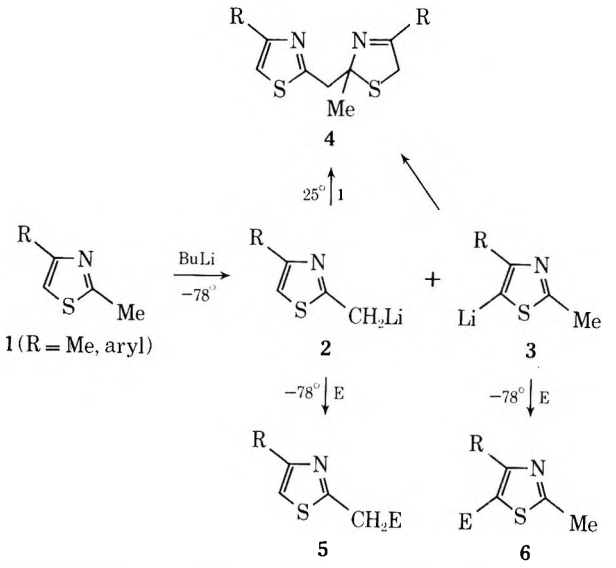
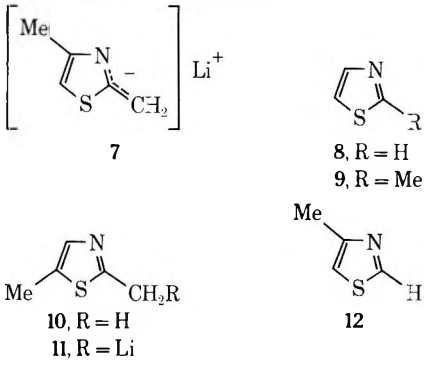
Metalation of 2-methyl-4-aryl-1,3-thiazoles proceeds predominantly at the C-5 position, whereas metalation of the 4-alkyl derivative occurs at the 2-methyl group. It is shown that the anions generated at −78° are the result of the respective kinetic acidities of these positions. Furthermore, at elevated temperatures, the thermodynamic acidities prevail, producing the lithio methyl anions regardless of the nature of the 4 substituent. An apparent primary kinetic isotope effect for the C-5 ring proton has been determined and agrees well with the isotope effect for other heterocyclic protons.

In the previous article[1] dealing with metalation of thiazoles 1 and related compounds, the lithio salt 2 was shown to alkylate trace quantities of the nonmetalated derivative 1 producing dimeric products 4 in high yield. This process appears only to take place if the solution of the lithiated thiazole 2 is allowed to warm from its temperature of formation (−78°) to ambient. However, if the lithiated thiazole is treated with an electrophile, E, at −78°, two alkylated products 5 and 6 are obtained. The ratio of these products is heavily dependent upon the nature of the 4 substituent, R, in the starting thiazole (Table I). Although Metzger[2] has reported, in an extensive temperature study on the metalation of 2-methylthiazole (1, R = H), that the two lithio salts 2 and 3 are formed independently and not through proton–metal exchange, it was felt that further evidence of this claim was necessary. In addition, examination of Table I reveals that metalation and subsequent alkylation of thiazoles containing the 4-aryl substituent leads to predominantly the 5-alkylthiazole 6. On the other hand, when the 4 substituent is methyl, me-



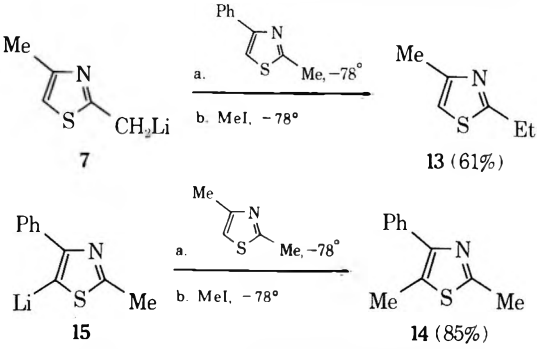
talation and alkylation take place mainly on the 2-methyl group, affording **5**. The trend depicted in Table I seems to be consistent with an inductive effect on the 5 position by the 4 substituent. Thus, aryl substituents with their −I effect tend to weaken the C-H bond of the 5 position, making proton removal a favorable process relative to that in the 2-methyl group.

When a methyl group is situated at the 4 position, its +I effect decreases the acidity at C-5, thus allowing the methyl protons at C-2 to be abstracted. The lithio salt derived from proton abstraction at C-2 should, however, be rather stable owing to its delocalized nature (**7**) and it is surprising that the side chain competes poorly for the *n*-butyllithium even in the 4-aryl substituted case. Ring-proton abstraction from heterocyclic systems is a well-known phenomenon, particularly in the thiophene series,[3] and Metzger[4] reported that the 2-H in thiazole **8** is readily removed by organolithium bases as is the methyl proton in 2-methylthiazole (**9**). Nevertheless, a recent review[5] stated that "even 4-methylthiazole (**12**) is metalated (and alkylated) at the 2 position. In fact, the preference for this position is so dominant that 2,5-dimethylthiazole (**10**) is metalated on the 2-methyl group (**11**)." This description of reactivity in metalations reveals the need for further studies in this series of heterocycles.



In order to confirm the fact that two distinct lithiated thiazoles (**2** and **3**) were indeed formed independently and, therefore, allowing the safe assumption that the product ratios in Table I are the result of the respective kinetic acidities of protons at C-5 and the 2-methyl group, several studies were undertaken to shed light on these points.

The first study was designed to assess the degree of proton transfer among the various possible lithio salts. This involved crossover experiments at −78 and 25° using thiazoles bearing different substituents. Reaction of 2,4-dimethylthiazole with 0.9 equiv of *n*-butyllithium at −78° generated **7**, which was treated with 2-methyl-4-phenylthiazole (**1**, R = Ph) after 2.5 hr and then quenched with methyl iodide after an additional 2.5 hr. The products isolated were **13** and the starting 2-methyl-4-phenylthiazole



(94% recovery), indicating that the lithio thiazole **7** did not abstract a proton from the former at −78°. The absence of **14** from the product mixture confirmed this result. Similarly, a reverse crossover experiment was performed by forming the lithio derivative of 2-methyl-4-phenylthiazole **15** followed by sequential addition of 2,4-dimethylthiazole (**1**, R = Me) and methyl iodide, both at −78°. The products isolated were **14** and starting 2,4-dimethylthiazole. Again, the absence of **13** from this experiment precluded lithium–hydrogen exchange under these conditions. It may, therefore, be concluded that the product ratios given in Table I are the result of independent metalation of the 2-methyl and the C-5 positions in a kinetically controlled process.

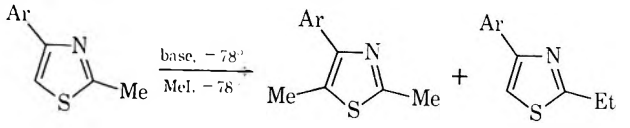
Since 2-methyl-4-arylthiazoles form the 5-lithio salt **3** (R = aryl) predominantly, as seen by alkylation data in Table I, the question immediately is raised, "How does **3** proceed on to the dimer **4**?" The above study already has shown that at −78° there is no lithium–hydrogen exchange. However, since the dimers are formed by allowing a solution of the lithio thiazoles to warm to ambient temperatures, lithium–hydrogen exchange (intra- or intermolecular) must take place and allow **3** to form **2**. The latter is a necessary precursor to dimerization. In order to test this hypothesis, another crossover experiment was performed involving **15**, generated at −78°, adding 2,4-di-

Table I
Reaction of 2-Methyl-4-Substituted 1,3-Thiazoles with *n*-Butyllithium and Electrophiles (E) at −78°

1, R	E	% 5[a]	% 6[a]
Me	MeI	88	12
Me	$PhCH_2Cl$	90	10[d]
Ph	MeI	4[b]	91
Ph	EtI	7[b]	86
p-MeOPh	MeI	6[b]	86
p-ClPh	MeI	3[b]	93
Ph	Me_3SiCl	4[c]	96
Ph	PhCHO		97
Ph		No reaction	
H	MeI	3–23	27–70[e]

[a] Relative yields determined by vpc. In all cases 3–8% starting thiazole was detected. Material balance was greater than 99%. [b] Contained, in addition to **5** and **6**, 5–8% of disubstituted thiazoles presumably by further alkylation of **5** with small amounts of *n*-butyllithium. [c] Decomposed upon exiting from vpc. [d] L. J. Altman and S. L. Richheimer, *Tetrahedron Lett.*, 4709 (1971), reported only crude alkylation product as being mainly **5**. [e] Data of J. Crousier and J. Metzger, *Bull. Soc. Chim. Fr.*, 4134 (1967). Reaction gave 26–50% starting thiazole, when anion formation and methylation were performed at −25 to −90°.

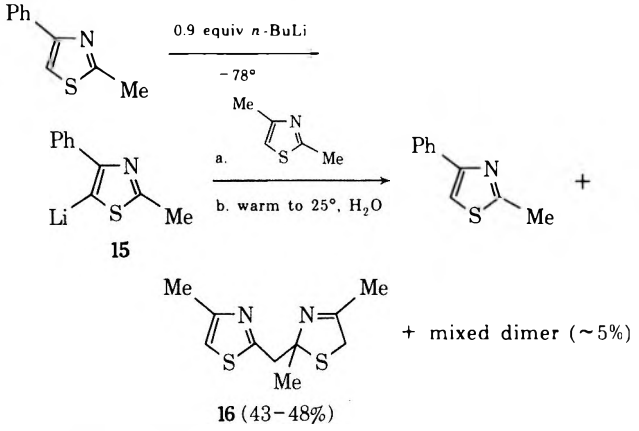
Table II
Metalation and Methylation of 2-Methyl-4-arylthiazoles with Various Bases



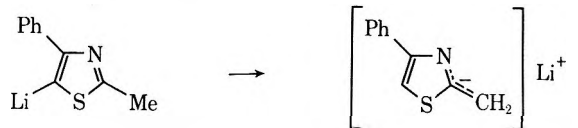
Ar	Base[a]	%[b]	%[b,c]
Ph	*n*-BuLi	94.8	5.2
Ph	(*i*-Pr)$_2$NLi	90.0	10.0
Ph	*t*-BuLi	34.0	66.0
p-MeOPh	*n*-BuLi	92.0	8.0
p-MeOPh	(*i*-Pr)$_2$NLi	80.0	20.0
p-MeOPh	*t*-BuLi	22.0	78.0

[a] 0.6–0.8 equiv of base used to avoid polyalkylation. [b] Average value for triplicate runs. [c] Starting material was recovered (25–40%) in all cases owing to the deficiency of base employed.

methylthiazole at this temperature, and allowing the solution to warm to room temperature. The products recovered were 2-methyl-5-phenylthiazole (75–80%), the symmetrical dimer **16** (43–48%), and a small amount (5%) of

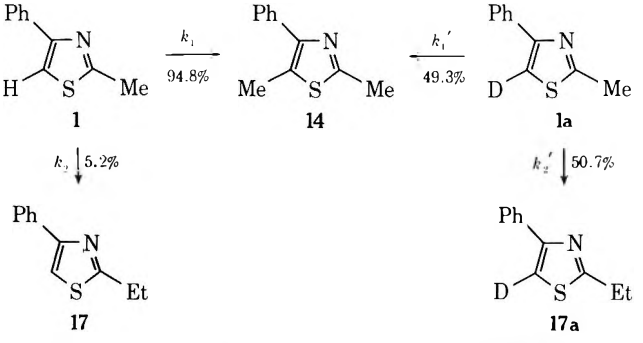


mixed dimers. This result indicates strongly that, *although no lithium-hydrogen exchange occurs at −78°, it does indeed become an important process at higher temperatures.* Thus, the question of how the lithio salt 3 leads to the dimer 4 (R = Ph) appears to have been answered. In the previous paper on this subject,[1] the reverse of the crossover experiment just described (**15** → **16**) was discussed in order to confirm that 2-lithiomethylthiazoles **2** do add to the C=N link of another thiazole molecule to ultimately form dimeric products. It would appear that the lithio salt **15** is kinetically formed at low temperatures owing to the −I effect of the adjacent aryl group, but as the energy of the system is increased (warming to room temperature) the acidity of the 2-methyl group by virtue of its incipient delocalized anion **15a** will prevail. It was therefore desirable to ascertain the relative acidities of the C-5 and 2-methyl protons in a competitive study and toward various bases.



Treatment of an equimolar mixture of 2-methyl-4-phenylthiazole and 2,4-dimethylthiazole with *ca.* 0.5 equiv of *n*-butyllithium at −78° gave, after quenching with methyl iodide, 2,5-dimethyl-4-phenylthiazole (**14**, 43–45%) and 2-ethyl-4-methylthiazole (**13**, 3–4%). These data indicate that proton removal from the 5 position is preferred over that from the 2-methyl group when both are allowed to compete for a deficiency of base. This is, therefore, consistent with the previous claim that the −I effect of the phenyl substituent increases the kinetic acidity of the C-5 proton over the acidity of the 2-methyl group. When bases of varying steric bulk were added to 2-methyl-4-arylthiazoles at −78°, followed by methylation to establish the site of metalation, it was found that the C-5 proton is removed preferentially by small bases, whereas the 2-methyl protons are removed by larger bases (Table II). Of further interest is the fact that, even though the C-5 proton was shown to be kinetically more acidic at −78°, the strongest base employed (*i.e., tert*-butyllithium) leads to mainly methyl proton abstraction. This may be due to a combination of steric factors (since the C-5 proton is less accessible owing to the adjacent aryl group) and the decrease in selectivity of proton abstraction by the stronger base. In any event, the acidity of the C-5 and 2-methyl protons are probably very close in order to produce this significant change in product ratios. It is also noteworthy to mention that the presence of the methoxyl substituent in Table II had little effect upon the product ratios when compared to the phenyl substituent regardless of the base employed. This further substantiates the −I effect operating in the proton abstraction process.

To further support the apparently small acidity differences in the C-5 and 2-methyl protons, an isotope study was undertaken. Owing to the high percentage of metalation in the 5 position of 2-methyl-5-phenylthiazole (**1**, R = Ph) it was a simple matter to prepare, by deuteration with D_2O, the 5-deuterio derivative **1a** (>95% D). Treatment of **1a** with *n*-butyllithium and methyl iodide at −78° gave 49.3% of the 2,5-dimethylthiazole **14** and 50.7% of the 2-ethyl-5-deuteriothiazole **17a.** This result is in sharp



contrast to the 94.8% of **14** and 5.2% of **17** obtained with the protiothiazole **1**. By assigning relative rates k_1 and k_1' to represent the rate of proton abstraction for the C-5 position of **1** and **1a**, respectively, an apparent kinetic isotope effect may be calculated. The relative rates k_2 and k_2' would be expected to be equal, since there should be little difference in the ease of proton removal from the 2-methyl group in **1** and **1a**. Since $k_1'/k_2' = 49.3/50.7 = 0.97$ and $k_1/k_2 = 94.8/5.2 = 18.2$, then we may write, assuming $k_2 = k_2'$, that $k_1/k_1' = k_H/k_D = 18.8$ at −78°. Translating this isotope effect to its value at 35°, using the relationship described by Hine,[6] gives $k_H/k_D = 6.4$. This is in excellent agreement with the primary kinetic isotope effect of 6.6 reported for the metalation of thiophene.[7]

The experimental isotope effect was shown to be valid by testing it in a competition experiment. Metalation of an equimolar mixture of the 5-protio- (**1**) and 5-deuterio- (**1a**) thiazoles with 0.4 equiv of *n*-butyllithium (−78°) followed by introduction of methyl iodide gave, in addition to 63% recovered starting material, 37% of **14** and (**17** + **17a**) in the ratio of 90.5:9.5. By using the total relative rates

given above, ($k_2 + k_2'$) and ($k_1 + k_1'$), the calculated isomer distribution for **14** and (**17** + **17a**) is 90.6:9.4. These results are qualitatively consistent with those obtained in the separate experiments and provide further evidence that two distinct lithio thiazoles are formed under kinetically controlled conditions and maintain their integrity prior to methylation.

In summary, the kinetic acidity of the C-5 and 2-methyl protons at −78° are quite close. When the 4 substituent is methyl (or alkyl) the +I effect increases the electron density at the 5 position, thus rendering the proton less acidic, and allows the 2-methyl protons to be preferentially removed. When the 4 substituent is aryl (regardless of its mesomeric nature) the −I effect is the only important one and this reduces the electron density at the 5 position, causing proton removal to be favored. This type of inductive effect in heterocyclic systems undergoing metalation has previously been pointed out.[8] On the other hand, when thermodynamic conditions are brought into play, namely, allowing the solutions of lithio salts to warm, the 2-methyl protons are indeed more acidic and lithium–hydrogen exchange ensues to produce predominantly the more stable anions.

Experimental Section[9]

General Procedure for Metalation and Alkylation of 2-Methyl-4-Substituted Thiazoles (1). A. *n*-Butyllithium. *n*-Butyllithium (10.0 mmol) in hexane was added dropwise to a stirred solution (N_2) of **1** (10.0 mmol) in dry tetrahydrofuran (30 ml). After stirring for 0.5–1.0 hr, the electrophile (1.2–1.3 equiv) was added dropwise. The reaction mixture was stirred for a further 1–3 hr, allowed to warm to room temperature, poured into water (saturated with sodium chloride), and extracted with ether (2 × 125 ml). The combined ether extracts were dried ($MgSO_4$) and evaporated under vacuum to give an oil. This material was analyzed directly by glpc on column A.[9] Each peak was collected and identified by its nmr spectrum.[10] The quantitative results are summarized in Table I. Table II summarizes the results when a deficiency of base (0.6–0.8 equiv) was employed.

B. Lithio Diisopropylamide. Metalation of **1** (R = Ph, *p*-$CH_3OC_6H_4$) with lithio diisopropylamide (0.6–0.8 equiv) prepared as previously described,[11] methylation with methyl iodide, work-up, and analyses of products were identical with the above-described procedure. The results are summarized in Table II.

C. *tert*-Butyllithium. Metalation of **1** (R = Ph, *p*-$CH_3OC_6H_4$) with *tert*-butyllithium (0.6–0.8 equiv), methylation with methyl iodide, work-up, and analyses of products were identical with the above-described procedure. The results are summarized in Table II.

Attempted Intermolecular Hydrogen–Lithium Exchange at −78°. A. 2-Methyllithio-4-methylthiazole (2, R = CH_3) and 2-Methyl-4-phenylthiazole (1, R = Ph). *n*-Butyllithium (4.4 ml, 9.8 mmol) in hexane was added dropwise to a stirred solution (N_2) of **1** (R = CH_3) (1.17 g, 10.3 mmol) in dry tetrahydrofuran (30 ml) at −78°. The resulting wine-colored reaction mixture was stirred for 1 hr at −78° and then a solution of **1** (R = Ph) (1.68 g, 9.6 mmol) in dry tetrahydrofuran (10 ml) was added. This was stirred for 2.5 hr (−78°) and methyl iodide (1.81 g, 12.7 mmol) was added dropwise. The resulting light yellow colored reaction mixture was stirred for a further 1 hr at −78°, poured into ice-water (150 g, saturated with sodium chloride), and extracted with ether (2 × 150 ml). The combined ether extracts were dried ($MgSO_4$) and evaporated carefully under vacuum to give a light yellow oil. Molecular distillation at room temperature (0.03 Torr) gave 0.79 g (61%) of a colorless liquid whose nmr spectrum was almost identical with that of 2-ethyl-4-methylthiazole. Further distillation at an oil bath temperature of 80–95° (0.03 Torr) gave 1.58 g (94% recovery) of 2-methyl-4-phenylthiazole (**1**, R = Ph). Glpc on column A exhibited the presence of only **1** (R = Ph).

B. 2-Methyl-4-phenyl-5-lithiothiazole (3, R = Ph) and 2,4-Dimethylthiazole (1, R = CH_3). Metalation of **1** (R = Ph) with *n*-butyllithium (0.90 equiv), addition of **1** (R = CH_3) (1.1 equiv), quenching with methyl iodide (−78°), and work-up as described above gave a light yellow oil. Molecular distillation at room temperature (0.03 Torr) gave a 68% recovery of **1** (R = CH_3). Glpc on column A exhibited the presence of only **1** (R = CH_3). Further molecular distillation gave an almost colorless oil. Glpc on column A exhibited the presence of **1** (R = Ph) (9.0%), **14** (86.5%), and **17** (4.5%).

Intermolecular Hydrogen–Lithium Exchange at 25°. 2-Methyl-4-phenyl-5-lithiothiazole (3, R = Ph) and 2,4-Dimethylthiazole (1, R = CH_3). *n*-Butyllithium (3.2 ml, 7.2 mmol) in hexane was added dropwise to a stirred solution of 2-methyl-4-phenylthiazole (**1**, R = Ph) (1.40 g, 8.00 mmol) in dry tetrahydrofuran (30 ml) at −78°. The resulting yellow-colored solution was stirred for 1 hr at −78° and then **1** (R = CH_3) (1.36 g, 12.0 mmol) was added in one portion. This was then allowed to warm to room temperature, at which time the reaction mixture was wine in color. After stirring for 4.5 hr (room temperature), the reaction mixture was quenched with ice-water (40 ml) and extracted with ether (2 × 125 ml). The combined ether extracts were dried ($MgSO_4$) and evaporated under vacuum to give a yellow oil. Molecular distillation at an oil bath temperature of 110° (0.07 Torr) gave 0.38 g (47%) of dimer **16** and 1.06 g (76% recovery) of **1** (R = Ph).

Metalation and Methylation of 2-Methyl-4-phenyl-5-deuteriothiazole (1a). *n*-Butyllithium (2.7 ml, 6.1 mmol) in hexane was added to a stirred solution (N_2) of **1a**[12] (1.40 g, 8.00 mmol) in dry tetrahydrofuran (30 ml) at −78°. Quenching with methyl iodide (−78°) and work-up was the same as that described above. Glpc analyses (average of three runs) on column A exhibited the presence of **14** (36.4%), **17a** (37.4%), and starting material **1a** (26.2%).

Competitive Metalation–Methylation of 2-Methyl-4-phenylthiazole (1, R = Ph) and 2-Methyl-4-phenyl-5-deuteriothiazole (1a). *n*-Butyllithium (1.3 ml, 3.0 mmol) in hexane was added dropwise to a stirred solution (N_2) of **1** (R = Ph) (1.40 g, 8.0 mmol) and **1a** (1.41 g, 8.0 mmol) in dry tetrahydrofuran (30 ml) at −78°. Quenching with methyl iodide at −78° and work-up was the same as that previously described. Glpc analyses (average of three runs) on column A exhibited the presence of starting material(s) (62.8%), **14** (33.7%), and **17a** (3.5%).

Competitive Metalation–Methylation of 2,4-Dimethylthiazole (1, R = Me) and 2-Methyl-4-phenylthiazole (1, R = Ph). *n*-Butyllithium (1.55 ml, 3.5 mmol) in hexane was added dropwise to a stirred solution (N_2) of **1** (R = Me) (0.81 g, 7.1 mmol) and **1** (R = Ph) (1.25 g, 7.1 mmol) in dry tetrahydrofuran (45 ml) at −78°. Quenching with methyl iodide at −78° and work-up as described previously gave **13** (3–4%), **14** (43–45%), **1** (R = Me, 96–97%), and **1** (R = Ph, 55–57%).

Acknowledgment. The authors wish to express their gratitude to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the National Science Foundation for financial support of this work.

Registry No.—**1** (R = Me), 541-58-2; **1** (R = Ph), 1826-16-0; **1** (R = *p*-MeOPh), 50834-78-1; **1** (R = *p*-ClPh), 24840-75-3; **1a**, 50834-79-2; **2** (R = Me), 20155-91-3; **3** (R = Ph), 50834-80-5; **16**, 41898-76-4.

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(8) G. Wittig, *Angew. Chem.*, **66**, 10 (1954).
(9) Nmr spectra were recorded on a Varian T-60 spectrometer. Glpc separation was carried out on a Hewlett-Packard 5750B gas chromatograph equipped with a Hewlett-Packard 3370B integrator using column A (5 ft × 0.125 in., 10% UCW-100).
(10) Since the nmr spectra of the alkylated products are exceedingly straightforward, they will not be tabulated.
(11) R. E. Ludt, J. S. Griffiths, K. N. McGrath, and C. B. Hauser, *J. Org. Chem.*, **38**, 1668 (1973).
(12) Prepared in quantitative yield by metalation with 1.1 equiv of *n*-butyllithium and quenching with D_2O at −78°. The deuterium incorporation at C-5, under these conditions, was shown to be >95% by nmr spectroscopy.

Asymmetric Thiazolium Salt Catalysis of the Benzoin Condensation

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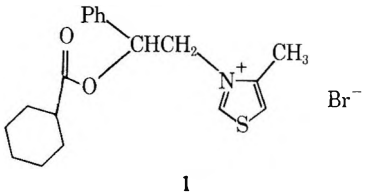
Starting from optically active α-substituted ethylamines, salts of the following thiazolium ions have been synthesized: (*R*)-(−)-3-α-benzylethyl-4-methylthiazolium (**4a**): (*R*)-(−)- and (*S*)-(+)-4-methyl-3-α-(1-naphthyl)ethylthiazolium (**4b**); and (*S*)-(+)-4-methyl-3-α-phenylethylthiazolium (**4c,d**). Asymmetric induction of the benzoin condensation using these thiazolium salts as catalysts has been studied. Optical purities as large as 51% were observed.

Although there have been various reports of reactions with asymmetric induction,[2] relatively few examples of homogeneous asymmetric catalysis are known. The benzoin condensation and related condensations catalyzed by thiazolium salts constitute unique examples of homogeneous catalysis by a relatively simple organic compound of a type of reaction which does not proceed otherwise (except by use of cyanide ion) in finite time. Benzoin is not produced from benzaldehyde by acid or base catalysis, or under thermal or free-radical conditions. Some years ago, a homogeneous, asymmetric benzoin condensation was reported[3] using optically active thiazolium salt **1** as catalyst. The product obtained had an optical purity as high as 22%. This type of reaction provides a good model for the mode of action of thiamine pyrophosphate (TPP) in enzymatic reactions. TPP is required as coenzyme in such systems as the decarboxylation of pyruvate to acetaldehyde and the formation of acetoin or α-acetolacetate from pyruvate.[4] The present study elucidates the stereochemical course of the asymmetric thiazolium salt catalysis of the benzoin condensation (Scheme I).



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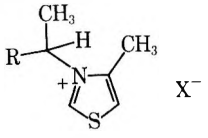
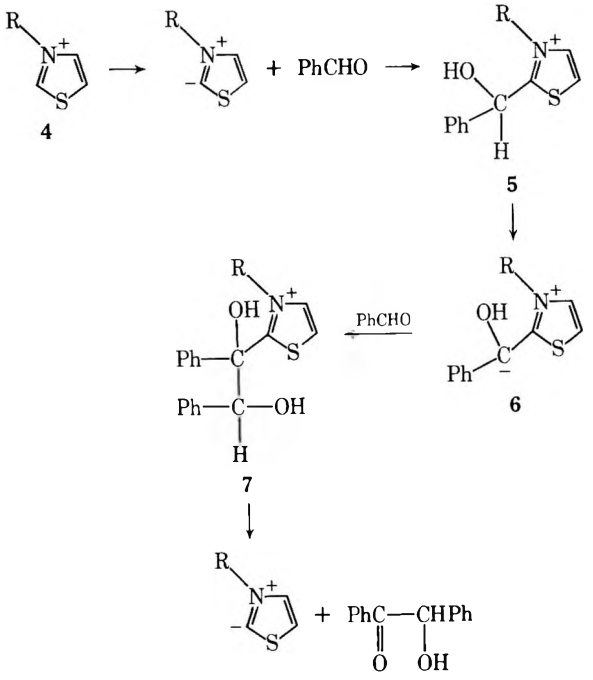
Synthesis of the Catalysts. The following considerations led to the synthesis of 4-methyl 3-α-substituted ethylthiazolium salts **4a–d** as asymmetric catalysts: (a) location of the asymmetric center next to the reacting site, and (b) the high yields of benzoin obtained with 3-benzyl- or 3-phenethylthiazolium salts.[5,6] The higher yields observed suggest an advantage in having a phenyl group in the α or β position of the N substituent.



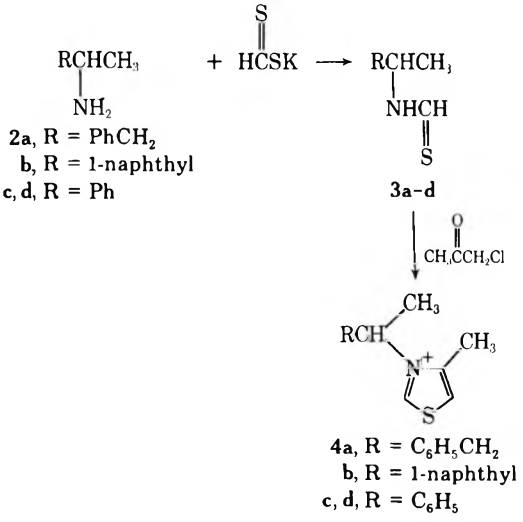
4a, R = $PhCH_2$; X = Cl
b, R = 1-naphthyl; X = Br
c, R = Ph; X = (+)-3-bromocamphor 9-sulfonate
d, R = Ph; X = (−)-3-bromocamphor 9-sulfonate

The crystalline thiazolium salts (*R*)-(−)-**4a**, (*R*)-(−)-**4b**, (*S*)-(+)-**4b**, and (*S*)-(+)-**4c,d** were synthesized according to the procedure of Götze[7] as outlined in Scheme II. Treatment of aqueous solutions of crude thiazolium chlorides with fluoroboric acid gave the thiazolium tetrafluoroborates. The tetrafluoroborate salts were used for purification since the chloride salts could not be recrystallized effectively. The halide salts were regenerated by use of an ion-exchange resin.

Scheme I



Scheme II



4a, R = $C_6H_5CH_2$
b, R = 1-naphthyl
c, d, R = C_6H_5

Thiazolium Salt Catalysis. Most reactions were carried out in methanol and triethylamine.[5] The benzoin produced was isolated by column chromatography on silicic acid. The results of the benzoin condensation reactions are compiled in Table I. Optically active benzoin was obtained by the catalysis of optically active **4b**, **4c**, and **4d**, but not by **4a**, indicating that the effective steric bulk of the benzyl group is considerably smaller than that of the phenyl group in this reaction. The similar optical

Table I
Thiazolium Salt Catalysis of the Benzoin Condensation

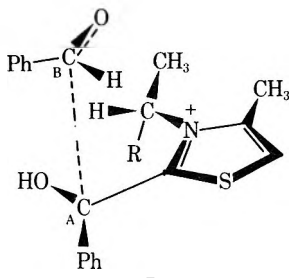
Salt	Reaction conditions,[a] solvent, base, time in hr	Yield,[b] %	Optical rotation[c] $[\alpha]_{436}$ Temp, °C	$[\alpha]$	c	Optical purity,[d] %
(*R*)-(−)-**4a**	MeOH, Et_3N 6	12	23	0	0.92	0
(*S*)-(+)-**4b**	MeOH, Et_3N 6	6.1	21	+221	0.46	51.5
(*R*)-(−)-**4b**	MeOH, Et_3N 24	21	23	−165	1.03	38.5
		17	20.5	−161	0.86	37.5
	MeOH, Et_3N 48	26	25	−126	1.03	29.4
	MeOH–H_2O, NaOH 24	22	23	−133	1.06	31.0
(*S*)-(+)-**4c**	MeOH, Et_3N 25	78	25	+33.6	1.01	7.8
(*S*)-(+)-**4d**	MeOH, Et_3N 25	68	20	+30.4	1.03	7.1

[a] Bath temperature, 30°. [b] Based on benzoin isolated by chromatography on silicic acid. [c] In methanol. [d] Calculated based on the following rotation of (−)-benzoin:[8] $[\alpha]_{436}^{20}$ −429 (*c* 1.01, MeOH).

purities of the benzoins obtained with **4c** and 4d confirm that the chiral anion of the salt does not participate in the asymmetric induction.

Catalysis by **4b** afforded benzoin of fairly high optical purity but low yield. The opposite is found with **4c** and **4d.** These observations indicate that, in the case of 4-methyl 3-α-substituted thiazolium salts, as one group on the asymmetric carbon atom becomes larger the catalytic activity of the salt decreases, presumably owing to steric effects. In addition, the optical purity of the isolated benzoin decreases with increasing time (**4b**). Moreover, it has been shown that benzoin does not racemize detectably under the conditions of the reaction in the absence of a thiazolium salt.[3,9]

The following structure (**7**), determined with the aid of models, is tentatively proposed for the intermediate leading to the predominant product. The criteria used are those established by conformational analyses of transition states by Cram[10] and Prelog.[11] Thus the steric interactions of the various groups help to determine the chirality of the product benzoin, although electronic effects are possible and have been minimized in this discussion. The main assumptions are that the anion formed by addition of benzaldehyde (A) tc the thiazolium ion is basically planar and that approach of a second molecule of benzaldehyde (B) should be from the side opposite the bulky group R. The conformation of the chiral carbon of benzoin (B) is formed in such a way as to minimize the steric interactions of the groups attached to carbons A and B.



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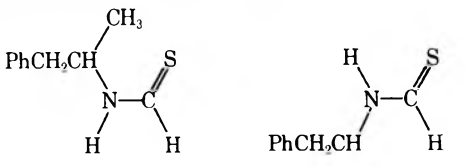
Intermediate **7** subsequently collapses to regenerate the thiazolium ion and an optical isomer of benzoin. If the thiazolium salt has the *S* configuration, the predominant benzoin isomer predicted according to this model also has the *S* configuration. It has been shown[12] that (+)-benzoin and (−)-benzoin are *S* and *R*, respectively, by synthesis from (*S*)-(+)- and (*R*)-(−)-mandelic acids. Thus the observed results are in agreement with the model presented.

Experimental Section

General. Melting points were determined on a Fisher-Johns hot-stage apparatus and are corrected. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Infrared spectra were recorded on a Perkin-Elmer 237 spectrophotometer; only significant maxima are listed. Nuclear magnetic resonance spectra were obtained on a Varian T-60 spectrometer with tetramethylsilane as internal standard. Optical rotations were measured at 436, 546, and 578 mμ on a Zeiss photoelectric precision polarimeter, and the values at 589 mμ (D line) were obtained by using the equation

$$X = \frac{\alpha_{578}}{\alpha_{546} - \alpha_{578}} \qquad \alpha_D = \frac{X(\alpha_{456})}{X + 1.37}$$

Salts of (*R*)-(−)-3-α-Benzylethyl-4-thiazolium Ion (4a). (*R*)-α-Benzyl-*N*-thioformylethylamine (3a). To a stirred solution of (*R*)-(−)-α-benzylethylamine (**2a**)·$\frac{1}{2}H_2SO_4$, $[\alpha]^{21}D$ −22.3° (*c* 0.51, H_2O) [lit.[13] $[\alpha]^{20}D$ −24.57° (*c* 2.00, H_2O)] (2.77 g, 7.52 mmol) in 40 ml of water was added crude dithioformate (prepared[14] from 11.5 g of 86.5% KOH) in 15 ml of water. The reaction proceeded with evolution of a gas. The mixture was stirred at room temperature for 21.5 hr. After the remaining gas was removed by evacuation at 30 mm, the reaction mixture was extracted with two 50-ml portions of ether, and the combined extracts were washed with three 10-ml portions of aqueous NaCl solution and dried over sodium sulfate. The crude material (2.50 g) obtained on evaporation of the solvent was chromatographed on silicic acid with methylene chloride as eluent, and 2.38 g of purified compound **3a** was obtained as an oil: tlc two spots, R_f 0.28 and 0.18 (silica gel, CH_2Cl_2); ir (neat) 3180 (s, broad, -NH-), 1540 (s), and 1450 cm^{-1} (s, C=S); nmr (CCl_4) δ 9.15 (2 H, m, NH and CHS), 7.27 (5 H, Ph), 4.86 (0.64 H, septet, m, $-CH(Z)CH_3$), 3.81 (0.36 H, m, $-CH(E)CH_3$), 3.22-2.52 (2 H, m, $-CH_2Ph$), 1.30 (d, J = 5.2 Hz, $-CH_3(E)$), 1.20 (d, J = 6.6 Hz, $-CH_3(Z)$).



Z form *E* form

(*R*)-(−)-3-α-Benzylethyl-4-methylthiazolium Tetrafluoroborate (4a·BF_4^-). To a stirred solution of (*R*)-**3a** (2.35 g, 0.013 mol) in 20 ml of benzene was added chloroacetone (1.22 g, 0.013 mol) dissolved in 10 ml of benzene, and the mixture was stirred at room temperature overnight and in an oil bath at 75–80° for 15 min. The upper benzene layer was removed from the cooled reaction mixture with a pipette, and the residual gummy material was partitioned between water (30 ml) and methylene chloride (20 ml). The aqueous layer was extracted with four 20-ml portions of methylene chloride, evacuated on a rotary evaporator to remove traces of methylene chloride, and then treated with 49% fluoroboric acid (1.8 ml) by dropwise addition. The precipitated, colorless solid was collected on a filter, washed with water, and dried over phosphorus pentoxide to give 2.05 g (52%), mp 136–

136.5°. Recrystallization from 1,2-dichloroethane gave 1.46 g of crystals, mp 136.8–137.2°, $[\alpha]^{21.5}D$ −104° (c 0.48, MeOH), and recrystallization of the material obtained by evaporating the mother liquor gave 0.38 g of crystals, mp 136.2–137°, $[\alpha]^{21}D$ −103° (c 0.625, MeOH). An analytical sample was obtained by additional recrystallization of the first crop: mp 138–139°; ir (KBr) 1573 (s, thiazolium ring), 1120–1020 cm^{-1} (very s, broad, BF_4^-); nmr (CD_2Cl_2) δ 9.96 (1 H, d, J = 2.8 Hz, ^+N=CHS–), 7.61 (1 H, m, –SCH=C), 7.35–6.94 (5 H, m, C_6H_5–), 4.93 (1 H, m, $CHCH_3$), 3.29–3.15 (2 H, AB of ABX, $C_6H_5CH_2$–), 2.27 (3 H, s, $-CH_3$ on the thiazolium ring), 1.74 (3 H, d, J = 6.9 Hz, $CHCH_3$).

Anal. Calcd for $C_{13}H_{16}BF_4NS$: C, 51.16; H, 5.29; F, 24.91; N, 4.59; S, 10.51. Found: C, 51.46; H, 5.24; F, 24.85; N, 4.58; S, 10.70.

(*R*)-(−)-3-α-Benzylethyl-4-methylthiazolium Chloride (4a·Cl⁻). A solution of the tetrafluoroborate salt (*R*)-(−)-**4a**·BF_4^- (2.23 g, 7.32 mmol) in 50 ml of methanol was applied to a column of anion exchange resin (Dowex 2-X8, chloride form, 20–50 mesh, 50 ml, *ca.* 66 mequiv) and 100 ml of methanol was used to elute the last portion of the solution. The eluent was evaporated to dryness to give 1.99 g of a glass, which slowly crystallized overnight, mp 149–150°, insoluble in acetone, CCl_4, and Et_2O and moderately soluble in $Cl(CH_2)_2Cl$. Recrystallization from $Cl(CH_2)_2Cl$–acetone gave 1.41 g of prisms, mp 150–151°, $[\alpha]^{23}D$ −131° (c 1.40, EtOH). An analytical sample was obtained by additional recrystallization: mp 150–151°; $[\alpha]^{21}D$ −130° (c 1.12, EtOH); ir (KBr) 1569 cm^{-1} (s, thiazolium ring); nmr ($CDCl_3$) δ 11.90 (1 H, d, J = 2.8 Hz, ^+N=CHS–), 8.19 (1 H, –SCH=C), 7.17 (5 H, m, C_6H_5–), 4.94 (1 H, m, $CHCH_3$), 3.79–3.13 (2 H, eight lines, AB of ABX, $C_6H_5CH_2$–), 2.30 (3 H, s, $-CH_3$ on the thiazolium ring), 1.91 (3 H, d, J = 7.0 Hz, $CHCH_3$).

Anal. Calcd for $C_{13}H_{16}ClNS$: C, 61.51; H, 6.36; Cl, 13.97. Found: C, 61.27; H, 6.43; Cl, 13.97.

Salts of 4-Methyl-3-α-(1-naphthyl)ethylthiazolium Ion (4b). (*R*)-(+)-α-(1-Naphthyl)-*N*-thioformylethylamine [(*R*)-(+)-3b]. To a cold, stirred solution of (*R*)-(+)-α-(1-naphthyl)ethylamine (**2b**, 5.13 g, 0.030 mol) in 30 ml of methanol was added dropwise crude potassium dithioformate (22.2 g, prepared[14] from 23 g of 86.5% KOH) dissolved in 30 ml of water, and the mixture was stirred at room temperature overnight. The precipitated solid was collected and washed three times by trituration with water to give 6.0 g (93%), mp 96–101°. The crude product was recrystallized from EtOH–H_2O (2:1) to give 4.32 g of crystals, mp 114.5–115.5°. An analytical sample was obtained by an additional recrystallization: mp 116.5–117.5°; $[\alpha]^{20.5}D$ +505° (c 1.47, EtOH); ir (KBr) 3195 (s, broad, NH), 1519 (s), 1510 (shoulder), 1458 (s), and 1440 cm^{-1} (s, NC=S); nmr (CD_2Cl_2) δ 9.14 (1 H, d, J = 6.9 Hz, –CHS), 8.2–7.1 (7 H, m, $C_{10}H_7$), 6.41 (1 H, m, $CHCH_3$), 1.65 (3 H, d, J = 6.4 Hz, $-CH_3$). When the solution was shaken with D_2O, the doublet at δ 9.14 and the quintet at δ 6.41 collapsed to a singlet and a quartet, respectively.

Anal. Calcd for $C_{13}H_{13}NS$: C, 72.50; H, 6.08; N, 6.51; S, 14.89. Found: C, 72.87; H, 6.09; N, 6.39; S, 14.50.

(*R*)-(−)-4-Methyl-3-α-(1-naphthyl)ethylthiazolium Tetrafluoroborate [(*R*)-(−)-4b·BF_4^-]. The compound was obtained from 1.08 g (5.0 mmol) of (*R*)-(+)-**3b** according to the method described for (*R*)-(−)-**4a**·BF_4^- to give 0.45 g (26.4%) of crude product insoluble in $CHCl_3$, CH_2Cl_2, and acetone, mp 170.5–173°. An analytical sample was obtained by recrystallizing twice from $Cl(CH_2)_2Cl$–EtOH (10:1): mp 178–179° dec (corrected); $[\alpha]^{23.5}D$ −121° (c 1.11, DMSO); ir (KBr) 1480 (s, thiazolium ring), 1160–1000 cm^{-1} (very s, broad, BF_4^-); nmr (DMSO-d_6) δ 10.36 (1 H, d, J = 2.7 Hz, ^+N=CHS–), 8.2–7.07 (8 H, –SCH=C and $C_{10}H_7$–), 6.91 (q, J = 6.5 Hz, $CHCH_3$), 2.38 (3 H, s, $-CH_3$ on the ring), 2.10 (3 H, d, J = 6.5 Hz, $CHCH_3$).

Anal. Calcd for $C_{16}H_{16}BF_4NS$: C, 56.33; H, 4.73; F, 22.27; N, 4.11; S, 9.40. Found: C, 56.91; H, 4.64; F, 22.47; N, 4.25; S, 9.08.

(*R*)-(−)-4-Methyl-3-α-(1-naphthyl)ethylthiazolium Bromide [(*R*)-(−)-4b·Br⁻]. The tetrafluoroborate (*R*)-(−)-**4b**·BF_4^- (1.61 g, 4.72 mmol) was converted to the bromide with anion-exchange resin (Dowex 2-X8, bromide form) as described for **4a**·Cl. The crude compound (1.56 g) showed mp 177–182° dec. After recrystallization from ethanol, 1.20 g of crystals were obtained: mp 178–182° dec; $[\alpha]^{22}D$ −116° (c 1.18, MeOH); ir (KBr) 1479 cm^{-1} (s, thiazolium ring); nmr (DMSO-d_6) δ 10.52 (1 H, d, J = 2.4 Hz, ^+N=CHS–), 8.3–6.8 (9 H, –SCH=C, $C_{10}H_7$–, and $CHCH_3$), 2.38 (3 H, s, $-CH_3$ on the thiazolium ring), 2.08 (3 H, J = 7.1 Hz, $CHCH_3$).

Anal. Calcd for $C_{16}H_{16}BrNS$: C, 57.49; H, 4.83; Br, 23.90; N, 4.19. Found: C, 57.24; H, 4.88; Br, 23.76; N, 4.04.

(*S*)-(−)-α-(1-Naphthyl)-*N*-thioformylethylamine [(*S*)-(−)-3b]. Compound **3b** was made from (*S*)-(−)-α-(1-naphthyl)ethylamine (**2b**), $[\alpha]^{20.5}D$ −90.7° (c 1.84, benzene), as described for (*R*)-(+)-**3b**. The product was recrystallized from EtOH–H_2O to give mp 115.5–116.5°.

Anal. Calcd for $C_{13}H_{13}NS$: C, 72.50; H, 6.08; N, 6.51. Found: C, 72.63; H, 6.10; N, 6.39.

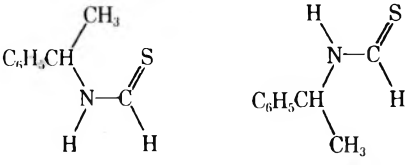
(*S*)-(+)-4-Methyl-3-α-(1-naphthyl)ethylthiazolium Tetrafluoroborate [(*S*)-(+)-4b·BF_4^-]. The compound was obtained from 5.50 g (25.6 mmol) of (*S*)-(−)-**3b** as described for (*R*)-(+)-**4b**·BF_4^- to give 2.93 g (34%) of crude product. Recrystallization from $Cl(CH_2)_2Cl$–EtOH gave 2.14 g of crystals, mp 170–174° dec, $[\alpha]^{21}D$ +118° (c 1.03, DMSO); recrystallization of the material obtained on evaporation of the mother liquor gave a second crop, mp 169–172° dec, $[\alpha]^{23}D$ +118° (c 0.99, DMSO).

Anal. (first crop). Calcd for $C_{16}H_{16}BF_4NS$: C, 56.33; H, 4.73; N, 4.11. Found: C, 56.09; H, 4.75; N, 4.09.

(*S*)-(+)-4-Methyl-3-α-(1-naphthyl)ethylthiazolium Bromide [(*S*)-(+)-4b·Br⁻]. The compound was obtained from (*S*)-(+)-**4b**·BF_4^- as described for (*R*)-(−)-**4b**·Br^-, mp 184.5–186.5°, $[\alpha]^{20}D$ +121° (c 0.98, MeOH). Spectra are identical with those of (*R*)-(−)-**4b**·Br^-.

Anal. Calcd for $C_{16}H_{16}BrNS$: C, 57.49; H, 4.83; N, 4.19. Found: C, 57.68; H, 4.68; N, 3.96.

Salts of 4-Methyl-3-α-phenylethylthiazolium Ion (4c). (*S*)-α-Phenyl-*N*-thioformylethylamine (3c) was prepared as described for **3b** starting with (*S*)-(−)-α-phenylethylamine (**2c**), $[\alpha]^{20.5}D$ −37.6° (neat) [lit.[15] $[\alpha]^{22}D$ −40.3° (neat)]. However, as the product was separated from the reaction mixture as an oil, it was extracted with ether. The crude product obtained from 1.82 g (0.015 mol) of (*R*)-**2c** was chromatographed on silicic acid (70 g) with methylene chloride, giving 1.93 g of purified compound as an oil: tlc two spots (silica gel, CH_2Cl_2), R_f 0.34 and 0.24; ir (neat) 3080 (s, broad, NH), 1524 and 1439 cm^{-1} (s, C=S); nmr (CCl_4) δ 7.27 (5 H, $-C_6H_5$), 5.72 (0.75 H, m, $-CH(Z)CH_3$), 4.69 (0.25 H, m, $-CH(E)CH_3$), 1.52 (3 H, d, J = 7.0 Hz, $-CH_3(Z)$ and $-CH_3(E)$).



(*S*)-(+)-4-Methyl-3-α-phenylethylthiazolium Iodide (4c·I⁻). To a stirred solution of (*S*)-**3c** (3.81 g, 0.231 mol) in benzene (50 ml) was added chloroacetone (2.14 g, 0.23 mol) dissolved in 5 ml of benzene, and the mixture was stirred at room temperature overnight and in an oil bath at 70° for 0.5 hr. The upper benzene layer was removed from the cooled reaction mixture with a pipette, and the residual gummy material was partitioned between water (80 ml) and benzene (50 ml). The aqueous layer was washed with four 50-ml portions of methylene chloride and then treated with potassium iodide (15 g) by portionwise addition. Immediate separation of an oil was observed. The mixture was extracted with two 70-ml portions of methylene chloride, and the combined extracts were washed with water (20 ml), dried over sodium sulfate, and evaporated to dryness to give 3.50 g (46%) of an oil, which failed to crystallize, although the ir spectrum suggested high purity, ir spectrum (neat) 1570 cm^{-1} (s, thiazolium ring).

(*S*)-(+)-4-Methyl-3-α-phenylethylthiazolium (+)-3-Bromocamphor-9-sulfonate [(*S*)-(+)-4c·(+)-CSA]. To a stirred solution of (*S*)-(+)-**4c**·I^- (1.20 g, 3.63 mmol) in ethanol (30 ml) was added powdered silver (+)-3-bromocamphor-9-sulfonate monohydrate[16] (1.58 g, 3.63 mmol), and the mixture was stirred at room temperature overnight and heated at reflux with stirring for 0.5 hr. The cooled reaction mixture was filtered to remove AgI, and the filtrate was evaporated to dryness to give 1.83 g of crude compound as a slightly yellow solid. After recrystallization from $Cl(CH_2)_2Cl$, the product showed mp 168–170.5°. An analytical sample was prepared by repeated recrystallization from $Cl(CH_2)_2Cl$: mp 173.5–175°; $[\alpha]^{25}D$ +94° (c 0.50, EtOH); ir (KBr) 1750 (s, C=O), 1573 (m, thiazolium ring), ~1200 and 1038 cm^{-1} (s, SO_2); nmr (DMSO-d_6) δ 10.54 (1 H, d, J = 3.0 Hz, ^+N=CHS–), 8.14 (1 H, –SCH=C), 7.43 (5 H, C_6H_5–), 6.11 (1 H, q, C_6H_5CH), 4.97 (1 H, d, J = 4.5 Hz, CHBr), 1.98 (3 H, d, J = 7.1 Hz, $CHCH_3$), 1.12 (3 H, s, $-CH_3$ of the anion), 0.83 (3 H, s, $-CH_3$ of the anion).

Anal. Calcd for $C_{22}H_{28}BrNS_2O_4$: C, 51.34; H, 5.48; Br, 15.53; N, 2.72; S, 12.46. Found: C, 51.72; H, 5.67; Br, 15.39; N, 2.76; S, 12.47.

(*S*)-(+)-4-Methyl-3-α-phenylethylthiazolium (−)-3-Bromo-

camphor-9-sulfonate [(*S*)-(+)-4c·(−)-CSA]. The compound was prepared from (*S*)-(+)-4c·I^- and silver (−)-3-bromocamphor-9-sulfonate monohydrate as described for (*S*)-(+)-4c·(+)-CSA^-. The crude solid was recrystallized twice from $Cl(CH_2)_2Cl$ to give colorless crystals: mp 179°; $[\alpha]^{20.5}D$ −25.2° (c 0.522, EtOH); ir (KBr) 3500 (s), 3450 (s), 1747 (s, C=O), 1649 (m), 1572 (m, thiazolium ring), ~1200 (s), and 1040 cm^{-1} (s, SO_2).

Anal. Calcd for $C_{22}H_{28}BrNS_2O_4$: C, 51.34; H, 5.48; N, 2.72; S, 12.46. Found: C, 51.11; H, 5.49; N, 2.78; S, 12.28.

Benzoin Condensation Catalyzed by Thiazolium Salts. The molar ratio of benzaldehyde:triethylamine:catalyst was 10:1:~0.95. The concentrations of the reaction mixtures ranged from 0.19 to 0.35 millimoles of catalyst/milliliters of solvent. In all reactions benzaldehyde was added to a solution of the catalyst in methanol (methanol-H_2O, 0.98:2.3 v/v) under nitrogen. A methanolic solution of triethylamine was added dropwise with stirring. After stirring for 24 hr at 30° the reaction mixture was evaporated to dryness and the residue was chromatographed on silicic acid with chloroform. After unreacted benzaldehyde, benzoin was eluted. When the initial separation of benzoin was incomplete, the overlapped portion was rechromatographed with chloroform–benzene (70:30).

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Registry No.—(*R*)-2a·½H_2SO_4, 51-62-7; (*R*)-(+)-2b, 3886-70-2; (*S*)-(−)-2b, 10420-89-0; (*S*)-2c, 2627-86-3; (*R*)-3a, 50486-64-1; (*R*)-(+)-3b, 50486-65-2; (*S*)-(−)-3b, 50486-66-3; (*S*)-3c, 50486-67-4; (*R*)-(−)-4a·BF_4^-, 50477-40-2; (*R*)-(−)-4a·Cl^-, 50486-68-5; (*R*)-(−)-4b·BF_4^-, 50477-41-3; (*R*)-(−)-4b·Br^-, 50486-69-6; (*S*)-(+)-4b·BF_4^-, 50477-42-4; (*S*)-(+)-4b·Br^-, 50486-70-9; (*S*)-(+)-4c·I^-, 50486-71-0; (*S*)-(+)-4c·(+)-CSA, 50486-72-1; (*S*)-(+)-4c·(−)-CSA, 51064-34-7.

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Stable Carbonium Ions from β-Arylalkyl Derivatives in $SbF_5·SO_2$. II. Ions Related to Mescaline[1,2]

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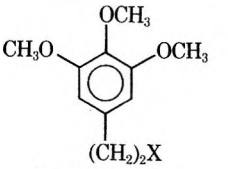
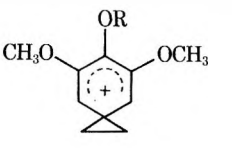
A study of carbonium ions formed from a series of β-di- and trimethoxyphenyl-1-chloroethanes and 2-(o-anisyl)-1-chloroethane in either $SbF_5·SO_2$ or $SbF_5·SO_2·BF_3$ was carried out. Methoxy-stabilized phenonium ions were generated only from BF_3 complexes of the di- and trimethoxyphenyl-1-chloroethanes in $SbF_5·SO_2$ wherein the number of ortho and para methoxy groups was greater than the number of meta "destabilizing" methoxys. The 2-(o-anisyl)-1-chloroethane gave the oxonium ion **14**, whereas its BF_3 complex gave phenonium ion **15**. In the reaction system $SbF_5·SO_2·BF_3$, the major reaction competing with phenonium ion formation appeared to be C-protonation by trace amounts of HF. The oxonium ion was obtained from 2-(2′,5′-dimethoxyphenyl)-1-chloroethane in $AgSbF_6·SO_2$ at −20°. No benzylic ion formation was observed in these systems, apparently because the stable ring carbon protonated ions will not readily undergo abstraction of Cl^- by SbF_5.

A variety of ideas have been offered in attempts to correlate physiological activity and structure in mescaline (**1a**), amphetamines, and other hallucinogens.[4]

A report[5] that 2-(3′,4′,5′-trimethoxyphenyl)ethanol (**1b**) (a minor rat mescaline metabolite[6c]) or 3′,4′,5′-trimethoxyphenylacetaldehyde produced potent biological effects in rats at significantly lower doses than mescaline, coupled with the isolation of demethylated products[6] from *in vivo* mescaline metabolism [such as 3′,4′-dihydroxy-5′-methoxyphenylacetic acid and 2-(3′-hydroxy-4′,5′-dimethoxyphenyl)ethylamine], suggests the interesting possibility of the intervention of ions or ion pairs such as **2** or **3** at some stage in the biochemistry of mescaline. Such ions seem reasonable, since both alkoxycarbonium ions and the *p*-anisonium ion (**4**) are known to be exceptionally stable, and at least in the case of simple methoxy carbonium ions excellent methylating agents as well.[7,8] Further, Sung and Parker have recently observed a linear correlation between intermolecular charge transfer transition energies and biological activity in mescaline units for a series of psychoac-



1a, X = NH_2
b, X = OH



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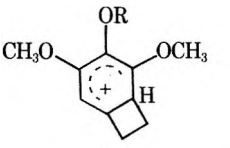

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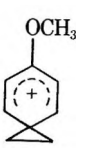

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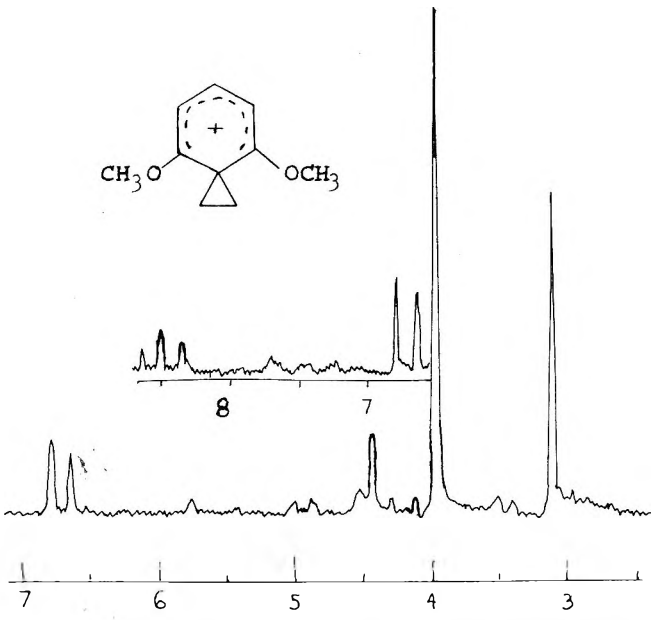


Figure 1. Nmr spectrum of the reaction mixture of 2-(2′,6′-dimethoxyphenyl)-1-chloroethane with BF_3 and SbF_5 in SO_2. Ionization at −70°, spectrum recorded at −30°.

tive methoxyamphetamines.[9] In view of the excellent correlation between charge transfer transition energies, or aryl group ionization potentials, and logarithms of solvolysis rate constants for β-arylalkyl derivatives,[10] this result would be very consistent with rate-determining formation of either phenonium ion or β-methoxyphenyl carbonium ion-like intermediates in the reactions responsible for hallucinogenic activity in mescaline and the amphetamines.

We report here a study of the formation of stable cations in SbF_5·SO_2 and similar solvents from methoxyphenethyl chloride precursors [$(CH_3O)_nC_6H_{5-n}CH_2CH_2Cl$, n = 2, 3] which could be expected to yield **2**, **3**, and analogous ions.

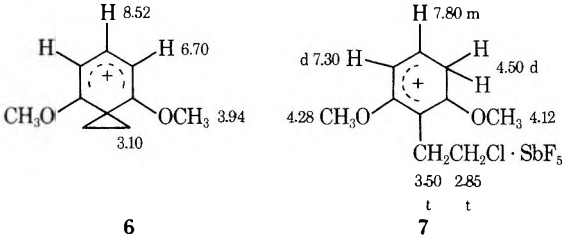
Results and Discussion

Initial attempts to ionize di- and trimethoxyphenethyl chlorides in SbF_5·SO_2 at −70° produced dark, viscous solutions with nmr spectra having only broad and unresolved bands. Since similar problems were not encountered in earlier studies of β-anisylalkyl derivatives,[1] we attributed these complications to increased reactivity of the di- and trimethoxy-substituted phenyl ring toward sulfination, polymerization, and protonation. We decided, therefore, to block one or more of the methoxyl groups by initial complexing with BF_3 in the hope that this would deactivate the aryl ring toward undesirable side reactions but would not prevent phenonium ion formation. This approach has met with modest success.

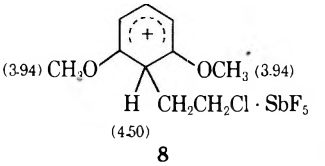
Proton nmr chemical shifts (−δ) (d or t is doublet or triplet) for the ions observed are indicated next to the appropriate hydrogens in the text structures. Chemical shifts in parentheses should be regarded as tentative in assignment.

2-(2′,6′-Dimethoxyphenyl)-1-chloroethane (5). Ionization of the BF_3 complex of **5** in SbF_5·SO_2 at −70° produces, after warming to −30°, a solution whose nmr spectrum is given in Figure 1. Quenching of the −70° solution in methanol yields 30–40% of 2-(2′,6′-dimethoxyphenyl)-ethyl methyl ether and 60–70% of unreacted chloride. The nmr spectrum (Figure 1) is easily assigned to the expected dimethoxyphenonium ion **6**. The sharp singlet at δ 3.10 (relative area 4.0) for the cyclopropyl hydrogens (compared to δ 3.47 for the parent *p*-anisonium ion) is a clear signal of phenonium ion formation. The two methoxyls appear at δ 3.94 (relative area 6.2) and ring protons are displayed very nicely as a doublet (δ 6.70) and triplet (δ 8.25) with relative areas of 1.8 and 1.0.

At −70°, nmr spectra[11] of SbF_5·SO_2 solutions of **5** indicate only very little, if any, phenonium ion formation. Comparisons of the −70° spectra with proton chemical shifts and spectra recently reported[12] for carbon-protonated di- and trimethoxybenzenes in similar solvents strongly support the formation of ions **7** (major) and **8** (minor), which then account for the recovered starting material. There is no evidence of benzylic ion formation from **5** either in the solution nmr spectra, where a strong characteristic $RCHCH_3^+$ methyl *doublet*[8b] would be expected near δ 3.0, or in the quenching products which normally provide benzylic methyl ethers from benzylic ions.[1]

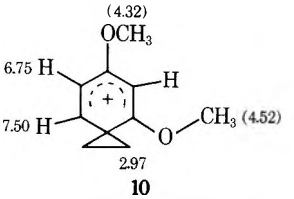


6 **7**



8

2-(2′,4′-Dimethoxyphenyl)-1-chloroethane (9). Acetolysis of 2-(2′,4′-dimethoxyphenyl)ethyl brosylate is about 20 times faster than that of the *p*-anisylethyl brosylate,[13] and easy formation of a phenonium ion from **9** was anticipated. Ionization of BF_3 complexes in SbF_5·SO_2, however, produced only complex spectra. Ionization at −60° of the mono-BF_3 complex of **9** in SOClF, however, produced a simple spectrum in which the presence of the expected dimethoxy phenonium ion **10** was clearly indicated by a sharp singlet of cyclopropyl protons (δ 2.97) and two singlet methoxyl resonances (at δ 4.32 and 4.52) in relative 4:3:3 areas.[11] The indicated assignment, **10**, was made on the basis of the chemical shift of the ortho anisonium ion (CH_3O δ 4.62) compared with that of the para anisonium ion (CH_3O δ 4.25),[8] although any cyclopropyl ring anisotropic effect should produce[14] an *upfield* shift of the ortho CH_3O relative to para CH_3O groups; it is possible that these assignments should be reversed.



10

Even −60° SO_2ClF solutions deteriorated rapidly, however, and methanolic quenching yielded only 15% of the dimethoxyphenyl methyl ether by glc analysis.

2-(2′,3′,6′-Trimethoxyphenyl)-1-chloroethane (11). Ionization of the tris-BF_3 complex of **11** at −70° in SbF_5·SO_2 produced a green solution with a complex nmr spectrum[11] containing at least six different CH_3O resonances between δ 3.60 and 4.50. A very strong isolated singlet at δ 2.98 in the nmr spectrum again, however, is indicative of the formation of ion **12**, and peak areas are in agreement with the indicated assignments. Further, methanolic quenching of solutions provided the expected methyl ether from **12**. The overall complexity, however, of the nmr spectrum suggests the presence of other ions

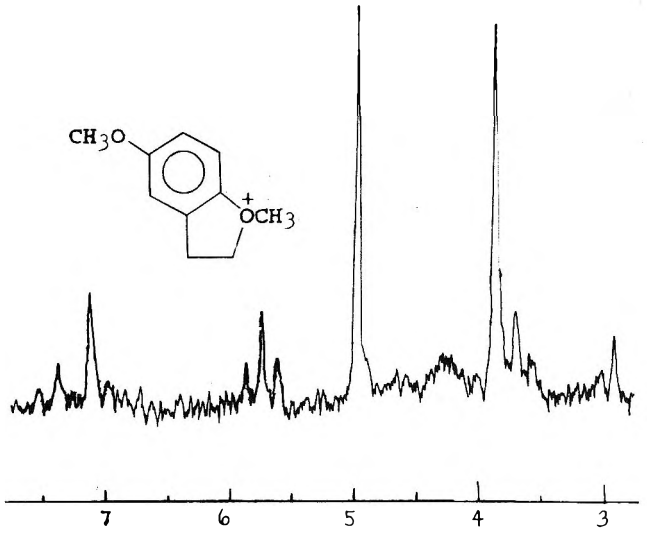
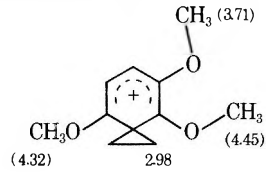


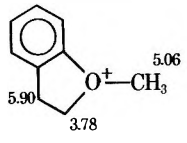
Figure 2. Nmr spectrum of the reaction mixture of 2-(2′,5′-dimethoxyphenyl)-1-chloroethane with $AgSbF_6$ in SO_2. Ionization at −70°, spectrum recorded at −20°.

formed by 1′ and 3′ ring protonation. As in previous cases, the absence of benzylic ions was notable.

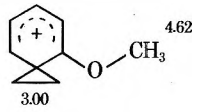


12

2-(o-Anisyl)-1-chloroethane (13). Since we reported earlier[1] that the ionization of o-anisylethyl chloride in $SbF_5 \cdot SO_2$ at −70° produced the oxonium ion **14** rather than the *o*-anisonium ion **15**, we have reinvestigated the ionization of the BF_3 complex under the conditions reported here. In addition to nmr resonances previously identified[1] with **14**, the nmr spectra of BF_3 complexes of **13** in $SbF_5 \cdot SO_2$ at −20° exhibit additional strong singlet resonances at δ 3.00 and 4.62 which may be assigned to the o-anisonium ion **15**. Methanolic quenching of **14** and **15** lead to recovery of the o-anisylethyl methyl ether.

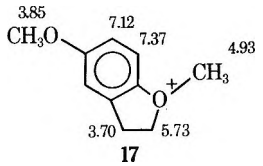


14



15

2-(2′,5′-Dimethoxyphenyl)-1-chloroethane (16). In the case of **16**, the 5′-methoxyl is in a position which actually leads to inductive destabilization of the phenonium ion which would normally result from aryl participation in the ionization. For example, the acetolysis rate of 2-(*m*-anisyl)-ethyl brosylate is roughly 80 times slower than that of the *p*-anisyl derivative, and even slightly slower than that of the parent 2-phenylethyl brosylate.[13] Attempts to generate a recognizable ion from **16** in $SbF_5 \cdot SO_2 \cdot BF_3$, $SbF_5 \cdot SO_2$, or $SbF_5 \cdot SO_2ClF$ by previous procedures were without success. A change, however, from the "superacid" system $SbF_5 \cdot SO_2$ to $AgSbF_6 \cdot SO_2$ produced a green solution of the oxonium ion **17** from precursor **16**. The ^1H nmr spectrum of **17** at −20° is given in Figure 2.



17

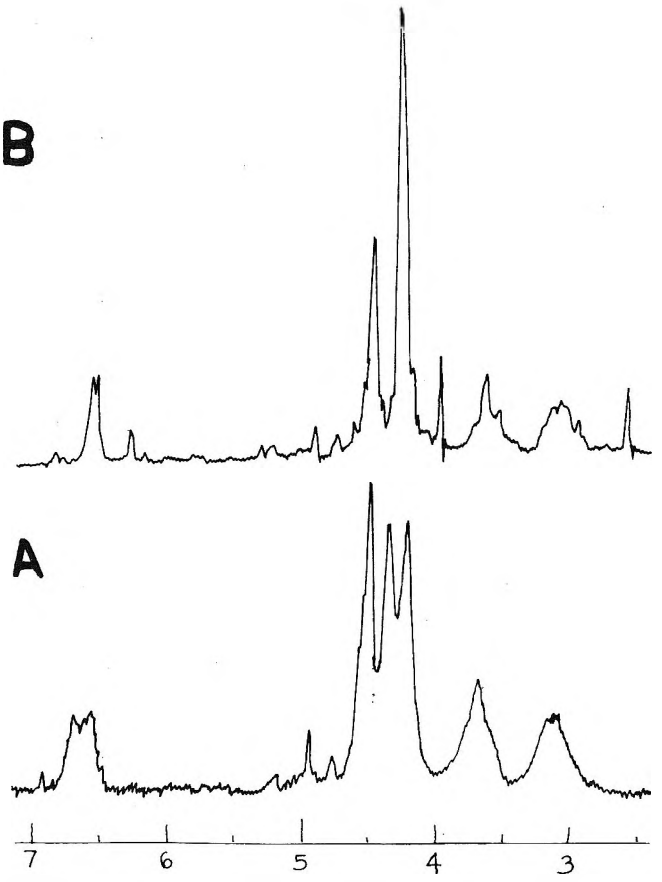
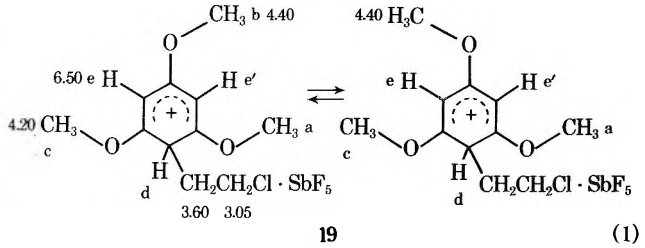


Figure 3. Nmr spectrum of the reaction mixture of 2-(2′,4′,6′-trimethoxyphenyl)-1-chloroethane with SbF_5 in SO_2, ionization at −70°: (A) spectrum at −60°; (B) spectrum at −20°.

2-(2′,4′,6′-Trimethoxyphenyl)-1-chloroethane (18). Ionization of either the mono-BF_3 complex of **18** or the free chloride in $SbF_5 \cdot SO_2$ at −70° and subsequent warming to −20° produced solutions whose nmr spectra gave no sign of any major benzylic phenonium ion formation (Figure 3). The spectrum (Figure 3) of **18** in $SbF_5 \cdot SO_2$ is most simply explained by equilibrating conformers of a carbon-protonated ion such as **19** (eq 1). Rapid proton exchange



19 (1)

at e and e′ in **19** would collapse the δ 4.40 singlet as methoxyls a and c became equivalent and may be excluded. The absence of a sharp two-proton singlet near δ 4.00 as found[12] for monoprotonated 1,3,5-trimethoxybenzene also rules out protonation at positions e or e′ at −20°. At −60° (Figure 3a) equilibration between conformers (eq 1) is sufficiently slow that the different CH_3O groups (a or c) begin to be resolved into a doublet centered about δ 4.30, and the three nonequivalent methoxyls of **19** may now be seen. The proton d is unobserved as a weak or buried triplet. This interpretation is supported by relative areas of 6:3 for the δ 4.30 doublet and 4.50 singlet at −60° and the δ 4.20 and 4.40 singlets at −20°. Steric models appear to preclude easy rotation of methoxyls a and c to form other rotational conformers.

The absence of significant phenonium ion formation from solutions of **18** in $SbF_5 \cdot SO_2$ could reflect the unusual

thermodynamic stability of the C-protonated species **19**, since 1,3,5-trimethoxybenzene protonates readily in 70% perchloric acid.[15]

Quenching of various SbF_5·SO_2 solutions of **15** in cold methanol and sodium ethoxide gave 2-(2′,4′,6′-trimethoxyphenyl)ethyl methyl ether in yields ranging from 35% (from BF_3 complex) to 15–20%. This suggests either that the C-protonated species may be in rapid equilibrium at quenching temperatures with the desired trimethoxyphenonium ion, or that S_N2 attack at $-CH_2Cl$·SbF_5 is favorable in this case. Phenonium ion concentrations of the order of 20% are consistent with the singlets at δ 2.55 (assigned to cyclopropyl) and 3.90 (CH_3O) (Figure 3b).

2-(3′,4′,5′-Trimethoxyphenyl)-1-chloroethane (20). Protonation of 1,2,3-trimethoxybenzene in strong acid occurs at the 4 position,[12] and one might expect analogous protonation of mescaline or the chloroethane **20**. However, the 4′ methoxy group of mescaline is easily and selectively hydrolyzed by 20% hydrochloric acid.[16] This is easily rationalized only by ring protonation at the 1′ position of mescaline in dilute aqueous acid, since 2′ protonation should produce hydrolysis of the 3′ (and 5′) methoxyl groups. Low-temperature nmr spectra at −70° of **20** in SbF_5·SO_2 are consistent at least with protonation at both 1′ and 2′ ring positions.

Only the starting chloride could be recovered when these solutions were quenched in cold methanol, and on this basis and the nmr spectra, formation of both benzylic and phenonium ions as major products may be ruled out.

2-(3′,4′- and 2′,3′-Dimethoxyphenyl)-1-chloroethane (21 and 22). Precursors **21** and **22** under the conditions reported here produced only unstable solutions whose nmr spectra contained no recognizable ions.

Conclusions

Except in the case of 2′,4′,6′-trimethoxyphenyl-1-chloroethane, provided that the number of ortho and para methoxy groups exceeded the number of meta "destabilizing" methoxyls, methoxy-stabilized phenonium ions could be generated from BF_3 complexes of di- and trimethoxyphenyl-1-chloroethanes in SbF_5·SO_2. Where ortho methoxy groups are available, unless these groups are coordinated to BF_3, our results here and those reported previously for *o*-anisylethyl chloride[1] suggest that, at least in SbF_5·SO_2, ortho oxygen participation to form an oxonium ion is favored over phenonium ion formation. In the reaction system reported here (BF_3·SO_2·SbF_5), the major reaction competing with phenonium ion formation appears to be C-protonation by trace amounts of HF. In fact, in the case of 2-(2′,4′,6′-trimethoxyphenyl)-1-chloroethane, our results seem to indicate that the C-protonated ion may be thermodynamically more stable than the corresponding trimethoxyphenonium ion, since the 2′,6′-dimethoxy-3′-C-protonated ion **7** is converted to a dimethoxyphenonium ion **6** at higher temperatures.

Benzylic ion formation is common[1] in SbF_5·SO_2 solutions of p-$CH_3OC_6H_5CR_2CR_2X$ (R = H or CH_3; X = OH or Cl) and the absence of benzylic ion formation in the polymethoxyphenethyl chloride systems investigated here is interesting. We have been unable to prepare SbF_5·SO_2 solutions free of the HF which results from hydrolysis of SbF_5 by trace amounts of water, and the increased basicity of polymethoxy-substituted phenyl rings clearly favors formation of thermodynamically stable ring-protonated ions such as **7** and **19**. Ionization of the primary carbon–chlorine bond in these ions with subsequent or concurrent hydride migration to form a benzylic ion is effectively prohibited by the positively charged protonated ring.

With regard to any proposed metabolic mechanism for *in vivo* activity or demethylation of mescaline, our results do demonstate the stability of polymethoxy-stabilized phenonium ions and encourage us to believe that the ions **2** and/or **3** could be obtained in suitable systems either free of protonic acids or with suitable steric requirements. These ions **2** and/or **3**, or similar ion pairs, remain reasonable intermediates in the *in vivo* reactions of mescaline derivatives.

Experimental Section

The nmr spectra were obtained on a Varian Model A-60 spectrometer with a variable-temperature probe. All synthesized compounds and isolated products from the quenching of ion solutions had nmr and infrared spectra consistent with the assigned structure. The nmr spectra of ions were obtained using internal capillary reference tetramethylsilane (TMS), and chemical shifts (δ, parts per million downfield from TMS) are indicated next to the appropriate hydrogens in the text structures.

Preparation of Ions. The complexing of the various methoxyphenylethyl chlorides with BF_3 was accomplished by first dissolving these compounds in SO_2. To the solution calculated amounts of BF_3 were transferred by means of a vacuum line. The reaction flask containing SO_2 and the BF_3–methoxyphenylethyl chloride complex was then removed from the vacuum line and equipped with a three-necked head containing two liquid nitrogen cold fingers with the center neck covered with a rubber septum. This assembly was then placed in a Dry Ice–acetone bath. A previously prepared SbF_5·SO_2 or SbF_5·SO_2ClF solution was then rapidly injected into the reactor by means of the rubber septum adapter, with vigorous stirring during addition. In some cases the SbF_5·SO_2 or SbF_5·SO_2ClF was frozen in liquid nitrogen and added at a slower rate as the solution warmed up.

The oxonium ion **17** was prepared by the dropwise addition of 2-(2′,5′-dimethoxyphenyl)-1-chloroethane (2 mmol) from a syringe (equipped with a 25-gauge needle) to a rapidly stirred solution of $AgSbF_6$ (4 mmol) in excess SO_2 (5–7 ml), following the general procedure of Olah.[17] After the solution had stood for 1 hr without stirring, a sample was withdrawn and the nmr spectrum was determined at −20° (Figure 2).

Drowning of the ions was accomplished by pouring the ion solution into methanol or methanol and sodium methoxide at −70°. The mixture was warmed to room temperature, poured into ether, and washed first with 5% sodium bicarbonate and finally with saturated sodium bicarbonate. The etheral solution was washed with water, dried, and evaporated to leave a crude residue, which was chromatographed on neutral alumina. The products were identified by infrared and nmr, and by comparison of glc retention times and peak enhancement with authentic compounds.

Synthesis of Arylethyl Alcohols and Chlorides. Details of the synthesis and physical properties of the alcohols 2-(2′,6′-dimethoxyphenyl)ethanol, 2-(2′,4′-dimethoxyphenyl)ethanol, 2-(2′,4′,6′-trimethyoxyphenyl)ethanol, and 2-(2′,5′-dimethoxyphenyl)ethanol as well as their corresponding chlorides are given[11] as supplementary material.

Registry No.—**5** BF_3 complex, 51016-46-7; **6**, 50986-73-7; **9** mono-BF_3 complex, 50987-63-8; **10**, 50986-72-6; **11** tris-BF_3 complex, 51016-48-9; **12**, 50986-71-5; **13** BF_3 complex, 51016-49-0; **14**, 35144-41-3; **15**, 50986-70-4; **16** BF_3, 51016-51-4; **17**, 50987-64-9; **18**, 832-86-0; **18** mono-BF_3 complex, 50987-65-0; **19**, 50986-69-1; **20**, 50987-66-1; SbF_5, 7783-70-2; SO_2, 7446-09-5; SOClF, 13637-84-8; $AgSbF_6$, 26042-64-8.

Supplementary Material Available. Full nmr spectra will appear following these pages in the microfilm edition of this volume of the journal for the following reaction mixtures as figures with comments: 2-(2′,6′-dimethoxyphenyl)-1-chloroethane with BF_3 and SbF_5 in SO_2 at −70°; 2-(2′,4′-dimethoxyphenyl)-1-chloroethane with BF_3 and SbF_5 in SO_2ClF, ionization at −70°, spectrum recorded at −20°; 2-(2′,3′,6′-trimethoxyphenyl)-1-chloroethane with BF_3 and SbF_5 in SO_2, ionization at −70°, spectrum recorded at −20° after 1 hr at −20° (peaks indicated by a are assigned to ion **12**). 2-(*o*-anisyl)-1-chloroethane with BF_3 and SbF_5 in SO_2, ionization at −70°, spectrum recorded at −20°; 2-(3′,4′,5′-trimethoxyphenyl)-1-chloroethane with SbF_5 in SO_2 at −70°. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-1199.

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Aromatic Substitution. XXXII.[1] Aluminum Chloride Catalyzed Arenesulfinylation of Benzene and Toluene with Benzenesulfinyl and Substituted Benzenesulfinyl Chlorides in Nitromethane Solution

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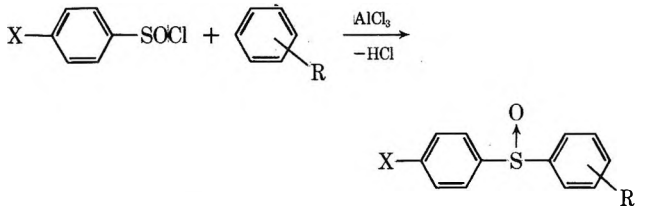
Aluminum chloride catalyzed arenesulfinylation of benzene and polymethylbenzene with substituted benzenesulfinyl chlorides in nitromethane showed that the reaction is of high selectivity. The linear correlation between logarithms of k_{tol}/k_{benz} values and Brown σ^+ substituent constants gives a positive ρ value. These data contrast with previously reported data of sulfonylation and indicate the differing nature of the reactions. The mechanism of the reaction is discussed based on experimental data.

Our preceding work has proved in the case of a series of studied reactions that the transition state of electrophilic aromatic substitutions is not rigidly fixed, resembling the Wheland intermediates (σ complex), but frequently represents a much earlier state on the reaction coordinate resembling starting aromatics (*i.e.*, being of the π-complex character).[3] It was possible to vary in a systematic way the electrophilicity of reagents, such as alkylating agents, by introducing suitable substituents. Thus, a regular change of the transition state of highest energy can be observed from σ-complex to π-complex nature corresponding to the "late" or "early" position of the transition state along the reaction coordinate.

Reactions studied included the titanium tetrachloride catalyzed benzylation of benzene and toluene with substituted benzyl chlorides, giving k_T/k_B rate ratios varying between 2.5 and 136.0 and a correspondingly significant change of the ortho/para isomer ratio.[4] The results of benzoylation of benzene and toluene with substituted benzoyl halides further proved the importance of substituents in the electrophilic substituting agent influencing both substrate and positional selectivity.[5] Aryl thiolcarboxylation also showed the same substituent effect on k_T/k_B and isomer ratio.[6]

Related to these carbocationic reactions, arenesulfonylation of aromatics was also investigated with arenesulfonyl halides.[7] In spite of the fact that the sulfonylation reaction is regarded as an analog of the acylation reaction, it is interesting that the para-substituent effects in arenesulfonyl chlorides on both substrate and positional selectivity show closer similarity to those found in benzylation than in benzoylation reactions. Therefore, from a mechanistic point of view, Friedel–Crafts sulfonylation cannot be considered as a simple analog of the acylation reaction. In order to further study the possible scope and implication of this observation, we undertook a study of the aluminum chloride catalyzed arenesulfinylation of aromatics with benzenesulfinyl and substituted benzenesulfinyl chlorides in which the electron-deficient center of the electrophilic reagent is also on sulfur.



Arenesulfinylation of aromatics giving diaryl sulfoxides was so far little studied. The literature contains but a single report[8] of the preparation of aryl sulfoxides by this reaction. The reaction was found in our hands to be of general utility and allowed us to study the mechanism of arenesulfinylation, including the effect of substituents in the arenesulfinylating agent on the reaction.

Results and Discussion

In order to study the inter- and intramolecular selectivities of Friedel–Crafts arenesulfinylation reactions, we determined, by the use of the competititve method, the relative rates (compared to benzene) of the *p*-toluenesulfinylation of a series of polymethylbenzenes, as well as the related isomer distributions of the alkyl and aryl sulfoxides formed. Data obtained are summarized in Table I.

The results summarized in Table I show that the sulfinylating agent obviously is a very weak electrophile, giving reactions of high selectivity with the aromatic substrates. Data of Table I in comparison with known σ basicities[9] (against $HF-BF_3$ as determined by equilibrium studies by Mackor) show good correlation, indicating that the transi-

Table I
Competitive Sulfinylation of Benzene and Polymethylbenzenes with *p*-Toluenesulfinyl Chloride[a]

Registry no.	Substituted benzene	Relative σ-complex stability ($HF-BF_3$)	Relative rate k_T/k_B	Isomer distribution of substituted diphenyl sulfoxides
71-43-2	H	1	1	
108-88-3	CH_3	790	420	8% 2,4, <0.5% 3,4,[b] 92% 4,4
95-47-6	1,2-$(CH_3)_2$	7,600	7,600	0.8% 2,3,4′-$(CH_3)_3$ 99.2% 3,4,4′-$(CH_3)_3$
108-38-3	1,3-$(CH_3)_2$	1,000,000	59,000	100% 2,4,4′-$(CH_3)_3$
106-42-3	1,4-$(CH_3)_2$	3,200	970	100% 2,5,4′-$(CH_3)_3$
108-67-8	1,3,5-$(CH_3)_3$	630,000,000	250,000	100% 2,4,6,4′-$(CH_3)_4$

[a] Reaction conditions: arenes, 0.4 mol; aluminum chloride, 0.01 mol; toluenesulfinyl chloride, 0.01 mol; nitromethane, 10 ml; reaction temperature, 25°; reaction time, 30 min. [b] Small amounts (<0.5%) of meta isomer (if any) could not be separated from the ortho isomer by glc (within the limit of experimental data).

Table II
Concentration Variation of Benzene and Toluene in Competitive *p*-Toluenesulfinylation

Benzene:toluene	k_T/k_B
10:1	440
5:1	390
3:1	380

Table III
Competitive Sulfinylation of Benzene and Toluene with Substituted Benzenesulfinyl Chlorides[a]

Registry no.	XC_6H_4SOCl, X	k_T/k_B	Isomer distributions, % Ortho	Meta	Para
31401-23-7	*p*-CH_3O	460	8	<0.5	92
10439-23-3	*p*-CH_3	420	8	<0.5	92
50986-83-9	*p*-F	560	5	<0.5	95
4972-29-6	H	660	10	<0.5	90
2901-92-0	*p*-Cl	560	5	<0.5	95
50986-84-0	*p*-CF_3	920	11	<0.5	89
13088-17-0	*p*-NO_2	1150	13	<0.5	87

[a] Reaction conditions: benzene-toluene (10:1), 0.4 mol and aluminum chloride, 0.01 mol in 10 ml of nitromethane; substituted benzenesulfinyl chloride, 0.01 mol; reaction temperature, 25°; reaction time, 30 min.

tion states of the reactions resemble closely the corresponding σ complexes.

In order to show that the studied arenesulfinylations were, indeed, kinetically controlled and first order in the aromatic substrates, the competitive *p*-toluenesulfinylation of benzene and toluene was carried out with varying ratios (10:1, 5:1, 3:1) of the substrates shown in Table II. It shows that the reaction, indeed, is first order in aromatics as the k_T/k_B rate ratio is well reproduced in the limit of experimental error in the range of concentration changes studied.

To study the effect of various para substituents in the sulfinylation reaction with benzenesulfinyl chlorides, aluminum chloride catalyzed sulfinylations in nitromethane solution were studied with *p*-methoxybenzene-, *p*-fluorobenzene-, benzene-, *p*-chlorobenzene-, *p*-trifluoromethylbenzene-, and *p*-nitrobenzenesulfinyl chlorides. k_T/k_B reactivity and isomer ratios were determined in the usual way. Results are summarized in Table III.

Isomer ratios of sulfinylated toluene do not vary significantly with the nature of the para substituent in benzenesulfinyl chloride. Data in Table III show that k_T/k_B relative rate ratios in the reaction of benzenesulfinyl chlorides substituted with an electron-donating substituent in the para position are lower than those of reactions with an electron-withdrawing substituent.

From a linear correlation of the logarithms of the k_T/k_B values plotted against Brown σ^+ constants (Figure 1), the value of $\rho = +0.25$ was obtained for the arylsulfinylation reaction. This positive ρ value contrasts with the negative ρ values obtained in previously studied substitutions such as benzylation, benzoylation, aryl thiolcarboxylation, and arenesulfonylation.[3-7] These data clearly indicate the differing nature of sulfinylation from sulfonylation.

Table IV
Glc Retention Times of Diaryl Sulfoxides

Registry no.	Diaryl sulfoxide, *p*-$XC_6H_4SOC_6H_4Y$ X	Y	Column conditions	Retention time, min
951-92-8	CH_3O	H	SE-30, 175°	5.7
10381-41-6	CH_3O	*p*-CH_3	SE-30, 175°	9.0
50986-85-1	CH_3O	*o*-CH_3	DE-30, 175°	7.8
948-56-1	CH_3	H	BDS, 200°	8.9
1774-35-2	CH_3	*p*-CH_3	BDS, 200°	12.7
10381-68-7	CH_3	*o*-CH_3	BDS, 200°	10.9
50986-86-2	CH_3	3,4-$(CH_3)_2$	BDS, 200°	24.0
50896-87-3	CH_3	2,3-$(CH_3)_2$	BDS, 200°	21.0
50986-88-4	CH_3	2,4-$(CH_3)_2$	BDS, 200°	21.4
16704-48-6	CH_3	2,5-$(CH_3)_2$	BDS, 200°	22.4
10381-69-8	CH_3	2,4,6-$(CH_3)_3$	BDS, 200°	14.9
945-51-7	H	H	BDS, 130°	7.0
	H	*p*-CH_3	BDS, 130°	11.6
50986-89-5		*o*-CH_3	BDS, 130°	8.5
40154-93-6	F	H	SE-30, 110°	10.0
50986-90-8	F	*p*-CH_3	SE-30, 110°	20.7
50986-91-9	F	*o*-CH_3	SE-30, 110°	13.7
1016-82-6	Cl	H	BDS, 170°	14.3
20608-64-4	Cl	*p*-CH_3	BDS, 170°	21.9
50986-92-0	Cl	*o*-CH_3	BDS, 170°	18.3
50986-93-1	CF_3	H	BDS, 170°	2.9
10381-67-6	CF_3	*p*-CH_3	BDS, 170°	4.0
50986-94-2	CF_3	*o*-CH_3	BDS, 170°	3.4
955-45-3	NO_2	H	SE-30, 180°	7.7
22865-49-2	NO_2	*p*-CH_3	SE-30, 180°	11.8
50986-95-3	NO_2	*o*-CH_3	SE-30, 180°	10.0

The high positional selectivity and predominant para substitution observed in the arenesulfinylation reaction clearly indicate that the reactions involve less reactive (and, therefore, highly selective) sulfinylating reagents. It is highly improbable that "free" arenesulfinyl cations are involved in the reactions (attempts to observe such cations under stable ion conditions were unsuccessful). Even if such sulfinyl cations were involved, their nature would be very different from those of arenesulfonyl cations (examples of which were reported in our preceding work,[7] containing strongly electron-donating para substituents, such as methoxy).

Considering the nature of the sulfonyl cation, it has a highly electron-deficient sulfur center, bound by partial double bonds to two oxygen atoms. The sulfur 3d orbital is, therefore, strongly attracted to the nucleus. This contracted orbital is able to efficiently conjugate with the π system of the aromatic ring, and thus substituent groups (particularly in the para position) can interact with the sulfur center by inductive and/or conjugative effects. A

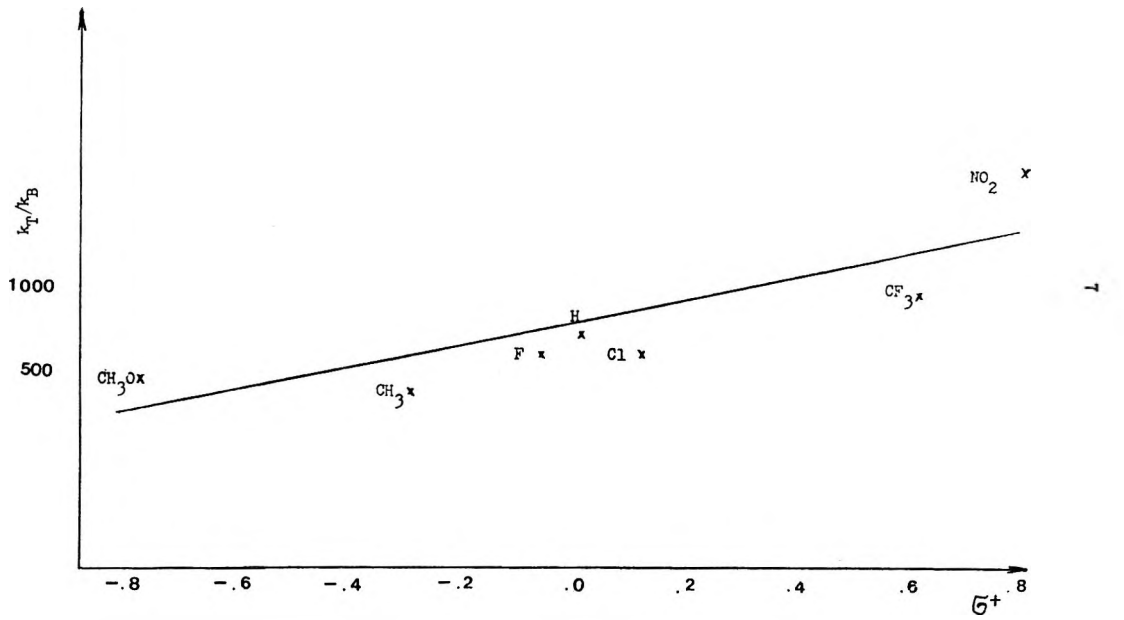


Figure 1. Correlation of relative rates of arenesulfinylation of benzene and toluene with para-substituted benzenesulfinyl chlorides (p-XC_6H_4SOCl) with Brown σ^+ constants.

(hypothetical) sulfinyl cation would have only one partially double-bonded oxygen atom bound to its sulfur center, containing also a lone pair of electrons, which thus could inductively donate electrons into the positive site. Thus the sulfinyl cation would be inductively stabilized. However, an interesting point is that the arenesulfinylating agents substituted by electron-withdrawing ring substituents show more selectivity and thus are weaker electrophiles than those substituted by electron-donating groups.

It is reasonable to consider that the sulfur 3d orbital in the sulfinylating agents is more extended than in the related sulfonylating species and, therefore, d_π-p_π overlap is less efficient than in the former cases. An electron-donating group in the ring will tend to inductively decrease the charge on sulfur. At the same time, however, this effect will expand the sulfur 3d orbital and make it less available for d_π-p_π conjugation. Conversely, the presence of electron-withdrawing groups increases the electron deficiency of the sulfur atom and causes the 3d orbital to contract. This results in the possibility of better d_π-p_π conjugation and consequently better conjugative stabilization, giving a less reactive and therefore somewhat less selective substituting agent. Consequently, in sulfinylation substrate selectivity is influenced mostly by the inductive and not by the conjugative effect of substituents.

Differences of physical properties between sulfones and sulfoxides due to differences in the efficiency of d_π-p_π conjugation have been noted.[10] Our present work now presents similar differentiation between reactivities of sulfonylating and sulfinylating systems, which also seem to be due to differences in the d_π-p_π conjugation.

Experimental Section

Materials. Benzene, toluene, and nitromethane were Spectrograde reagents and used without further purification. Commercial sublimed aluminum chloride of high purity was used. Most benzenesulfinyl chlorides were prepared by chlorination of the corresponding acids with thionyl chloride.[11] However, p-nitrobenzenesulfinyl chloride was prepared from the related disulfide with chlorine in acetic acid.[12] Substituted diaryl sulfoxides were prepared by literature methods.[13-24]

Competitive Arylsulfinylation. Under a dry nitrogen atmosphere, benzene (28.4 g, 0.364 mol), toluene (3.64 g, 0.036 mol), and aluminum chloride (1.33 g, 0.01 mol) in 5 ml of nitromethane were placed into a 100-ml reaction flask equipped with a dropping funnel, nitrogen seal, and thermometer kept in a constant-temperature bath at 25°. With vigorous stirring, a solution (0.01 mol) of arenesulfinyl chloride in 5 ml of nitromethane was added. After 30 min, the reaction mixture was poured into ice-water and extracted with ether, and the ether solution was washed with water, aqueous NaOH, and again with water and dried over $MgSO_4$. After evaporation of ether and part of excess aromatics, solutions were analyzed by glc.

Glc Analysis. A Varian Aerograph Model 1200 gas chromatograph, equipped with flame ionization detector, was used to analyze reaction mixtures using a SE-30 coated (5% on Chromosorb) packed 3-ft column. Characteristic retention times and conditions are listed in Table IV.

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Stable Carbocations. CLXV.[1] Carbon-13 Nuclear Magnetic Resonance Spectroscopic Study of Alkenoyl Cations. The Importance of Delocalized "Ketene-like" Carbenium Ion Resonance Forms

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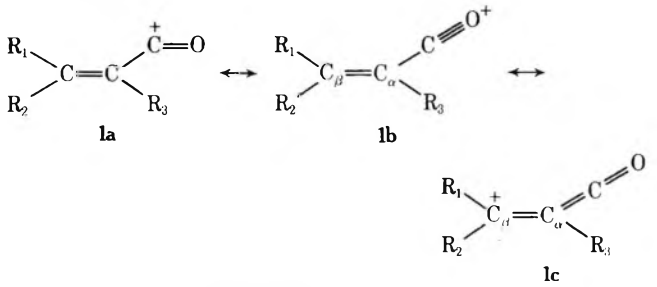
The proton-coupled carbon-13 nmr spectra of a series of alkenoyl cations in SO_2–SbF_5 solution have been studied by the Fourier transform method. Comparison of the data with chemical shifts and ^{13}C–H coupling constants in the acid chloride precursors and with ketene, a suitable model compound, indicate that there is substantial contribution to the structure of alkenoyl cations from delocalized "ketene-like" resonance forms.

The preparation and proton nmr spectra of a series of alkenoyl cations **1** have been reported by Olah and Comisarow.[4] Since carbon-13 nmr spectral studies[5] were able to show more adequately than pmr spectral studies that there are significant contributions to the structure of aroyl cations from delocalized "ketene-like" resonance forms, we decided to examine further the structure of the related alkenoyl cations by cmr spectroscopy.



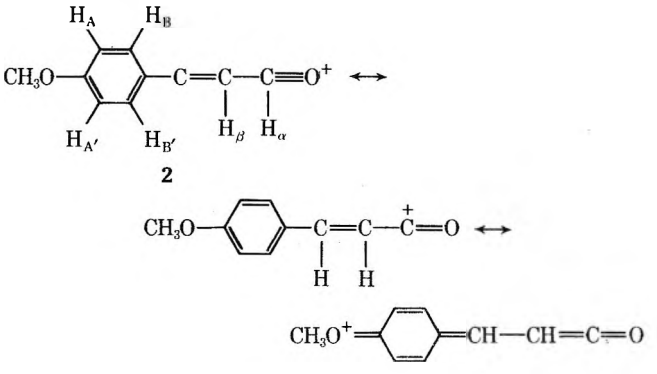
1a **1b** **1c**

Results and Discussion

Preparation of Alkenoyl Ions and Their Pmr Spectra. The α,β-unsaturated alkenoyl cations in Table II whose syntheses have not been reported[4] were prepared by the same or slightly modified general method (see Experimental Section). Pmr spectral parameters for previously prepared ions in Table II have been reported.[4]

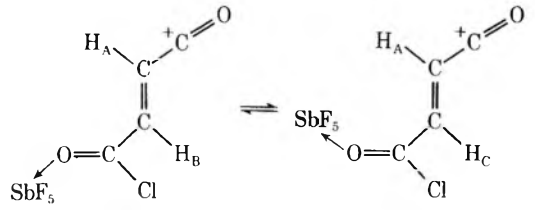
The pmr spectrum of the 3,3-diphenylpropenoyl cation in SbF_5–SO_2 at −70° consists of signals at δ 6.88 (s, 1, C=CH) and 7.6–8.4 (m, 10, aromatic). On warming the solution to −40°, another set of absorptions appeared at δ 7.32 (s) and 8.7–9.3 (m), indicating that decomposition of the ion was occurring. The decomposition product is irreversibly formed and as yet has not been identified.

A solution of the 3-(*p*-anisyl)propenoyl cation (*E*)[6] **2** in SO_2 at −60° gives a pmr spectrum with signals at δ 4.73 (s, 3, OCH_3), 7.08 (d, 1, J = 17.0 Hz, H_α), 7.8 (d, 2, $J \cong 8$ Hz, H_A and $H_{A'}$), 8.34 (d, 2, $J \cong 8$ Hz, H_B and $H_{B'}$), and 9.4 (d, 1, J = 17.0 Hz, H_β). The ion decomposes slowly at this temperature and a satisfactory cmr spectrum could not be obtained.



2

The carbocation formed when fumaroyl chloride was treated with an excess of SbF_5–SO_2 shows a pmr spectrum with absorptions at δ 8.55 (d, 1, J = 17.5 ± 0.1 Hz, H_A), 9.28 (d, 0.5, J = 17.5 ± 0.1 Hz, H_B or H_C), and 9.33 (d, 0.5, J = 17.5 ± 0.1 Hz, H_C or H_B). The observed pmr and subsequently discussed cmr (Table II) spectral parameters were accounted for by the monocation monodonor–acceptor complex (**3**), in which SbF_5 is complexed to the carbonyl oxygen in cis and trans configurations.[7] The nonequivalence of H_B (H_C) arises from the slow (on the nmr "time scale") equilibrium **3a** ⇌ **3b**. The equilibrium is still slow at −20°, since there is no change in the pmr spectrum at this temperature.



3a **3b**

Cmr Spectroscopic Studies. The proton-decoupled carbon-13 nmr spectra of solutions of alkenoyl cations in SbF_5–SO_2 and their acid chloride precursors in SO_2 were obtained by the Fourier transform method on Varian XL-100 and HA-100 (modified) nmr spectrometers. Carbon–hydrogen coupling constants were measured on the former instrument. The results are summarized in Tables I and II. Assignments were made by the usual methods, which included "off-resonance" proton decoupling, the applications of previously observed substituent effects, as well as symmetry and relative intensity considerations.

We are changing with this publication to give cmr shifts in reference to tetramethylsilane, instead of carbon disulfide used in our previous work. This more consistent and convenient reference is gaining general acceptance. [The conversion factor for CS_2 is 193.8 (capillary), 192.8 (external)].

A. Cmr Spectra of Precursor Alkenoyl Halides. The cmr spectra of most alkenoyl chloride precursors are as expected. The ^{13}C carbonyl shifts of the acyl chlorides appear 4–8 ppm shielded from the corresponding resonances in carboxylic acids.[8] A similar order is also observed for alkenoyl chlorides and their corresponding carboxylic acids;[9a] only the difference is smaller (1–4 ppm).

The deshielding (Table I) of the β carbon, that occurs on replacement of a hydrogen in the parent olefin ($R_1R_2C{=}CHR_3$) with a COCl group, may be rationalized in terms of a contribution to the structure of alkenoyl chlorides from the resonance form $R_1R_2{}^+CCR_3{=}C(Cl)O^-$. All α-carbon shieldings are also deshielded by the COCl group with respect to the parent olefin,[9b] but to a lesser extent than the β carbon.

The effect of the COCl group on a cis methyl carbon shielding is evident from the 5.7-ppm shift difference in the two methyl carbon shieldings of 3,3-dimethylpropenoyl chloride. Similarly, a difference of 2.0 ppm is found in the two ipso carbon shieldings of 3,3-diphenylpropenoyl chloride.

Carbon–hydrogen coupling constants in alkenoyl chlorides are also shown in Table I. $J_{C\beta-H}$ in propenoyl chloride is given as a single value, although in most vinyl derivatives[9c] $J_{C\alpha-H(cis)}$ and $J_{C\beta-H(trans)}$ have been shown to be slightly different. The effect of the polar COCl substituent on $J_{C\alpha-H}$ is seen by the larger values of $J_{C\alpha-H}$ in propenoyl, butenoyl, and 3,3-dimethylpropenoyl chlorides than in the appropriate parent olefins.

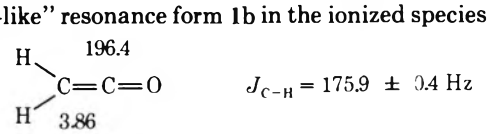
B. Cmr Spectra of Alkenoyl Cations. Carbon-13 nmr spectral parameters of alkenoyl cations studies are summarized in Table II. The changes of cmr parameters occurring in acid chlorides upon ionization with SbF_5 are shown in Table III. In the case of propenoyl chloride there is a deshielding of 39.8 ppm at C_β, which we interpreted to be a result of a larger contribution of resonance form **4a** to the structure of the alkenoyl cation than that of resonance form **4b** to the structure of the alkenoyl chloride

4a **4b**

precursor. Shift differences of this magnitude between alkenoyl cation and precursor could hardly arise from just neighboring-group effects (*e.g.*, solvent and antisotropy effects), nor could differences in the local diamagnetic term σ_d be invoked,[1c] since the same substituents are attached to C_β in ion and precursor. The C_β shift in the propenoyl cation is the most deshielded (by about 40 ppm) β-carbon shift observed in vinyl derivatives.[9c]

In keeping with the above structural views, it was found that attachment of a stabilizing alkyl, cycloalkyl, or aryl group to C_β gave an even larger deshielding at C_β in the resulting ion. The deshielded para carbon resonance in the 3-phenylpropenoyl cation is additional evidence for delocalized "ketene-like" resonance forms. Attachment of a methyl group at C_α has very little effect on β-carbon shift, but an electron-withdrawing group such as COCl → SbF_5 at C_β results in a much smaller deshielding (compared with the propenoyl cation) upon ionization of the acid chloride (Table III).

On ionization of propenoyl chloride with SbF_5, a large shielding effect of 38.7 ppm at C_α is observed. Apart from vinyl iodide,[9d] where "heavy atom" effects operate, this is the most shielded shift yet observed for C_α in a vinyl derivative. As for neutral vinyl compounds, the C_α shielding is more difficult to rationalize than the C_β shielding. However, the shielded (compared with a normal alkene carbon) terminal carbon shift (^{13}C δ 3.86) in the model compound, ketene, suggests that the large shielding in the α-carbon shift which occurs in the alkenoyl chlorides upon ionization arises from a significant contribution from the "ketene-like" resonance form **1b** in the ionized species.



$J_{C-H} = 175.9 \pm 0.4$ Hz

Consistent with this viewpoint, ions with a substituent at C_β, which is capable of stabilizing an adjacent carbenium ion center, have the most shielded C_α shifts (Table III).

This observation is consistent with the relatively deshielded (compared with the carbonyl shift of acyl cations) central carbon shift in ketene. The carbonyl shifts in alkenoyl cations are most deshielded in those ions which have the most deshielded C_β shifts and the most shielded C_α shifts, *i.e.*, those ions which have the largest contribution to their structure from the delocalized "ketene-like" resonance form.

To determine the extent of the contribution from "ketene-like" resonance forms we have observed the pmr spectrum of 3-methyl-2-propenoyl cation over a range of temperatures. At 80°, where decomposition of the ion began to occur, there was no change in the position of the two nonequivalent methyl signals, indicating that at this temperature rotation about the C_α–C_β bond was still slow on the nmr "time scale." Therefore, although there is a substantial contribution from resonance form **1c**, it appears that forms **1a** and **1b** are still major contributors.

The value of the C_α-H coupling constant in the propenoyl cation is 28 Hz larger than the corresponding value in the acid chloride precursor. This most likely is a result of the greater electronegativity of the $C{\equiv}O^+$ group compared with the COCl group. The same trend is also apparent for all the alkenoyl cations in Table II. $J_{C\beta-H}$ in these ions is also larger than in the precursors, but to a lesser extent.

In the alkenoyl cations in Table II, as the contribution of the "ketene-like" resonance form increases there is a corresponding decrease in $J_{C\alpha-H}$ until in the 3,3-diphenylpropenoyl cation, $J_{C\alpha-H}$ is only slightly larger than the C–H coupling constant of ketene (175.9 Hz). This trend is additional evidence for the structural considerations outlined above for alkenoyl cations.

Experimental Section

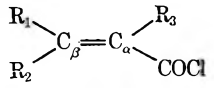
Propenoyl, isopropenoyl, (*E*)-2-butenoyl, (*E*)-2-methyl-2-butenoyl, 3,3-dimethylpropenoyl,[12] fumaroyl, 3-phenylpropenoyl, and 3-(*p*-anisyl)propenoyl[13] chlorides were either commercially available or were prepared from the appropriate carboxylic acid and thionyl chloride by usual procedures. Attempts to prepare (*Z*)-2-butenoyl chloride from the unstable 2-butenoic acid[14] and thionyl chloride gave only *E*-2-butenoyl chloride. 3,3-Diphenylpropenoyl chloride was prepared from the reaction of 1,1-diphenylethene with oxalyl chloride,[15] pmr (CCl_4) δ 6.52 (s, 1, C=CH), 6.8–7.7 (m, 10, C_6H_5). Ketene prepared by the described procedure[16] had a pmr spectrum consistent with the reported data.[17]

(*E*)-3-Cyclopropyl-2-butenoic Acid. A 3.6-g (0.028 mol) portion of ethyl (*E*)-3-cyclopropyl-2-butenoate[18] was heated under reflux for 1 hr in a solution of 3.6 g of sodium hydroxide in ethanol (40 ml) and water (3 ml). The reaction mixture was cooled and concentrated, and the residue was dissolved in a minimum amount of water. The aqueous solution was washed with ether (2 × 20 ml), acidified with 10% hydrochloric acid, and extracted with ether (2 × 100 ml). The combined ether extracts were dried ($MgSO_4$) and concentrated to give the crude acid. Recrystallization from petroleum ether (bp 60–80°) afforded 2.7 g (90%) of (*E*)-3-cyclopropyl-2-butenoic acid: mp 101–102° (lit.[19] mp 99–100°); nmr (CCl_4) δ 0.67–0.89 (m, 4, CH_2), 1.28–1.80 (m, 1, CH), 2.0 (s, 3, CH_3), 5.68 (s, 1, C=CH), 12.12 (s, 1, COOH).

Reaction of (*E*)-3-Cyclopropyl-2-butenoic Acid with Thionyl Chloride. A 1-g portion of (*E*)-3-cyclopropyl-2-butenoic acid was stirred at room temperature with 1 ml of thionyl chloride and 10 ml of carbon tetrachloride. The solvent and excess thionyl chloride were removed with a rotatory evaporator, using a water bath at room temperature. The nmr spectrum of the crude product indicated it to be predominantly 3-cyclopropyl-2-butenoyl chloride and an impurity which could not be separated by fractional distillation. This as yet unknown by-product was also present when the reaction was repeated at different temperatures, or in the absence of solvent: ir (film) 1755 (C=O) and 1578 cm^{-1}; nmr (CCl_4) δ 0.4–1.05 (CH_2), 1.6–2.2 (CH), 1.65 (CH_3), 1.9 (CH_3), 6.02 (C=CH).

3,3-Dicyclopropyl-2-propenoic Acid. A 1.8-g (0.01 mol) portion of ethyl 3,3-dicyclopropyl-2-propenoate[18,20] was heated under reflux for 1 hr in a solution of 1.5 g of sodium hydroxide in ethanol (20 ml) and water (1 ml). The product was isolated in the usual method and recrystallized from petroleum ether to give 1.05 g (82%) of 3,3-dicyclopropyl-2-propenoic acid: mp 136–137°; ir (Nujol) 3200–2600 (OH), 1695 (C=O), 1590 cm^{-1} (C=C); nmr (CCl_4) δ 0.47–1.15 (m, 10, cyclopropyl), 5.4 (s, 1, C=CH), 12.1 (s,

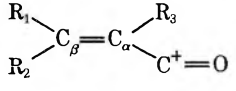
Table I
Carbon-13 Shielding[a] and Carbon–Hydrogen Coupling Constants[b] of α,β-Alkenoyl Chlorides[c]



Registry no.	Substituent R1	Substituent R2	Substituent R3	Chemical shift Cα	Chemical shift Cβ	Chemical shift CO	Chemical shift Others	Coupling constants $J_{C\alpha-H}$	Coupling constants $J_{C\beta-H}$	Coupling constants Others
814-68-6	H	H	H	131.4	137.3	165.6		173.2 ± 0.5	164.2	
625-34-4	CH_3	H	H	126.1	155.2	165.8	18.4 (CH_3)	171.4	163 ± 1	128.2 (J_{CH_3})
3350-78-5	CH_3	CH_3	H	121.5	163.2	166.9	27.4 (CH_3)	172.1		128.3 (J_{CH_3})
							21.7 (CH_3)			130.8 (J_{CH_3})
920-46-7	H	H	CH_3	140.5	135.4	169.0	18.0 (CH_3)		161.5	127.1 (J_{CH_3})
35660-94-7	H	CH_3	CH_3	132.7	149.6	169.0	15.6 (CH_3)		158 ± 2	127.5 (J_{CH_3})
							13.1 (CH_3)			128.8 (J_{CH_3})
4456-79-5	C_6H_5	C_6H_5	H	121.5	162.3	164.2	137.6, 139.6 (C_i)	*f*	*f*	*f*
							132.0, 130.1 (C_p)			
							129.8 (C_m)			
							129.4, 128.9 (C_o)			
645-45-4	C_6H_5	H	H[d]	116.9	143.2	167.2	132.5 (C_i)	160.3	156.5	161.5 (J_{Cp-H})
							128.5 (C_p)			162.5
							127.0			160.4
							126.3			
42996-84-9	*p*-$CH_3OC_6H_4$	H	H[e]	119.0	152.1	167.2	162.6 (C_i)	165.6	156.2	162.7
							115.1			164.9
							132.0			147.1 (J_{OCH_3})
							55.0 (CH_3O)			
50921-72-7	c-$C_3H_5(CH_3)$	CH_3(*c*-C_3H_5)		121.4	175.1	163.3	9.3, 10.1 (CH_2)			
							21.5, 26.2			
627-63-4	COCl	H	H	140.3	140.3	166.2		176.1	176.1	

[a] Parts per million from external capillary of tetramethylsilane. [b] Hertz. Precision is ±0.3 Hz. [c] In SO_2 at −40° unless otherwise indicated. [d] In $CDCl_3$. [e] In SO_2 at −25°. [f] Poor-quality proton-coupled spectrum.

Table II
Carbon-13 Shieldings and Carbon–Hydrogen Coupling Constants in Some α,β-Alkenoyl Cations[a]



Registry no.	Substituent R1	Substituent R2	Substituent R3	Chemical shift[b] Cα	Chemical shift[b] Cβ	Chemical shift[b] CO	Chemical shift[b] Others	Coupling constants[c] $J_{C\alpha-H}$	Coupling constants[c] $J_{C\beta-H}$	Coupling constants[c] Others
35335-84-3	H	H	H	92.7 (30.1)[d]	177.1 (54.3)[d]	147.1		201.0	176.5	
50921-73-8	CH_3	H	H	84.3	202.6	151.5	26.7 (CH_3)	197.6	168.3	131.3 (J_{CH_3})

44391-34-6	CH_3	CH_3	H	79.0	223.0	154.2	30.0 (CH_3) 28.6 (CH_3)	192.6		130.8 (J_{CH_3}) 128.0 (J_{CH_3})
44158-09-0	H	H	CH_3	104.3	172.8	148.1	16.0		173.9 ± 0.8	132.7 (J_{CH_3})
44367-88-6	H	CH_3	CH_3	94.3	193.5	151.3	21.7 (CH_3) 10.5		165.2	132.3 (J_{CH_3}) 136.6 (J_{CH_3})
50921-56-7	C_6H_5	C_6H_5	H[e]	68.7	201.1	158.7	136.0, 135.7 (C_i) 134.7, 132.7 (C_o) 131.0, 130.5 (C_m) 140.2, 138.5 (C_p)	180 ± 5		*f*
35335-84-3	C_6H_5	H	H	69.4	183.3	157.0	131.6 (C_i) 133.9 (C_o) 130.0 (C_m) 142.1 (C_p)	191.3	166.0	165.6 (J_{Cp-H}) 168.5 (J_{Cm-H})
50921-70-5	c-C_3H_5	CH_3	H[g]	71.2	227.0	160.4	32.3 (CH) 25.2 (CH_2) 22.4 (CH_3)	185 ± 5		
50921-22-7	$COCl-SbF_5$	H	H	102.8	165.3 162.0	146.7 143.1	157.1 ($COCl)-SbF_5$	206.4	190 ± 1	

[a] In SO_2 at −40° unless otherwise indicated. [b] Parts per million from external capillary of 5% ^{13}C-enriched tetramethylsilane. In several cases where the HA-100 nmr spectrometer was used, shifts were measured from external capillary of 70% ^{13}C-enriched methyl iodide (lock signal) and converted using $\delta(CH_3I)$ −20.2. This conversion factor is temperature dependent, changing 0.029 ppm per centigrade degree. [c] Hertz. Precision in ±0.3 Hz. [d] Deshielding from ethane. [e] In SO_2 at 70°. [f] Aromatic signals too complicated in coupled spectrum. [g] In SO_2 at −80°.

Table III
Changes in Carbon-13 Shieldings and Carbon–Hydrogen Coupling Constants upon Formation of the Alkenoyl Cations from the α,β-Alkenoyl Chlorides

Substituent[a]			Chemical shift[b]				Coupling constants[c]	
R_1	R_2	R_3	$C\alpha$	$C\beta$	CO	Others	C_α	$C\beta$
H	H	H	−38.7	39.8	18.5		27.8	12.3
CH_3	H	H	−41.8	47.2	14.3	8.3 (CH_3)	26.3	5
CH_3	CH_3	H	−42.5	59.8	12.7	2.6 (CH_3) 6.9 (CH_3)	20.5	
H	H	CH_3	−36.2	37.4	21.6	2.0 (CH_3)		12.4
H	CH_3	CH_3	−38.4	43.9	17.7	6.1 (CH_3) 2.6 (CH_3)		4
C_6H_5	C_6H_5	H	−52.8	38.8	5.5			
C_6H_5	H	H	−47.5	40.1	10.2	−0.9 (C_i) 13.6 (C_p)	31.0	9.5
c-C_3H_5	CH_3	H	−50.2	52.1	2.9	15.9 (CH_2) 0.9 (CH_3)		
COCl	H	H	−37.5	25.0 21.7	19.5 23.1		30.3	14

[a] R_1, R_2, and R_3 refer to structures in Tables I and II. [b] Parts per million. Positive sign indicates deshielding in the alkenyl oxocarbenium ion. [c] Hertz. Positive sign indicates increased coupling constant in the alkenoyl cation.

1, COOH). *Anal.* Calcd for $C_9H_{12}O_2$: C, 71.01; H, 7.96. Found: C, 70.94; H, 7.96.

Attempts to prepare the acid chloride by the reaction of the acid with thionyl chloride under a variety of conditions were unsuccessful, and gave complex mixtures of unidentified products.

Preparation of Ions. Solutions of alkenoyl cations were prepared by adding the appropriate alkenoyl chloride, either directly or as a saturated SO_2 solution at −78°, to an excess of SbF_5 in SO_2 at −78°.

Proton Nuclear Magnetic Resonance Spectra. Pmr spectra were obtained using Varian Associates Model A56/60A and HA-100 spectrometers equipped with variable-temperature probes. External tetramethylsilane (capillary) was used as reference. Pmr spectra of ions reported previously were found identical with described spectra.[4]

Carbon-13 Nuclear Magnetic Resonance Spectra. A Varian Associates Model XL-100 spectrometer equipped with a broad-band proton decoupler and variable-temperature probe was used. The instrument operates at 25.2 MHz for ^{13}C, and is interfaced with a Varian 620-L computer. The combined system was operated in the pulse-Fourier transform mode, employing a Varian Fourier transform accessory. Typically 3000–5000 pulses, each of width 20–30 μsec, needed to be accumulated in order to give a satisfactory signal-to-noise ratio for all signals of interest. Field-frequency stabilization was maintained by locking on the ^{19}F signal of an external sample of fluorobenzene. Chemical shifts were measured from the ^{13}C signal of 5% ^{13}C-enriched tetramethylsilane in a 1.75-mm capillary held concentrically inside the standard 12-mm sample tube.

Some spectra were obtained using a Varian Associated Model HA-100 nmr spectrometer equipped with a Fourier transform accessory (V-4357 Pulsing and Control Unit), broad-band proton decoupler, and variable-temperature probe. The instrument, lock, and referencing systems have been described in more detail elsewhere.[21]

Acknowledgment. Support of our work by the National Institutes of Health is gratefully acknowledged.

Registry No.—(*E*)-3-Cyclopropyl-2-butenoic acid, 50921-71-6; ethyl (*E*)-3-cyclopropyl-2-butenoate, 21014-28-8; 3,3-dicyclopropyl-2-propenoic acid, 37520-24-4; ethyl 3,3-dicyclopropyl-2-propenoate, 21046-02-6.

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Reactions of Sulfur Diimides with Phenyl- and Phenylchloroketenes

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The reactions of sulfur diimides **1a–d** with phenylketene (**2a**) below −50° gave 1-substituted 3,4-diphenylpyrroline-2,5-diones **6a–d** and 2-substituted 4,5-diphenyl 5-substituted carbamoyl-1,2-thiazolidin-3-ones **7a–d** as major products. Reduction of **7a** by Raney Ni afforded only *N,N'*-di-*tert*-butyl-2,3-diphenylbutane diamide (**11a**) in 85% yield, while **7b** and **7c** under the identical condition led to the corresponding amides, **11b** (70%) and **11c** (44%), and 1-substituted 3,4-diphenyl-4-carbamoylazetidin-2-ones, **12b** (12%) and **12c** (16%), respectively. Oxidation of **7a–d** by *m*-chloroperbenzoic acid gave 1,2-thiazolidin-3-one 1-oxides **13a–d** in good yields. The reactions of sulfur diimides **1b and 1c** with phenylchloroketene (**2b**) yielded similarly **6b and 6c** as the major product, but the reaction of **1d** afforded mainly 1,3,4-triphenyl-3,4-dichloropyrrolidine-2,5-dione (**16d**). The formation mechanism of the above products was discussed.

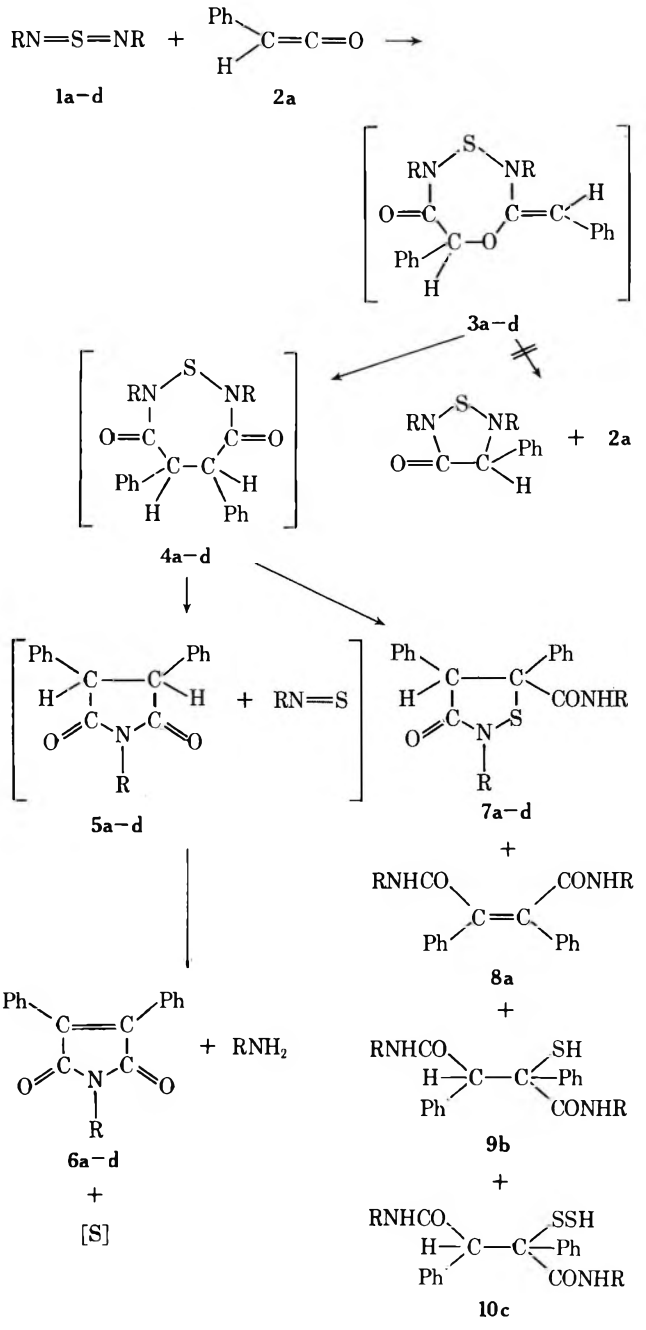
In previous work[1] we investigated the reactions of sulfur diimides with ketenes and found that the reaction products depend on substituents both on the starting sulfur diimides and ketenes, that is, (a) in the reaction with diphenylketene, diphenylsulfur diimide gave 1:2 and 1:1 cycloadducts at low and at high temperatures, respectively, and di-*tert*-butylsulfur diimide afforded two types of 1:1 cycloadducts; (b) in the reaction with alkylketenes, sulfur diimides afforded no cycloadduct but the unexpected thiobis(amine) derivatives, regardless of the substituents on the sulfur diimides. Further results on substituent effects in these reactions are reported in this paper.

Results and Discussion

Reaction of Sulfur Diimides with Phenylketene. The reactions of sulfur diimides **1a–d** with phenylketene (**2a**) (Scheme I), generated *in situ* from phenylacetyl chloride and triethylamine, unexpectedly gave 1-substituted 3,4-diphenlypyrroline-2,5-diones **6a–d** and 2-substituted 4,5-diphenyl 5-substituted carbamoyl-1,2-thiazolidin-3-ones **7a–d**, which arise from 1 mol of **1** and 2 mol of **2a**, along with small amounts of some by-products.

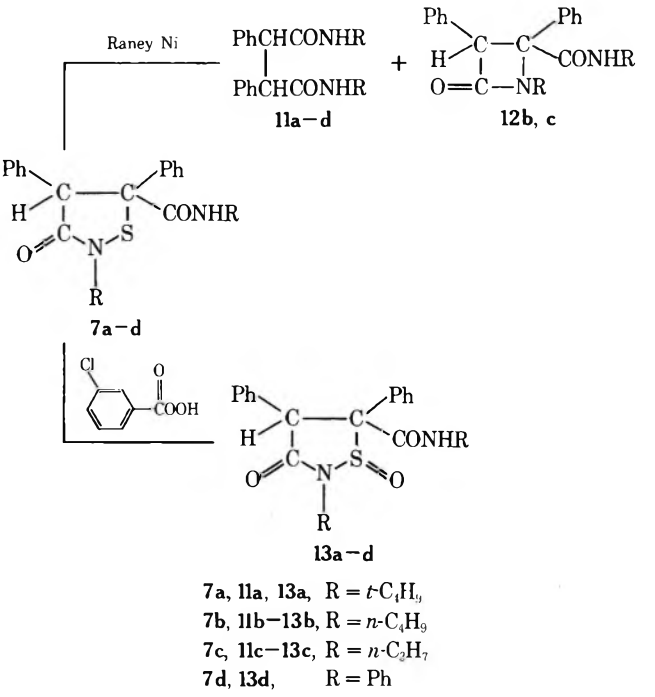
The reaction products were independent of the ratio of **1** to **2a** used in the reaction. The structure of **7** was established by a combination of spectral and chemical evi-

Scheme I



1a, 3a–8a, R = t-C_4H_9
1b, 3b–7b, 9b, R = n-C_4H_9
1c, 3c–7c, 10c, R = n-C_3H_7
1d, 3d–7d, R = Ph

dence. The ir spectrum of **7a** displays characteristic absorption bands at 3380 and 1670 cm^{-1} assignable to N–H and carbonyl bonds, respectively. The nmr spectrum ($CDCl_3$) shows a *tert*-butyl (s, 9 H) at N-2, carbamoyl *tert*-butyl (s, 9 H), methine (s, 1 H), NH (broad, 1 H), and phenyl protons (m, 10 H) at 1.35, 1.50, 4.85, 6.95, and 7.15–7.85 ppm. respectively. The mass spectrum exhibits the parent peak with negligible abundance at m/e 410 and other peaks at m/e 310 (M^+ − 100, 18%) and 254 ($C_{15}H_{12}NOS$, base peak) arising from the loss of *tert*-butylcarbamoyl from the parent ion and further fragmentation of the ion of m/e 310 by the loss of butene. Oxidation of **7a** with *m*-chloroperbenzoic acid led to a sulfoxide **13a** which contains carbonyl and sulfoxide absorption at 1680 and 1070 cm^{-1} in the ir spectrum and two singlet *tert*-butyl protons at 1.40 and 1.60 ppm and methine and NH and phenyl protons at 4.70 and 7.30–7.75 ppm in the nmr spectrum, respectively, in 96% yield. Furthermore, reduction by Raney Ni in refluxing ethanol gave only *N,N'*-di-*tert*-butyl-2,3-diphenylbutane diamide (**11a**), structural assignment to which could be made with confidence on the basis of spectra, in 85% yield. These chemical properties and physical data are consistent with the structure **7a**.



7a, 11a, 13a, R = t-C_4H_9
7b, 11b–13b, R = n-C_4H_9
7c, 11c–13c, R = n-C_3H_7
7d, 13d, R = Ph

Similar treatment of **7b–d** with *m*-chloroperbenzoic acid afforded the sulfoxides **13b–d** corresponding to **13a** in good yields, while reduction of **7b** and **7c** by Raney Ni led to the β-lactam derivatives **12b** and **12c** [$\nu_{C=O}$ (Nujol) 1740 and 1650 cm^{-1}] in 12 and 16% yields, respectively, in addition to the expected diamides, **11b** and **11c**. Thus the formation of the diamides **11** and the β-lactams **12** suggests that reduction of **7** by Raney Ni involves a diradical intermediate, followed by abstraction of the hydrogen on Raney Ni and an intramolecular coupling reaction. The failure of the *N-tert*-butyl β-lactam analog **12a** to form could be explained in terms of inhibition of the coupling reaction by the bulky *tert*-butyl group.

Structural assignment of the other major product **6** was based on its analysis and spectroscopic properties (see Experimental Section).

The results obtained are shown in Table I.

Reaction of Sulfur Diimides with Phenylchloroketene. The reaction of **1b** with phenylchloroketene (**2b**) (Scheme II), generated *in situ* from α-chlorophenylacetyl chloride and triethylamine, gave 1-butyl-3,4-diphenylpyrroline-2,5-dione (**6b**) in 26% yield together with a 1:2 cycloadduct **15b** (4%) and 1-butyl-3,4-dichloro-3,4-diphenylpyrrolidine (**16b**, 3%).

The structure of the cycloadduct **15b** was determined as follows. The ir spectrum of **15b** exhibits two strong carbonyl absorptions at 1700 and 1670 cm^{-1} and no absorption in the olefinic region. The nmr spectrum shows methyl and methylene (m, 14 H), methylene adjacent to N-2 and N-7 (t, 4 H), and phenyl protons (m, 10 H) at 0.70–1.85, 3.70, and 7.20–7.85 ppm, respectively. The mass spectrum exhibits the molecular ion at m/e 478 and peaks at m/e 408 (M^+ − 2Cl) and 306 (M^+ − BuN=S=NBu). On the basis of these physical data, the structure of **15b** was assigned as 2,3,4,5,6,7-hexahydro-2,7-dibutyl-4,5-dichloro-4,5-diphenyl-1,2,7-thiadiazepine-3,6-dione.

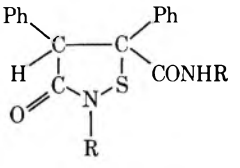
Table I
Reaction of Sulfur Diimides 1 with Phenylketene (2a)

R in 1	Reaction conditions: Solvent	Ratio of 2a:1	Product yields, %: 6	7	8	9	10
t-Bu	Petroleum ether	1.0	32	10	7		
t-Bu	Ether	3.0	34	18	15		
n-Bu	Ether	3.0	49	35		4	
n-Pr	Ether	3.0	35	39			7
Ph	Ether	2.5	9	19			

Table II
Reaction of Sulfur Diimides 1 with Phenylchloroketene (2b)

R in 1	Reaction conditions: Solvent	Ratio of 2b:1	Product yields, %: 6	15	16	18
n-Bu	Ether	3.0	26	4	3	
n-Pr	Ether	3.0	32			3
Ph	Ether	2.5	5		22	

Table III
4,5-Diphenyl-5-carbamoyl-1,2-thiazolidin-3-ones, 7



Compd	R	Mp, °C	Ir (Nujol), $\nu_{C=O}$, cm^{-1}	Empirical formula[a]
7a	*t*-Bu	153–154	1670	$C_{24}H_{30}N_2O_2S$
7b	*n*-Bu	120–121	1670, 1650	$C_{24}H_{30}N_2O_2S$
7c	*n*-Pr	120–122	1675, 1650	$C_{22}H_{26}N_2O_2S$
7d	Ph	225–227	1690, 1670	$C_{28}H_{22}N_2O_2S$

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

The thiadiazepine **15b** was found to be thermally labile. When a benzene solution of **15b** containing triethylamine was heated at 80° for 2 hr, the pyrroline **6b** was obtained in 93% yield.

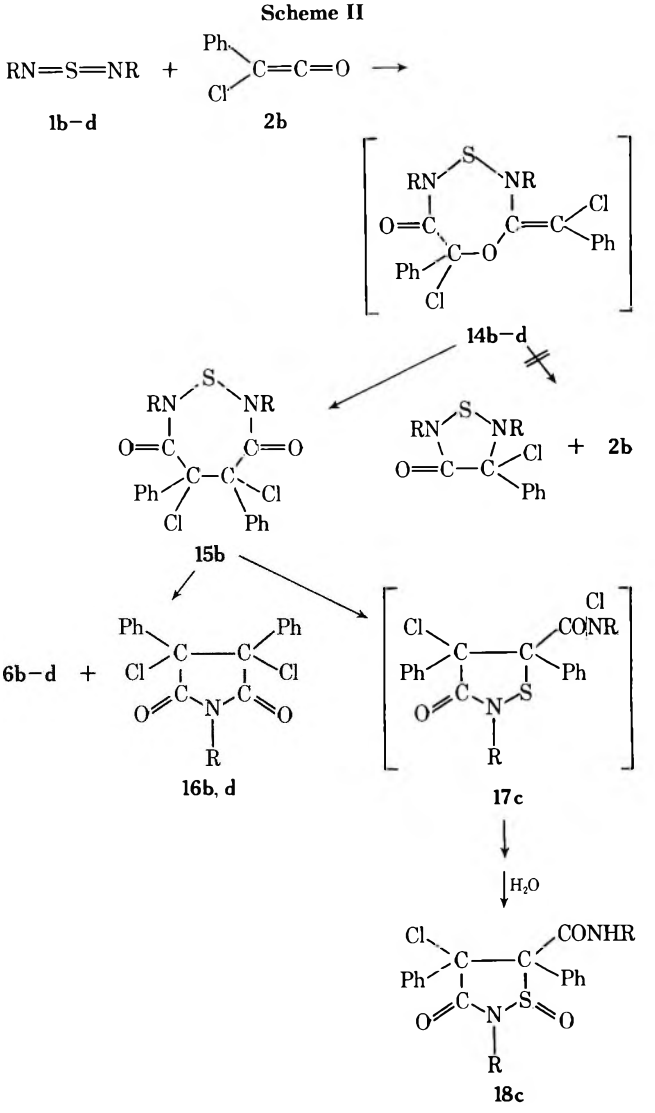
Structural assignment of **16b** was made by comparison of its ir spectrum [$\nu_{C=O}$ (Nujol) 1785 and 1715 cm^{-1}] with that of **6b** [$\nu_{C=O}$ (Nujol) 1760 and 1700 cm^{-1}].

The reaction of **1c** with **2b** similarly afforded the pyrroline derivative **6c** as the major product, while the reaction between **1d** and **2b** produced 3,4-dichloro-1,3,4-triphenylpyrrolidine-2,5-dione (**16d**) as the main product along with small amounts of the pyrroline derivative **6d**. Of above reactions, only a reaction of **2b** with **1c** gave the 1,2-thiazolidine derivative **18c** corresponding to the 1:2 adduct **7**, which is one of the main products in the reaction using **2a**, in 3% yield.

The results are summarized in Table II.

Mechanistic Considerations. As the reaction of diphenylsulfur diimide (**1d**) with diphenylketene at low temperature yielded an unstable thiaoxadiazepine derivative,[1] it is probable that the reaction between sulfur diimides **1** and **2a** (or **2b**) also gives the thiaoxadiazepine **3** (or **14**), followed by rearrangement to the unstable thiadiazepine **4** (or **15**), of which only **15b** could be isolated. Alternatively, the thiadiazepines could be produced directly from a dipolar intermediate in the reaction of **1** and **2a** (or **2b**). The thiadiazepine derivatives **4** (or **15**) would readily undergo homolytic or heterolytic ring cleavage at the N–S bond to lead ultimately to the 1,2-thiazolidine derivatives **7** (or **18**) (Tables III and IV) and the pyrroline derivatives **6** (and/or the pyrrolidine derivatives **6**) as shown in

Scheme II



1b, 6b, 14b–16b, R = *n*-C_4H_9
1c, 6c, 14c, 18c, R = C_3H_7
1d, 6d, 14d, 16d, R = Ph

Scheme I (or Scheme II). Thermolysis of the thiadiazepine **15b** to the pyrroline **6b** supports the scheme.

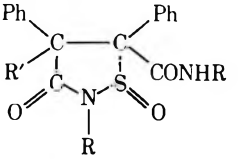
N,N'-Di-*tert*-butyl diphenylmaleamide (**8a**) and (1,2-diphenyl-1,2-di-*n*-butylcarbamoyl)ethanethiol (**9b**) would be formed by further similar degradation of the corresponding 1,2-thiazolidine derivative **7**. On the other hand, the formation of (1,2-diphenyl-1,2-di-*n*-propylcarbamoyl)-ethyl hydrogen disulfide (**10c**) could be explained by the addition of atomic sulfur eliminated in the reaction system to the corresponding ethanethiol derivative, which would be similarly produced by decomposition of **7c**. Thus the formation of such products as **8a**, **9b**, and **10c** seems to be clearly dependent upon bulkiness of the substituent on the sulfur diimide.

In all cases using **2a**, the failure to isolate the expected pyrroline derivatives **5** could be due to the ease of oxidation of **5** by the thioamine moiety, which would be generated by elimination of **5** from the thiadiazepine derivatives **4**.

While the reaction using **2a** proceeds with an overall yield of about 70%, a low overall yield (about 30%) for the reaction using **2b** is considered to be due to the tendency of **2b** to readily polymerize in the presence of amine.

Although the reaction of **1** with **2a** (or **2b**) gave quite different results from those in the reaction of **1** with diphenylketene, both reactions would proceed *via* the same

Table IV
4,5-Diphenyl-5-carbamoyl-1,2-thiazolidin-3-one 1-Oxides, 13 (or 18)



Compd	R	R′	Mp, °C	Ir (Nujol), cm⁻¹ νC=O	Ir (Nujol), cm⁻¹ νS=O	Empirical formula[a]
13a	*t*-Bu	H	178–180	1680	1070	$C_{24}H_{30}N_2O_3S$
13b	*n*-Bu	H	163–165	1680	1050	$C_{24}H_{30}N_2O_3S$
13c	*n*-Pr	H	181–183	1685, 1650	1080	$C_{22}H_{26}N_2O_3S$
13d	Ph	H	219–220	1690	1050	$C_{28}H_{22}N_2O_3S$
18c	*n*-Pr	Cl	193–194	1715, 1650	1135	$C_{22}H_{23}N_2O_3SCl$

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

type of cycloadducts, thiaoxadiazepines, as mentioned above. Accordingly it could be concluded that the differences in stability between the adducts would control the results.

Experimental Section

General. All melting points of products were determined with a Yanagimoto micro melting apparatus and are uncorrected. The nmr spectra were obtained on a Joellmm 3H-60 spectrometer with tetramethylsilane as an internal standard. The ir spectra were recorded with a Jasco IR-E spectrometer. The mass spectra were taken with a Hitachi RMU-6E spectrometer.

Materials. Diphenylsulfur diimide,[2] di-*n*-butylsulfur diimide,[3] di-*tert*-butylsulfur diimide,[3] di-*n*-propylsulfur diimide,[3] and α-chlorophenylacetyl chloride[4] were prepared according to the established procedures.

Reaction between Di-*tert*-butylsulfur Diimide (1a) and Phenylketene (2a). Phenylacetyl chloride (9.28 g, 0.06 mol) in 50 ml of dry ether was added dropwise to a stirred solution containing **1a** (3.48 g, 0.02 mol) and triethylamine (6.10 g, 0.06 mol) in 200 ml of dry ether below −50° under a nitrogem atmosphere. After the solution was stirred for 12 hr, the resulting amine salt was removed by filtration. The filtrate was evapcrated under reduced pressure and the residue was chromatographed on neutral alumina using hexane, hexane–benzene, and benzene as eluent. The first fraction was concentrated and the residue was recrystallized from ethanol to give 2.10 g (34%) of **1-*tert*-butyl-3,4-diphenylpyrroline-2,5-dione (6a)**, mp 140°, as greenish-yellow needles: ir (Nujol) 1760 and 1700 cm⁻¹ (C=O); nmr ($CDCl_3$) δ 1.65 (s, 9 H, *t*-Bu) and 7.30 (broad s, 10 H, phenyl protons); mass spectrum (70 eV) *m/e* 305 (M^+), 290 ($M^+ - CH_3$), and 249 ($M^+ - C_4H_8$).

Anal. Calcd for $C_{20}H_{19}NO_2$: C, 78.66; H, 6.27; N, 4.59. Found: C, 78.60; H, 6.30; N, 4.64.

Similar treatment of the second fraction afforded 1.50 g (18%) of **2-*tert*-butyl-4,5-diphenyl-5-*tert*-butylcarbamoyl-1,2-thiazolidin-3-one (7a)** as white needles: ir (Nujol) 3380 (NH), 1670 (C=O), and 1500 cm⁻¹ (NH); nmr ($CDCl_3$) δ 1.35 (s, 9 H, >N-*t*-Bu), 1.50 (s, 9 H, CONH-*t*-Bu), 4.85 (s, 1 H, methine proton), 6.95 (broad, 1 H, NH), and 7.15–7.85 (m, 10 H, phenyl protons); mass spectrum (70 eV) *m/e* (rel intensity) 410 (M^+), 310 (M^+ − *t*-BuNHCO, 18), and 254 (M^+ − *t*-BuNHCO − C_4H_8, 100).

Similar treatment of the third fraction yielded 1.10 g (15%) of ***N,N′*-di-*tert*-butyl diphenylmaleamide (8a)**, mp 232–242° subl (benzene–hexane), as white needles: ir (Nujol) 3300 (NH), 1630 (C=O), and 1525 cm⁻¹ (NH); nmr ($CDCl_3$) δ 1.10 (s, 9 H, *t*-Bu), 1.40 (s, 9 H, *t*-Bu), 5.22 (broad, 1 H, NH), 5.82 (broad, 1 H, NH), and 7.13–7.65 (m, 10 H, phenyl protons); mass spectrum (70 eV) *m/e* 378 (M^+), 306 (M^+ − NH-*t*-Bu), 278 (M^+ − *t*-BuNHCO), and 178 ($PhC{\equiv}CPh^+$).

Anal. Calcd for $C_{24}H_{30}N_2O_2$: C, 76.15; H, 7.99; N, 7.40. Found: C, 76.11; H, 8.10; N, 7.47.

In the reaction using an equimolar amount of **1a** to **2a** in petroleum ether (bp 30–60°) under the same condition, **6a**, **7a**, and **8a** were obtained in 32, 10, and 7% yields, respectively.

Reaction between Di-*n*-butylsulfur Diimide (1b) and Phenylketene (2a). The reaction was carried out using the procedure described above with **1b** (3.48 g, 0.02 mol), triethylamine (6.10 g, 0.06 mol), and phenylacetyl chloride (9.28 g, 0.06 mol) in dry ether. Similar treatment gave **1-*n*-butyl-3,4-diphenylpyrroline-2,5-dione (6b**, 49%), **2-*n*-butyl-4,5-diphenyl-5-*n*-butylcarbamoyl-1,2-thiazolidin-3-one (7b**, 35%), and **(1,2-diphenyl-1,2-di-*n*-butylcarbamoyl)ethanethiol (9b**, 4%).

6b had mp 73–75° (ethanol); yellow needles; ir (Nujol) 1760 and 1700 cm⁻¹ (C=O); nmr ($CDCl_3$) δ 0.65–1.90 [m, 7H, methyl (3 H) and methylene protons (4 H)], 3.55 (t, *J* = 7 Hz, 2 H, $>NCH_2-$), and 6.95–7.50 (m, 10 H, phenyl protons); mass spectrum (70 eV) *m/e* 305 (M^+).

Anal. Calcd for $C_{20}H_{19}NO_2$: C, 78.66; H, 6.27; N, 4.59. Found: C, 78.35; H, 6.48; N, 4.38.

7b was obtained as white needles (benzene–hexane): ir (Nujol) 3290 (NH), 1670 (ring C=O), 1650 (carbamoyl C=O), and 1525 cm⁻¹ (NH); nmr ($CDCl_3$) δ 0.60–1.75 [m, 14 H, two methyl (6 H) and four methylene protons (8 H)], 3.00–3.60 (m, 4 H, $>NCH_2-$), 5.12 (s, 1 H, methine proton), 6.75 (t, 1 H, NH), and 7.20–7.65 (m, 10 H, phenyl protons); mass spectrum (70 eV) *m/e* 410 (M^+), 310 (M^+ − BuNHCO), and 254 (M^+ − BuNHCO − C_4H_8).

9b had mp 194–196° (benzene–ethanol); white needles; ir (Nujol) 3310 (NH), 1640 (C=O), and 1530 cm⁻¹ (NH); nmr (100 MHz, $CDCl_3$) δ 0.68–1.00 (q, 6 H, two methyl protons), 1.00–1.68 (m, 8 H, four methylene protons), 2.16 (s, 1 H, SH), 3.20 (m, 4 H, $>NCH_2-$), 4.28 (s, 1 H, methine proton), 6.27 (t, 1 H, NH), 6.60 (t, 1 H, NH), and 7.00–7.70 (m, 10 H, phenyl protons); mass spectrum (70 eV) no molecular ion, *m/e* 380 (M^+ − S), 378 (M^+ − H_2S − BuNH).

Anal. Calcd for $C_{24}H_{32}N_2O_2S$: C, 69.88; H, 7.82; N, 6.79. Found: C, 70.18; H, 7.73; N, 6.81.

Reaction between Di-*n*-propylsulfur Diimide (1c) and Phenylketene (2a). The reaction was carried out by the procedure described above with **1c** (2.92 g, 0.02 mol), triethylamine (6.10 g, 0.06 mol), and phenylacetyl chloride (9.28 g, 0.06 mol) in dry ether. Similar treatment afforded **1-*n*-propyl-3,4-diphenylpyrroline-2,5-dione (6c**, 35%), **2-*n*-propyl-4,5-diphenyl-5-*n*-propylcarbamoyl-1,2-thiazolidin-3-one (7c**, 39%), and **(1,2-diphenyl-1,2-di-*n*-propylcarbamoyl)ethyl hydrogen disulfide (10c**, 7%).

6c had mp 66–68° (ethanol); yellow needles; ir (Nujol) 1760 and 1700 cm⁻¹ (C=O); nmr ($CDCl_3$) δ 0.90 (t, *J* = 7 Hz, 3 H, $-CH_3$), 1.65 (m, 2 H, $-CH_2-$), 3.60 (t, 2 H, $>NCH_2-$), and 6.95–7.55 (m, 10 H, phenyl protons); mass spectrum (70 eV) *m/e* 291 (M^+).

Anal. Calcd for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81. Found: C, 78.38; H, 5.86; N, 5.00.

7c was obtained as white needles (benzene–hexane): ir (Nujol) 3320 (NH), 1670 (ring C=O), 1650 (carbamoyl C=O), and 1530 cm⁻¹ (NH); mass spectrum (70 eV) *m/e* 382 (M^+) and 296 (M^+ − $CONHC_3H_7$).

10c had mp 201° (benzene–ethanol); white needles; ir (Nujol) 3280 (NH), 1645 (C=O), and 1535 cm⁻¹ (NH): nmr ($CDCl_3$) δ 0.90 (t, *J* = 7 Hz, 6 H, two methyl protons), 1.20–1.75 (m, 4 H, two methylene protons), 3.23 (q, 4 H, $>NCH_2-$), 4.59 [s, 2 H, methine proton (1 H) and −SSH (1 H)], 6.45 (t, 2 H, NH), and 7.33 (s, 10 H, phenyl protons); mass spectrum (70 eV) *m/e* 416 (M^+), 352 (M^+ − 2S), 209 [$PhCH(SH)CONHC_3H_7^+$], and 207 [$S{=}C(Ph)CONHC_3H_7^+$].

Anal. Calcd for $C_{22}H_{28}N_2O_2S_2$: C, 63.44; H, 6.78; N, 6.73. Found: C, 63.40; H, 6.89; N, 6.86.

Reaction between Diphenylsulfur Diimide (1d) and Phenylketene (2a). A solution of triethylamine (7.07 g, 0.07 mol) in 50 ml of dry ether was added to a stirred solution containing **1d** (4.28 g, 0.02 mol) and phenylacetyl chloride (7.73 g, 0.05 mol) in 200 ml of dry ether below −50° under a nitrogen atmosphere. After the solution was stirred for 12 hr, the resulting amine salt was re-

moved by filtration and the filtrate was concentrated under reduced pressure. The residue was chromatographed on alumina to give 0.55 g (9%) of **1,3,4-triphenylpyrroline-2,5-dione (6d)**, 1.68 g (19%) of **2,4,5-triphenyl-5-phenylcarbamoyl-1,2-thiazolidin-3-one** (7d), and 0.40 g of phenylacetanilide as distinguishable products. The crude **6d** was recrystallized from benzene–alcohol, giving a pure sample, mp 180–181° (lit.[5] mp 180–181°), as yellow needles. The crude **7d** was recrystallized from alcohol–benzene, giving a pure sample as white needles: ir (Nujol) 3280 (NH), 1690 (ring C=O), and 1670 cm^{-1} (carbamoyl C=O); nmr ($CDCl_3$) δ 5.25 (s, 1 H, methine proton) and 6.80–7.55 [m, 21 H, NH (1 H) and phenyl protons (20 H)]; mass spectrum (70 eV) m/e 450 (M^+) and 330 (M^+ − PhNHCO).

In the reaction using the same procedure described above, no adduct was formed but a phenylketene polymer was obtained together with unreacted **1d**.

Oxidation of 4,5-Diphenyl-5-carbamoyl-1,2-thiazolidines 7a–d. A solution of 7 (1 mmol) and *m*-chloroperbenzoic acid (1.2 mmol) in 50 ml of chloroform was allowed to stand at room temperature for 1 week. The solution was washed with 50 ml of 10% aqueous sodium sulfite, followed by washing with 50 ml of 5% aqueous sodium bicarbonate and 3 × 50 ml of water, and dried over sodium sulfate. After removal of solvent *in vacuo*, recrystallization of the residue gave pure **4,5-diphenyl-5-carbamoyl-1,2-thiazolidin-3-one 1-oxides 13a–d** (Table IV).

2-*tert*-Butyl-4,5-diphenyl-5-*tert*-butylcarbamoyl-1,2-thiazolidin-3-one 1-oxide (13a) was obtained as white crystals (alcohol), 96%: ir (Nujol) 1680 (C=O), 1540 (NH), and 1070 cm^{-1} (SO); nmr ($CDCl_3$) δ 1.42 (s, 9 H, >N-*t*-Bu), 1.60 (s, 9 H, CONH-*t*-Bu), 4.70 (s, 1 H, methine proton), and 7.30–7.75 [m, 11 H, NH (1 H) and phenyl protons (10 H)]; mass spectrum (70 eV) m/e 426 (M^+) and 370 (M^+ − C_4H_8).

2-*n*-Butyl-4,5-diphenyl-5-*n*-butylcarbamoyl-1,2-thiazolidin-3-one 1-oxide (13b) was obtained as white crystals (alcohol), 65%: ir (Nujol) 1680 (C=O), 1530 (NH), and 1050 cm^{-1} (SO); mass spectrum (70 eV) m/e 426 (M^+).

2-*n*-Propyl-4,5-diphenyl-5-*n*-propylcarbamoyl-1,2-thiazolidin-3-one 1-oxide (13c) was obtained as white crystals (alcohol), 86%: ir (Nujol) 3300 (NH), 1685 (ring C=O), 1650 (carbamoyl C=O), 1510 (NH), and 1080 cm^{-1} (SO); nmr ($CDCl_3$) δ 0.85 (t, J = 7 Hz, 6 H, methyl protons), 1.10–1.95 (m, 4 H, methylene protons), 2.95–3.95 (m, 4 H, methylene protons), 4.10 (s, 1 H, methine proton), 6.10 (broad, 1 H, NH), and 7.05–7.65 (m, 10 H, phenyl protons); mass spectrum (70 eV) m/e 398 (m^+) and 350 (M^+ − SO).

2,4,5-Triphenyl-5-phenylcarbamoyl-1,2-thiazolidin-3-one 1-oxide (13d) was obtained as white crystals (benzene–alcohol), 80%: ir (Nujol) 1690 (C=O), 1545 (NH), and 1050 cm^{-1} (SO); mass spectrum (70 eV) m/e 466 (M^+).

Reduction of 7a. A solution of **7a** (0.30 g, 0.73 mmol) in 50 ml of alcohol containing 0.50 g of Raney Ni was refluxed for 3 hr. The organic layer was separated and concentrated. Recrystallization of the residue from benzene–hexane gave 0.23 g (85%) of ***N,N'*-di-*tert*-butyl-2,3-diphenylbutane diamide (11a)**: mp 250–260° subl (benzene–hexane); ir (Nujol) 3350 (NH), 1640 (C=O), and 1530 cm^{-1} (NH); nmr ($CDCl_3$) δ 1.30 (s, 18 H, two *t*-Bu), 3.95 (s, 2 H, >CHCH<), 5.45 (broad, 2 H, two NH), and 7.05 (s, 10 H, two phenyl protons); mass spectrum (70 eV) m/e 381 (M^+ + 1) and 308 (M^+ + 1 − $C_4H_9NH_2$).

Anal. Calcd for $C_{24}H_{32}N_2O_2$: C, 75.75; H, 8.48; N, 7.36. Found: C, 75.82; H, 8.57; N, 7.34.

Reduction of 7b. A solution of **7b** (0.62 g, 1.50 mmol) in 50 ml of alcohol containing 1.0 g of Raney Ni was similarly carried out. After similar work-up the residue was recrystallized from alcohol to give 70 mg (12%) of **1-*n*-butyl-3,4-diphenyl-4-*n*-butylcarbamoylazetidin-2-one (12b)**: mp 160–162°; ir (Nujol) 3320 (NH), 1740 (ring C=O), 1655 (carbamoyl C=O), and 1530 cm^{-1} (NH); nmr ($CDCl_3$) δ 0.60–1.80 (m, 14 H, two methyl and four methylene protons), 2.50–3.00 (m, 2 H, CONH CH_2–), 3.25 (t, J = 7 Hz, 2 H, >NCH_2–), 4.87 [broad, 2 H, NH (1 H) and methine proton (1 H)], and 7.15–7.50 (m, 10 H, phenyl protons); mass spectrum (70 eV) m/e 378 (M^+), 307 (M^+ − NBu), and 278 (M^+ − BuNHCO).

Anal. Calcd for $C_{24}H_{30}N_2O_2$: C, 76.15; H, 7.99; N, 7.40. Found: C, 76.08; H, 7.97; N, 7.47.

The filtrate was evaporated and the residue was recrystallized from benzene–hexane to give 0.40 g (70%) of ***N,N'*-di-*n*-butyl-2,3-diphenylbutane diamide (11b)**: mp 85–86.5°; ir (Nujol) 3260 (NH), 1640 (C=O), and 1560 cm^{-1} (NH); nmr ($CDCl_3$) δ 0.55–1.60 (m, 14 H, two methyl and four methylene protons), 3.00–3.50 (m, 4 H, >NCH_2–), 3.80 (s, 2 H, methine protons), 5.90 (s, 1 H, NH), 6.35 (broad, 1 H, NH), and 7.15–7.40 (d, 10 H, phenyl protons); mass spectrum (70 eV) m/e 380 (M^+).

Anal. Calcd for $C_{24}H_{32}N_2O_2$: C, 75.75; H, 8.48; N, 7.36. Found: C, 75.66; H, 8.68; N, 7.23.

Reduction of 7c. A solution of **7c** (1.0 g, 2.62 mmol) in 50 ml of alcohol containing 1.0 g of Raney Ni was similarly carried out. After similar work-up the residue was recrystallized from alcohol to give 0.15 g (16%) of **1-*n*-propyl-3,4-diphenyl-4-*n*-propylcarbamoylazetidin-2-one (12c)**: mp 159–161°; ir (Nujol) 3320 (NH), 1745 (ring C=O), 1650 (carbamoyl C=O), and 1530 cm^{-1} (NH); nmr ($CDCl_3$)[6] δ 0.55–1.20 (m, 8 H, H_a + H_b + H_e), 1.35–2.00 (m, 2 H, H_f), 2.80 (q, J = 6 Hz, 2 H, H_c), 3.28 (t, J = 7.5 Hz, 2 H, H_g), 4.80–5.15 (broad, 2 H, H_d + H_h), and 7.20–7.55 (d, 10 H, phenyl protons); mass spectrum (70 eV) m/e 350 (M^+) and 264 (M^+ − C_3H_7CONH).

Anal. Calcd for $C_{22}H_{26}N_2O_2$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.52; H, 7.57; N, 8.05.

The filtrate was concentrated and the residue was recrystallized from hexane–benzene to give 0.40 g (44%) of ***N,N'*-di-*n*-propyl-2,3-diphenylbutane diamide (11c)**: mp 90–91°; ir (Nujol) 3220 (NH), 1635 (C=O), and 1565 cm^{-1} (NH); nmr ($CDCl_3$) δ 0.50–1.00 (m, 6 H, methyl protons), 1.00–1.65 (m, 4 H, methylene protons), 2.90–3.50 (m, 4 H, CONHCH_2–), 3.75 (s, 2 H, methine protons), 5.95 (s, 1 H, NH), 6.40 (broad, 1 H, NH), and 7.15–7.35 (d, 10 H, phenyl protons); mass spectrum (70 eV) m/e 352 (M^+).

Anal. Calcd for $C_{22}H_{28}N_2O_2$: C, 74.96; H, 8.01; N, 7.95. Found: C, 74.84; H, 8.10; N, 8.00.

Reaction between Di-*n*-butylsulfur Diimide (1b) and Phenylchloroketene (2b). The reaction was carried out as described above using **1b** (3.50 g, 0.02 mol), triethylamine (8.10 g, 0.08 mol), and α-chlorophenylacetyl chloride (11.34 g, 0.06 mol). After similar work-up, the residue was chromatographed on alumina using hexane and hexane–benzene as eluent. The first fraction gave a mixture of **2,3,4,5,6,7-hexahydro-2,7-di-*n*-butyl-4,5-dichloro-4,5-diphenyl-1,2,7-thiadiazepine-3,6-dione (15b)** and **1-*n*-butyl-3,4-dichloro-3,4-diphenylpyrrolidine-2,5-dione (16b)**. Pure samples of individual **15b** (0.35 g, 4%) and **16b** (0.25 g, 3%) were isolated by repeated recrystallization of the mixture from hexane–benzene.

15b had mp 125–126°; ir (Nujol) 1700 and 1670 cm^{-1} (C=O); nmr ($CDCl_3$) δ 0.70–1.95 [m, 14 H, two methyl (6 H) and four methylene protons (8 H)], 3.70 (t, J = 7 Hz, 4 H, >NCH_2–), and 7.15–7.90 (m, 10 H, phenyl protons); mass spectrum (70 eV) m/e 478 and 480 (M^+), 408 and 410 (M^+ − 2Cl), and 306 and 308 (M^+ − BuN=S=NBu).

Anal. Calcd for $C_{24}H_{28}N_2O_2SCl_2$: C, 60.12; H, 5.89; N, 5.84. Found: C, 59.78; H, 5.79; N, 5.83.

16b had mp 135°; ir (Nujol) 1785 and 1715 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.02 (t, J = 7 Hz, 3 H, methyl protons), 1.16–2.00 (m, 4 H, methylene protons), 3.83 (t, J = 7 Hz, 2 H, >NCH_2–), and 7.40 (s, 10 H, phenyl protons); mass spectrum (70 eV) m/e 375 and 377 (M^+) and 305 and 307 (M^+ − 2Cl).

Anal. Calcd for $C_{20}H_{19}NO_2Cl_2$: C, 63.83; H, 5.08; N, 3.72. Found: C, 63.49; H, 5.05; N, 3.64.

The second fraction afforded 1.60 g (26%) of **1-*n*-butyl-3,4-diphenylpyrroline-2,5-dione**, which was consistent with **6a** obtained in the above experiment.

Thermolysis of 15b. A solution of **15b** (0.11 g, 0.23 mmol) in 10 ml of benzene containing triethylamine (0.5 ml) was refluxed for 2 hr. After the resulting amine salt (60 mg) was removed by filtration, the filtrate was evaporated under reduced pressure and the residue was chromatographed on alumina to give **6b** (65 mg, 0.21 mmol, 93%).

Reaction between Di-*n*-propylsulfur Diimide (1c) and Phenylchloroketene (2b). The reaction was carried out as described above using **1c** (4.38 g, 0.03 mol), triethylamine (10.10 g, 0.1 mol), and α-chlorophenylacetyl chloride (17.01 g, 0.09 mol). After similar work-up, the residue was chromatographed on alumina to give 2.80 g (32%) of **6c** and 0.40 g (3%) of **2-*n*-propyl-4-chloro-4,5-diphenyl-5-*n*-propylcarbamoyl-1,2-thiazolidin-3-one 1-oxide (18c)**: ir (Nujol) 3340 (NH), 1715 (ring C=O), 1650 (carbamoyl C=O), and 1135 cm^{-1} (SO); nmr ($CDCl_3$) δ 0.85 (t, 6 H, methyl protons), 1.25–1.95 (m, 4 H, methylene protons), 3.30 (q, 2 H, >NCH_2–), 370 (t d, 2 H, CONHCH_2–), 5.80 (broad, 1 H, NH), and 7.05–7.70 (m, 10 H, phenyl protons); mass spectrum (70 eV) m/e 432 (M^+), 397 (M^+ − Cl), 350 (M^+ + 1 − Cl − SO), and 332 (M^+ − NHC_3H_7 − C_3H_6).

Anal. Calcd for $C_{22}H_{25}N_2O_3SCl$: C, 61.03; H, 5.82; N, 6.47. Found: C, 60.77; H, 5.74; N, 6.86.

Reaction between Diphenylsulfur Diimide (1d) and Phenylchloroketene (2b). The reaction was carried out using the proce-

dure described in the reaction between **1d** and **2a** with **1d** (4.28, 0.02 mol), α-chlorophenylacetyl chloride (9.45 g, 0.05 mol), and triethylamine (10.1 g, 0.1 mol). After similar treatment **6d** and **1,3,4-triphenyl-3,4-dichloropyrrolidine (16d)** were obtained in 5 (0.33 g) and 22% (1.70 g) yields.

16d had mp 197–199°; ir (Nujol) 1790 and 1735 cm^{-1} (C=O); nmr ($CDCl_3$) δ 7.20–7.50 (d, phenyl protons); mass spectrum (70 eV) *m/e* 395 and 397 (M^+) and 325 and 327 ($M^+ - 2Cl$).

Anal. Calcd for $C_{22}H_{15}NO_2Cl_2$: C, 66.68; H, 3.82; N, 3.53. Found: C, 66.71; H, 3.91; N, 3.81.

Registry No.—**1a**, 2056-74-8; **1b**, 23386-62-1; **1c**, 28924-14-3; **1d**, 3839-89-2; **2a**, 3496-32-0; **2b**, 29804-92-0; **6a**, 51003-31-7; **6b**, 51003-32-8; **6c**, 51003-33-9; **7a**, 51003-34-0; **7b**, 51003-35-1; **7c**, 51021-64-8; **7d**, 51003-36-2; **8a**, 51003-02-2; **9b**, 51003-37-3; **10c**, 51003-38-4; **11a**, 51003-39-5; **11b**, 51003-40-8; **11c**, 51003-41-9; **12b**, 51003-42-0; **12c**, 51003-45-1; **13a**, 51003-44-2; **13b**, 51003-45-3; **13c**, 51003-46-4; **13d**, 51003-47-5; **15b**, 51003-48-6; **16b**, 51003-49-7; **16d**, 51003-50-0; **18c**, 51003-51-1; phenylacetyl chloride, 103-80-0; α-chlorophenylacetyl chloride, 2912-62-1.

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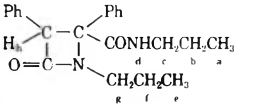

The Mechanism of Cycloaddition of Diphenylketene with Azo Compounds[1]

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Cycloadditions of diphenylketene with cis azo compounds, PhN=NY [Y = CO_2Et, $CH(CH_3)_2$, and $N(CH_3)_2$], with *cis*-azobenzenes, PhN=NC_6H_4X [X = CH_3O, CH_3, H, Cl, CN, NO_2] and with *trans*-PhN=NCO_2Et have been studied. 1,2-Diazetidin-3-one products form cleanly in most cases, by a near-concerted mechanism, as shown by small effects of solvents and substituents on rates, small regioselectivity among the azobenzenes, and absence of trappable intermediates. In contrast to diphenylketene, isocyanates give no evidence of reaction with azo compounds.

Since Staudinger first reported the cycloaddition of ketenes with azo compounds in 1912,[2] the reaction has been used many times for the synthesis of 1,2-diazetidinones.[3] However, little effort has been directed toward study of the mechanism of this cycloaddition. In contrast, extensive studies of the cycloaddition reactions of ketenes with alkenes[4] and with enol ethers[5] have shown that these reactions are essentially concerted, as shown by stereospecificity, isotope effects, and small solvent effects on rates. Cycloadditions of ketenes with enamines[6] and imines[7] have been found to be at least partly ionic processes, based upon trapping of dipolar intermediates and large solvent effects on rates. Cycloadditions of ketenes with nitroso compounds have been alleged to occur in part by concerted and in part by dipolar mechanisms.[8,9] Barker[10] has studied the cycloaddition of ketenimines with azo compounds and found it to be nearly concerted.

In order to observe cycloaddition between *trans*-azobenzene and diphenylketene (**1**), the neat reactants had to be heated at 130°.[2] However, it was subsequently found that *cis*-azobenzene, unlike *trans*-azobenzene, reacted rapidly with diphenylketene at room temperature.[11] The reaction is often run, therefore, by *in situ* generation of cis azo compound by irradiation of the trans azo compound in the presence of the ketene.[12] We have usually followed this same procedure.

Two of the most important tools of mechanistic exploration, stereochemistry and hydrogen isotope effects, are rendered unusable by the nature of the products and reactants, respectively, in the ketene + azo cycloaddition. Therefore, the mechanistic criteria employed in this study include the regioselectivity of the reaction; kinetic criteria, including effects of substituents and solvents on reaction rates; and attempts to intercept intermediates. Direct substitution on the azo group was employed in order to effect maximum regioselectivities, as well as traditional benzene-ring substitution to provide isolable cis isomers for kinetic studies.

Results and Discussion

Azobenzene. Solutions of *trans*-azobenzene (**2a**) and diphenylketene (**1**) at room temperature are indefinitely stable; no reaction can be detected. In contrast, *cis*-azobenzene reacts rapidly with the ketene,[11] whether isolated chromatographically from irradiated azobenzene solutions or generated *in situ* by irradiation.[12] After 5-hr irradiation through a 5% cupric sulfate–6.5% cobaltous sulfate filter solution,[13] the cycloaddition is complete, as judged by absence of infrared absorption of the ketene at 2130 cm^{-1}. 1,2,4,4-Tetraphenyldiazetidin-3-one was isolated in 76% yield from a carbon tetrachloride solution; comparable yields (64–75%, correcting for recovered azobenzene) were obtained from the reaction in ethyl ether, benzene, or cumene solution. The reaction was also run in benzene and methylene chloride, using a fivefold excess of **1**; again, only the diazetidinone could be isolated. The infrared spectra of the reaction mixtures gave no evidence of 2:1 adducts arising from reaction of **1** with dipolar intermediates,[6,7] such as unaccountable carbonyl peaks.

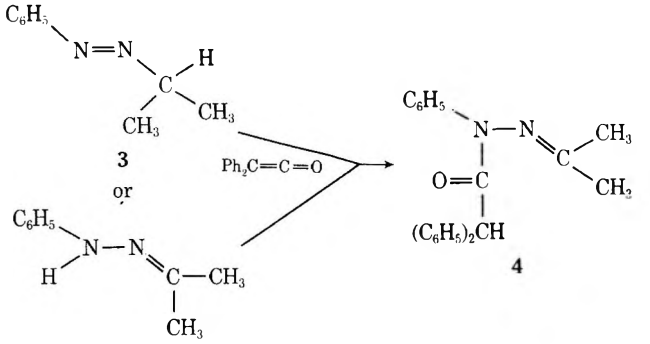
The rate of cycloaddition of *cis*-azobenzene (**2a**) with **1** was studied by irradiating a solution of *trans*-azobenzene of known concentration and absorbance so as to partially convert it to cis, adding a small excess of **1**, and following the rapid decrease of absorbance at 475 nm. After at least 10 half-lives the final absorbance gave the amount of unreacted *trans*-azobenzene left and, by subtraction, the amount of *cis*-azobenzene present before adding the ketene. Good second-order kinetics were observed, based on this initial concentration and the known concentration of ketene added. Rate coefficients found follow: cyclohexane (E_T 31.2),[14] 2.1 ± 0.4 × 10^2 M^{-1} sec^{-1}; benzene (E_T 34.5),[14] 5.4 ± 1.0 × 10^2 M^{-1} sec^{-1}; methylene chloride

(E_T 41.4),[14] 6.9 ± 0.4 × 10^2 M^{-1} sec^{-1}; acetonitrile (E_T 46.0),[14] 20 ± 2 × 10^2 M^{-1} sec^{-1}. These remarkably fast rates provide a vivid contrast with the completely unreactive *trans*-azobenzene.

2-(Phenylazo)propane.[15] The visible spectrum of 2-(phenylazo)propane (**3**) in cyclohexane shows an n → π* transition at 403 nm (ε 137), indicating a trans geometry. After 20-min irradiation with a mercury lamp through a 5% cupric sulfate filter solution,[16] the absorbance at *ca.* 400 nm had increased by 12%, and the maximum had shifted to slightly shorter wavelength. No significant change in the spectrum occurred when the irradiated solution was allowed to stand in the open for 45 min, but, upon addition of a small quantity of **1**, there was an immediate decrease in absorbance, which leveled off within 1 min and remained unchanged thereafter, despite the presence of excess ketene. The wavelength of maximum absorbance appeared at 405 nm.

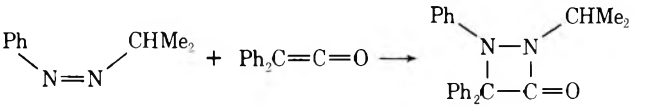
These observations suggest that *trans*-**3**, like *trans*-**1a**, is relatively unreactive toward diphenylketene, but is converted by irradiation to a reactive cis isomer.

When *trans*-**3** and **1** were stirred together in carbon tetrachloride solution, a slow reaction did occur, the ketene being consumed after 15 hr. The ir spectrum of the mixture did not, however, indicate any cycloadduct. The product was an air- and moisture-sensitive solid which could not be purified owing to decomposition during chromatography or crystallization. Its ir spectrum showed important bands at 1675 (amide) and 1610 cm^{-1} (>C=N–), and its nmr spectrum showed a complex multiplet around τ 2.7 (aromatic protons), a weak singlet at τ 5.0 (CH), and two singlets at τ 2.05 and 2.30 (CH_3). These data suggested that the material might be acetone *N*-(diphenylacetyl)-*N*-phenylhydrazone (**4**). In confirmation of this hypothesis, the same material was formed quantitatively by reaction of acetone phenylhydrazone with diphenylketene.



The product **4** apparently arises from an "ene" reaction[17] involving the α hydrogen of the isopropyl group of **3**. An analogous reaction was also observed in the only previous study of the reaction of a ketene and an aliphatic azo compound (α-azotoluene).[18] Thus *trans*-**3** and **1** do react thermally, but not by cycloaddition.

However, if a solution of **3** and diphenylketene in carbon tetrachloride was irradiated through a 5% cupric sulfate filter solution[16] in order to produce *cis*-**3**, all the ketene disappeared within 5 hr, and the ir spectrum did show a sharp diazetidinone carbonyl absorption at 1778 cm^{-1}, in addition to the bands of **4**. Chromatography of the reaction mixture on alumina gave, in 12% yield, a white solid, mp 117–118.5°, which gave a correct analysis for a 1:1 cycloadduct. The nmr spectrum of this material showed a multiplet at τ 2.4–3.3 (*ca.* 15 H), a septet at τ 6.28 (1 H), and a doublet at τ 8.63 (6 H). The low-field resonance of the α H of the isopropyl group suggested that the isopropyl was in the 2 position of the diazetidinone ring (*i.e.*, the amide nitrogen) rather than the 1 position; *cf.* *N*-isopropylacetamide, τ 6.00,[19] and *N*-isopropyl-*N'*-phenylhydrazine, τ 7.11. That the cycloadduct was 1,4,4-triphenyl-2-isopropyldiazetidin-3-one was proven by its mass spectrum, in particular by the presence of peaks at *m/e* 257 ($Ph_2C{=}NPh^+$) and 180 ($PhC{\equiv}NPh^+$). Thus, *cis*-**3**, unlike *trans*-**3**, reacts with **1** by cycloaddition (at least in part).



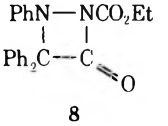
1-Phenyl-3,3-dimethyltriazene. This triazene, **5**, apparently has the trans configuration, based on its dipole moment of 2.28 D[20] (*cf.* *trans*-*p*-dimethylaminoazobenzene, 2.48 D).[21] When **5** was stirred with **1** in carbon tetrachloride for 4 days, no reaction occurred. However, irradiation of such a solution through a 5% $CuSO_4$ filter solution[16] resulted in consumption of all the ketene within 4 hr, as indicated by infrared, which also showed two new bands, at 4.4 (isocyanate) and 5.62 μ (carbonyl). The isocyanate band was due to phenyl isocyanate, as shown by isolation of 25% 1,3-diphenylurea upon addition of aniline to the reaction mixture. Chromatography then yielded unreacted **5** (56%) and a thermally sensitive white solid, which proved to be 3,3,4,4-tetraphenyl-1-dimethylamino-2-azetidinone (**6**, 35% yield) based on spectra, analysis, and synthesis of an authentic sample from **1** and benzophenone dimethylhydrazone.[22] We conclude that the reaction occurred by the sequence outlined in Scheme I.

We interpret the effect of light on this reaction, by analogy with the reactions of **2a** and **3**, as due to formation of *cis*-**5**, which reacts rapidly with **1**. Attempts to detect *cis*-**5** directly by irradiation of solutions of *trans*-**5** [λ_{max} 285, 308 nm (sh)][20] in carbon tetrachloride, cyclohexane, or benzene failed; rapid loss of all ultraviolet absorption above 250 nm occurred. We infer that *cis*-**5** is thermally unstable and decomposes rapidly[23] or, if **1** is present, undergoes rapid cycloaddition.

The apparent instability of the diazetidinone formed from **1** and **5** is consistent with previous observations that electron-donating groups cause lowered thermal stability in diazetidinones,[2,12] and with our own observations (*vide infra*) to the same effect.

Again, reaction of **5** with excess **1** gave the same products. The infrared spectrum of the product mixture gave no evidence of 2:1 adducts, and none was isolated.

Ethyl Phenylazoformate. The product of thermal reaction of ethyl phenylazoformate (**7**) with **1**, originally assigned the structure **8** by Ingold and Weaver,[24] was more recently found to be **9**.[25]



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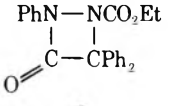
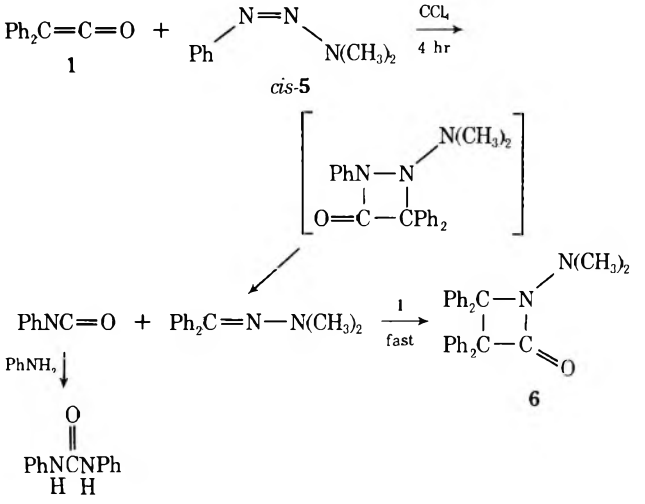


9

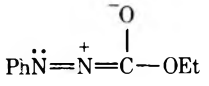
7 is the only azo compound of those we investigated which gives cycloaddition with diphenylketene in the absence of irradiation.[26] This is not due to its possessing a cis structure; the intensity of the n → π* transition at 418 nm (ε 146, dioxane solution)[27] indicates that **7** has the trans structure. However, the relatively slow reaction of **7** with diphenylketene in cyclohexane was found to be accelerated by irradiation with a mercury lamp through a 5% cupric sulfate filter solution.[16] The product was **9**, the same as from the unirradiated reaction,[25] isolated in 69% yield. An infrared spectrum of the mixture immediately

Scheme I
Reaction of Diphenylketene with 1-Phenyl-3,3-dimethyltriazene



after reaction showed only the two peaks belonging to **9** at 1788 and 1742 cm^{-1} in the carbonyl region, and a small shoulder at *ca.* 1820 cm^{-1} possibly due to 8. Again reaction with excess **1** gave the same results, with no evidence of any 2:1 adduct.

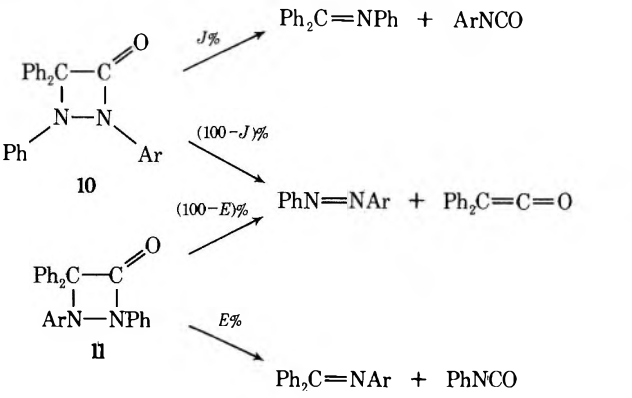
The acceleration upon irradiation is again thought to be due to formation of transient *cis*-**7**. Irradiation of a cyclohexane solution of *trans*-**7** at room temperature resulted in no change in either the wavelength or intensity of the $n \rightarrow \pi^*$ band at 425 nm. Apparently the cis isomer formed reverts to *trans*-**7** very rapidly, perhaps *via* a linear transition state involving carbonyl-group-stabilization.[28]



The reaction of **7** with diphenylketene in cyclohexane at 25.00° was followed by monitoring the absorbance at 475 nm. The reaction was first order in each reactant, and proceeded with a second-order rate coefficient of 3.9 ± 0.4 × 10^{-3} M^{-1} sec^{-1}. In acetonitrile at the same temperature, the rate coefficient was 11.7 ± 0.6 × 10^{-3} M^{-1} sec^{-1}, only three times faster than in cyclohexane. Clearly *trans*-**7** is much less reactive (*ca.* 10^5) than the cis azo compounds discussed herein, but much more reactive than other trans azo compounds. The reason for the latter remains obscure.

Substituted Azobenzenes PhN=NC$_6$H$_4$X. Reaction of **1** with unsymmetrically substituted azobenzenes leads to two isomeric diazetidinones. The analysis of the product mixtures was performed by a gas chromatographic method in which the mixture was injected into a vaporizer block at a temperature sufficiently high as to pyrolyze the diazetidinones. The main products of such pyrolysis (Scheme II) were an isocyanate and a Schiff base; to some degree the azo compound **2** and ketene **1** were also produced. The analysis was based on determination of the amounts of the two Schiff bases. In order to correct for the different branching ratios for decomposition of the isomers **10** and **11** in the two possible directions, one (or both) of the diazetidinones was isolated from each reaction by extensive column chromatography and/or recrystallization, and its (their) branching ratio was determined directly and used in correcting the observed Schiff base ratio, so as to yield an accurate diazetidinone ratio. Three to six determinations were made in all cases. The data obtained for reaction of azo compounds **2b-f** with **1** are given in Table I; the uncertainties shown are maximum deviations observed among the various determinations.

Scheme II
Thermolysis of Diazetidinone Mixtures



The data indicate that reaction time at 80° and the lamp used (runs 3 and 12) have essentially no effect on the ratio of **11** to **10**. However, the temperature of the reaction does slightly affect the product distribution (runs 1, 6, 10): the amount of **11** decreases from 70% at 30° to 64% at 80° and remains about the same at 120°. Moreover, prolonged refluxing at 120° does produce some change, presumably the consequence of partial reversibility of the initial cycloaddition, leading to incipient thermodynamic control.

The most striking fact about the product ratios is the *very low regioselectivity* observed in all cases. The ratio of **11**/**10** in no case exceeds 4, indicating a very slight rela-

Table I
Results from Reactions of 1 with Azobenzenes 2a-f

Run	Compd	X	Solvent	Lamp[a]	Temp, °C	Time, hr	Injector temp, °C	% E (from **11**)	% J (from **10**)	—Produced in reaction— % **11**	% **10**
1	**2b**	OCH_3	C_6H_6	uv	80	15	202	91.8 ± 0.6	95.4 ± 0.6	64 ± 2	36 ± 2
2	**2c**	CH_3	C_6H_6	uv	80	39	235	79 ± 4	78 ± 2	54 ± 3	46 ± 3
3	**2d**	Cl	C_6H_6	uv	80	8	238	85 ± 2	77 ± 2	59 ± 2	41 ± 2
4	**2e**	NO_2	C_6H_6	ir	80	1	270	52 ± 3	68 ± 2	61 ± 2	39 ± 2
5	**2f**	CN	C_6H_6	ir	80	42	290	58 ± 3	54 ± 3	64 ± 3	36 ± 3
6	**2b**	OCH_3	C_6H_6	R	30	15	210	94.6 ± 0.1	94.6 ± 0.4	70 ± 1	30 ± 1
7	**2b**	OCH_3	CH_2Cl_2	R	30	15	210	94.6 ± 0.1	94.6 ± 0.4	79 ± 1	21 ± 1
8	**2b**	OCH_3	CH_3CN	R	30	15	210	94.6 ± 0.1	94.6 ± 0.4	77 ± 1	23 ± 1
9	**2b**	OCH_3	$PhCH_3$	uv	120	24	225	94.6 ± 0.1	94.6 ± 0.4	58 ± 1	42 ± 1
10	**2b**	OCH_3	$PhCH_3$	uv	120	0.5	225	94.6 ± 0.1	94.6 ± 0.4	66 ± 1	34 ± 1
11	**2b**	OCH_3	$PhCH_3$	uv	120	1	225	94.6 ± 0.1	94.6 ± 0.4	65 ± 1	35 ± 1
12	**2d**	Cl	C_6H_6	ir	80	22	280	75 ± 3	74 ± 2	58 ± 1	42 ± 1

[a] Lamps used for *in situ* generation of *cis*-**2** from *trans*-**2**: uv indicates a Gates 420-U1 360-W equipped with a G. E. UA-3 lamp; ir indicates a Fisher Infrarediator equipped with G. E. 250-W infrared lamps; R indicates a Rayonet Photochemical Reactor equipped with RPR-3500 A lamps.

Table II
Rates of Cycloaddition in Benzene at 25°

Compd	X	k_T[a]	k of 11[a,c]	k of 10[a,c]
2b	OCH_3	20 ± 5[b]	13 ± 4[b]	7 ± 2
2c	CH_3[d]	7.8 ± 0.2	4.2 ± 0.1	3.6 ± 0.1
2a	H	5.4 ± 1.0	2.7 ± 0.5	2.7 ± 0.5
2d	Cl	2.5 ± 0.2	1.5 ± 0.1	1.0 ± 0.1
2f	CN[d]	21 ± 10	13 ± 7	8 ± 5

[a] Rates are in units of 10^2 M^{-1} sec^{-1}. [b] Standard deviations, based on 4–12 runs. [c] Obtained by multiplying overall rate, k_T, by the fractions of **11** or **10** from Table I. [d] At 21.8°.

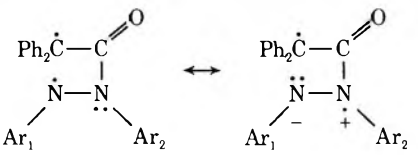
tive effect of substituents on the two transition states. The second important observation is that *the same isomer,* **11**, *predominates whether the substituent X is electron withdrawing or electron donating.* Under the same conditions (runs 1–5), somewhat greater regioselectivity is obtained with strongly interacting substituents (X = OCH_3, **11**/**10** = 1.8; CN, 1.8; NO_2, 1.6) than with weaker ones (Cl, 1.4; CH_3, 1.2). The regioselectivity is higher in more polar solvents than in less polar ones, but again the effect is small (runs 6–8).

In order further to assess substituent effects, the rates of reaction of *cis*-**2b–f** with **1** were studied. The cis isomers were prepared by photolysis of *trans*-**2b–f**, isolated by column chromatography at 0°, and used directly. The reactions were followed by monitoring the decrease in the long-wavelength n → π* bands of *cis*-**2b–f** at *ca.* 440 nm. Second-order kinetics (first order in each reactant) were observed. The results are given in Table II.

Again, the striking fact is the *very small effect of substituents on rates,* all falling within a power of 10. There is no overall trend relating rate to electronic effect of substituent; the fastest rates are observed with both the best electron-withdrawing and the best electron-donating group. The rate of formation of **11** appears to be slightly more affected by substituents than that of **10**, but the difference is modest. The rate of cycloaddition of **2a** with **1** is only modestly dependent on solvent (*vide supra*).

Discussion of Mechanism. Like any cycloaddition, that of **1** and **2** may in principle proceed by a dipolar, diradical, or concerted mechanism. The results obtained (low regioselectivity, the preferred direction of regioselectivity, low solvent effect on rates and regioselectivity, no evidence of trappable intermediates) seem wholly inconsistent with a dipolar mechanism.

A diradical mechanism for reaction of **1** and **2** would appear, *a priori,* to be relatively favorable, involving the intermediacy of the stable diradical **12**. Qualitative studies of hydrazyl radical–tetrazane equilibria indicate that hydrazyl radicals like **12** are stabilized by electron-donating groups on either nitrogen and by electron-withdrawing groups on the divalent nitrogen, but destabilized by electron-withdrawing groups on the trivalent nitrogen.[29] This is qualitatively consistent with the observed preference for formation of isomer **11** rather than **10** in all cases. The products observed in the reactions of azo compounds PhN=NY [Y = CO_2Et, $CH(CH_3)_2$, and $N(CH_3)_2$] are likewise qualitatively consistent with a diradical mechanism, the following diradicals evidently being preferred over the isomeric ones.



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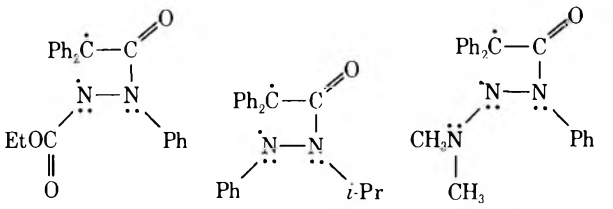
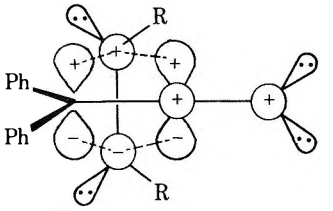


However, for a diradical intermediate, one would have expected greater regioselectivity with electron-withdrawing X groups than with electron-donating X groups, which is not found to be the case. Moreover, the small size of the effects of substituents on rates and on product distribution does not seem to support a true diradical intermediate.

The relative insensitivity of the reaction to substituents X is most easily explained in terms of a nearly concerted reaction mechanism. A reagent as unsymmetrical as diphenylketene would be unlikely to react by a perfectly synchronous process, but a practically concerted process similar to that proposed by Woodward and Hoffmann[30,31] for the reaction of ketenes with alkenes appears quite feasible. In this [$_\pi 2_s + {}_\pi 2_a$] process, the cis azo compound and the ketene approach orthogonally, an arrangement which is made favorable by (a) a donor–acceptor interaction between the π_{CC} orbital of the ketene and the π^*_{NN} orbital of the azo compound; (b) most important, a donor–acceptor interaction between the π_{NN} orbital of the azo compound and the unusually low-lying[32] π^*_{CO} orbital of the ketene; (c) favorable alignment of dipoles of cis azo compound and ketene; and (d) absence of steric repulsions among the substituent groups.



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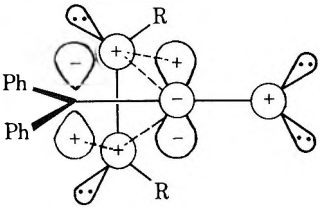

b

In contrast, one R group of a trans azo compound must project to the left in the above diagrams, and may be expected to seriously interfere with one phenyl group of the diphenylketene. This, in addition to the intrinsically lower ground-state energy of trans azo compounds (*trans*-**2a** is 10 kcal lower in energy than *cis*-**2a**),[33] accounts for the generally low reactivity of trans azo compounds in these cycloadditions. In summary, we feel that the evidence is most consistent with a concerted but not synchronous mechanism, with lack of perfect concert reflected in a small amount of diradical character in the transition state.

The notion of partial diradical character has been repeatedly invoked to explain regioselectivity and substituent effects on concerted reactions, particularly the Diels–Alder[34] and 1,3-dipolar addition[35] reactions. Mild rate accelerations by both electron-donating and -withdrawing groups have been reported for these reactions, analogous to those reported here.[36]

The Woodward-Hoffmann concept of concerted ketene cycloadditions involving the low-lying π^*_{CO} orbital of the ketene[30] is also supported by the unreactivity of isocyanates, which lack a sufficiently low-lying π^* orbital (PhNCO, for example, has its longest wavelength $n \rightarrow \pi^*$ absorption at 278 nm,[37] compared to Ph_2CCO at 407 nm). Attempts to force reaction of aryl isocyanates or sulfonyl isocyanates with *cis*-**2a** or with **7** at temperatures up to 200° were uniformly unsuccessful, only starting materials being recovered.[47]

Experimental Section[38]

Diphenylketene (**1**) was prepared by the method of Martin.[39] Ethyl phenylazoformate (**7**)[40] and 1-phenyl-3,3-dimethyltriazene (**5**)[41] were prepared by literature methods. *p*-Methoxyazobenzene (**2b**) was prepared by methylation of *p*-phenylazophenol by a literature procedure.[42] Azobenzenes **2c–e** were prepared by condensation of the appropriate aniline with nitrosobenzene, and purified by column chromatography and recrystallization. *p*-Cyanoazobenzene (**2f**) was prepared by nitrosation of *p*-phenylazoaniline, followed by treatment with cupric sulfate–potassium cyanide.[43] All had melting points in agreement with literature values.

***N*-Benzhydrylidene-*p*-cyanoaniline.** Benzophenone (10.0 g, 55 mmol), *p*-cyanoaniline (6.05 g, 52 mmol), and 3 drops of concentrated HCl were heated together under nitrogen at 200° for 30 min, and then the mixture was distilled at 170° (2 mm) to remove excess reactants. The undistilled residue was chromatographed on a silica gel column, from which eluted first benzophenone, then the Schiff base (solvent 60% benzene–40% pentane). The latter was recrystallized four times from ethanol: mp 126–128°; ir (KBr) 4.53 (m, –C≡N), 6.18 (s, >C=N–), 6.28 (s), 11.8 (s), 13.6 (m), 14.2μ (s).

Anal. Calcd for $C_{20}H_{14}N_2$: C, 85.11; H, 4.97; N, 9.93; mol wt, 282. Found: C, 84.66; H, 5.25; N, 9.86; mol wt, 284.

The other Schiff bases, $Ph_2C{=}N\text{-}p\text{-}C_6H_4X$ (X = H, OCH_3, Cl, CH_3, NO_2), were prepared similarly, and gave melting points in agreement with literature values.

Reaction of 1 with 2a. Solutions of **1** (4.03 g, 0.02 mol) and **2a** (3.69 g, 0.020 mol) each in 25 ml of carbon tetrachloride were combined in a 125-ml erlenmeyer flask fitted with a reflux condenser and drying tube and having a syringe-stoppered side arm for removal of samples. The solution was stirred magnetically and irradiated with an external mercury lamp for 5.5 hr, after which no ketene peak at 4.8 μ remained in the ir. The solvent was stripped and the residue was washed with methanol and recrystallized from ethyl acetate, giving 5.09 g (68%) of 1,2,4,4-tetraphenyl-1,2-diazetidin-3-one, mp 175–178° (lit.[12] mp 175–176°). Crude **2a** (*ca.* 11%) was recovered from the mother liquor by ethanol recrystallization.

Reaction in cumene gave 66% of diazetidinone and 31% of recovered azobenzene (by alumina chromatography); similar results were also obtained in ethyl ether and benzene. Reaction with a fivefold excess of **1** gave a product mixture whose ir spectrum showed no extraneous >C=O absorptions due to 2:1 adducts; the diazetidinone was isolated in 50% yield despite difficulties due to hydrolysis and oxidation products from the excess **1**.

Reaction of 1 with 3. A. With Photolysis. **1** (2.59 g, 0.014 mol) and **3** (2.04 g, 0.014 mol) in 50 ml of carbon tetrachloride were irradiated as above, but through a 5% cupric sulfate filter solution.[16] After 5 hr, the ir showed no remaining ketene, but did show two >C=O absorptions, at 5.61 and 5.97 μ. The solvent was stripped and the residue was chromatographed on neutral alumina. Elution with 15% ether in benzene gave 0.512 g (12%) of white solid: mp 117–118.5° after crystallization from pentane; ir (Nujol mull) 5.66 (s), 6.25 (m), 6.31 (m), 7.79 (m), 9.83 (m), 12.73 (m), 13.21 (m), 13.56 (m), and 14.35 μ (m); nmr ($CDCl_3$) see text; mass spectrum (direct inlet, 40°) *m/e* (rel intensity, interpretation) 342 (3.5, P), 313 (1.8, P – C_2H_5), 299 (2.3, P – C_3H_7), 271 (2.3, P – C_3H_7 – CO), 257 (4.4, Ph_2CNPh), 194 (85.4, Ph_2CCO), 180 (16.7, PhCNPh), 166 (36.4, Ph_2C), 165 (42.4, fluorenyl), 105 (47, PhN_2), 77 (100, Ph), 43 (29.2, C_3H_7), 41 (30.0, C_3H_5). These data show this product to be 2-isopropyl-1,4,4-triphenyl-1,2-diazetidin-3-one.

Anal. Calcd for $C_{23}H_{22}N_2O$: C, 80.70; H, 6.43; N, 8.19. Found: C, 80.77; H, 6.53; N, 8.08.

Prior elution of the column with benzene yielded a small amount (*ca.* 5%) of benzophenone. The major product produced in the reaction was **4**, judging by ir, but **4** was destroyed on chromatography, allowing isolation of the diazetidinone.

B. Without Photolysis. **1** (1.94 g, 0.010 mol) and **3** (1.49 g, 0.010 mol) were stirred together in 50 ml of carbon tetrachloride for 15 hr. The ir spectrum showed a large >C=O peak at 5.97 μ, with at most a trace at 5.61 μ. Evaporation of the solvent left a solid product which could not be purified due to air and moisture sensitivity, but which was identical (ir, nmr) with the product **4** formed by reaction of **1** with acetone phenylhydrazone.

Reaction of 1 with Acetone Phenylhydrazone. **1** (1.94 g, 0.010 mol) and acetone phenylhydrazone (1.52 g, 0.010 mol) were allowed to react in 50 ml of carbon tetrachloride for 18 hr. Partial evaporation of the solvent followed by addition of pentane precipitated an air- and moisture-sensitive yellow solid, **4**: ir (CCl_4) 5.97 (s, amide >C=O), 6.25 (s), 6.70 (s), 6.90 (m), 7.35 (m), 9.69 (m) 14.29 μ (s); nmr (CCl_4) see text.

Reaction of 1 with 5. **1** (1.94 g, 0.010 mol) and **5** (1.49 g, 0.010 mol) in 50 ml of carbon tetrachloride were irradiated through a 5% copper sulfate solution[16] as above for 4 hr. The ir showed a peak at 4.4 (–NCO) and 5.62 μ (>C=O). Aniline (0.936 g, 0.010 mol) was added to react with the isocyanate; filtration after 2.5 days gave a solid, which was recrystallized from ethanol to give 0.532 g (25%) of 1,3-diphenylurea, mp 242–244°, mmp 242–244° (authentic mp 244–245°). The filtrate was evaporated, and the residue was chromatographed on neutral alumina, which yielded a mixture of a solid and an oil. The pentane-soluble oil was recovered **5** (ir, nmr), 0.84 g (56%). The pentane-insoluble white solid, mp 145–148°, 0.724 g (35%), was 1-(dimethylamino)-3,3,4,4-tetraphenylazetidin-2-one.

Anal. Calcd for $C_{29}H_{26}N_2O$: C, 83.25; H, 6.22; N, 6.70. Found: C, 83.13; H, 6.35; N, 6.64.

The infrared of a reaction mixture using five times as much **1** showed only peaks attributable to the ketene, phenyl isocyanate, and the azetidinone.

Reaction of 1 with Benzophenone Dimethylhydrazone.[44] **1** (1.95 g, 0.010 mol) and the hydrazone (2.35 g, 0.010 mol) were stirred for 10.5 hr in 75 ml of carbon tetrachloride, after which the solvent was stripped, and pentane was added to precipitate the product: mp 145–148°; ir (Nujol mull) 5.62 (s >C=O), 6.05 (m), 6.26 (m), 6.62 (m), 13.25 (m), 13.42 (m), 13.75 (m), 14.20 μ (m); nmr ($CDCl_3$) τ 2.92 (m, 20 H), 6.92 (s, 6 H). The mixture melting point with the azetidinone from above was 145–148°.

Reaction of 1 with 7. **1** (1.94 g, 0.010 mol) and **7** (1.79 g, 0.010 mol) in 75 ml of cyclohexane were irradiated for 3 hr through a 5% $CuSO_4$ filter solution,[16] after which ir revealed only peaks at 5.59 and 5.73 μ in the carbonyl region, with a small shoulder at 5.50 μ. The residue from evaporation of the solvent was recrystallized from 95% ethanol, yielding 2.38 g (64%) of **9**: mp 128–130° (lit.[24] mp 132–133°); ir (Nujol mull) 5.59 (s, diazetidinone C=O), 5.73 (s, ester C=O), 6.25 (m), 7.91 (m), 8.91 (m), 9.88 (m), 13.30 (s), 13.69 (s), 14.50 μ (s); nmr ($CDCl_3$) δ 0.78 (t, 3 H), 3.80 (q, 2 H), 7.05–7.68 (m, 15 H). Chromatography of the mother liquor on silica gel gave a 7% recovery of **7**.

Attempted Reactions of Isocyanates with Azo Compounds. A. Azobenzene **2a** (2.31 g, 0.013 mol) and *p*-toluenesulfonyl isocyanate (**14**, 2.39 g, 0.012 mol) were refluxed in 75 ml of dioxane, while the solution was irradiated with an unfiltered mercury lamp. After 4 days, water was added to hydrolyze the isocyanate, and then the water and dioxane were removed at reduced pressure. The residue was dissolved in benzene and extracted with 2% aqueous NaOH. *p*-Toluenesulfonamide (0.91 g, 43%), mp 136–138.5°, was isolated by acidification of the aqueous layers. **2a** (2.34 g, 99%, mp 63–65°) was recovered by drying and evaporating the benzene layer.

B. Azobenzene **2a** (5.68 g, 0.031 mol) and **14** (6.41 g, 0.032 mol) were heated together neat for 2 hr, irradiated with a mercury lamp for 10 hr, and then stirred for an additional 48 hr, all at 100°. The mixture was added to water and worked up as above, giving 3.82 g (70%) of *p*-toluenesulfonamide and 4.84 g (85%) of **2a**.

C. Chlorosulfonyl isocyanate (*ca.* 1.4 g, 0.01 mol) and **2a** (1.697 g, 0.009 mol) in 25 ml of carbon tetrachloride were allowed to reflux for 13 hr and then irradiated for 2 hr at reflux. Water (2 ml) was then cautiously added. After 1 hr, the volatile materials were removed at reduced pressure and the residue was chromatographed on silica gel. Elution with pentane gave 1.58 g (93%) of **2a**; small amounts of unidentified polar materials were eluted with more polar solvents.

D. *p*-Nitrophenyl isocyanate (1.64 g, 0.010 mol) and **2a** (1.83 g, 0.010 mol) were heated together at 205° for 22 hr. After cooling,

Table III
Data on Products from Diphenylketene and Substituted Azobenzenes in Benzene at 80°

Substituent X	Time, hr	Lamp[a]	Yield, %[b]	Compd or mixture[c]	Mp, °C	λ_{CO}[d]
CH_3	42	uv	83	**10c + 11c**	174–179[e]	5.66
CH_3	11	uv		**10c**	178–179	5.61
Cl	8	uv	78	**10d + 11d**	133–135[e]	5.62
Cl	8	uv		**11d**	164	5.62
NO_2	1	ir	94	**10e + 11e**	171–180[e]	5.58
						5.60
NO_2	10.5	uv	18[f]	**11e**	167–168[e]	5.60
CN	12.2	ir		**11f**	188–190[e]	5.65
CN	12.2	ir		**10f**	219–221[e]	5.67

[a] See Table I, footnote *a*. [b] Total yield of diazetidinones **10** + **11** isolated. [c] Material to which data in remaining columns refer, as identified by pyrolytic vpc. [d] Diazetidinone carbonyl wavelength, in microns. [e] Satisfactory combustion data for C, H, N (±0.4%) were reported for these materials: Ed. [f] Compound **10e** decomposes on uv irradiation.

benzene was added and the solution was analyzed by vpc (5 ft × 0.25 in. 3% SE-30 column, 145°). Only starting materials were detected. Addition of 14 mg of phenyl isocyanate to the mixture (equivalent to a 1% yield) gave a readily detectable third peak in the vpc. A similar reaction with 2a and *m*-chlorophenyl isocyanate at 36° gave similar negative results, with 1,3-bis(*m*-chlorophenyl)urea being obtained in 89% yield and **2a** recovered in 99% yield.

Reaction of 1 with 2b. A. A solution of **1** (1.005 g, 5,20 mmol) in 12 ml of benzene was added to a solution of **2b** (1.06 g, 5.00 mmol) in 25 ml of benzene in a 125-ml erlenmeyer flask having a syringe-stoppered side arm and a reflux condenser with Nujol bubbler gas-exit tube. The system was flushed with nitrogen and then irradiated with a mercury lamp for 5 hr with magnetic stirring. The benzene was stripped off, and the residue was chromatographed on neutral alumina. Pentane eluted 0.14 g (13% recovery) of **2b**. Benzene–pentane (1:1) eluted 0.13 g of material, mp 130–131°, which was found to be 1-(*p*-anisyl)-2,4,4-triphenyl-1,2-diazetidin-3-one (**11b**, 7%: ir (KBr) 5.61 (s, diazetidinone C=O), 6.59 (s), 6.64 (s), 7.34 (s), 8.00 (s), 8.46 (m), 9.61 (m), 11.96 (s), 13.22 (s), 14.16 (m), and 14.27 μ (s); nmr ($CDCl_3$) τ 2.5–2.9 (m, 15 H), 3.13 (d, *J* = 9 Hz, 2 H), 3.35 (d, *J* = 9 Hz, 2 H), 6.39 (s, 3 H).

Anal. Calcd for $C_{27}H_{22}N_2O_2$: C, 79.80; H, 5.42; N, 6.87. Found: C, 79.93; H, 5.54; N, 6.72.

Analysis by vpc (5 ft × 0.125 in. 3% QF-1 column, injector 202°, column 180°) showed only **1**, **2b**, and *N*-benzhydrylidene-*p*-anisidine, from pyrolysis of **11b**; phenyl isocyanate could also be detected using a 130° column temperature. The ratio of Schiff base to azo compound, *J*, was 95.4/4.6 ± 0.6.

Elution of the alumina column with methanol then yielded 1.1 g (63%) of a mixture of **10b** and **11b**, mp 120–156° after rechromatographing and recrystallizing from methanol, ir (KBr) 5.61 μ (diazetidinone C=O, broad, s), nmr ($CDCl_3$) two CH_3 groups at τ 6.33 and 6.45. Vpc under the above conditions gave the same four peaks, plus those due to *N*-benzhydrylideneaniline and *p*-anisyl isocyanate, from **10b**. From data on pure **11b** and this pure binary mixture, the ratio of Schiff base to azo compound from pyrolysis of **10b** was 91.8/8.2, ± 0.6.

B. A solution of 0.500 g (2.36 mmol) of **2b** and 1.105 g (5.7 mmol) of **1** in 10 ml of benzene was irradiated with a mercury lamp for 15 hr, after which tlc showed no unreacted **2b**. Direct vpc analysis of this mixture under the conditions described above, using the data obtained above, indicated the products formed to be 64 ± 2% **11b** and 36 ± 2% **10b**.

The reactions of **2b** in the other solvents and of the remaining azo compounds **2c–f** were performed similarly to the above. Data obtained on the compounds **10** and **11** are given in Table III. These pure compounds were obtained by repeated chromatography and/or recrystallization until vpc indicated only one Schiff base upon pyrolysis in the injector block. The infrared lamp was used in the case of **2e** and **2f** because one or both diazetidinones was decomposed by ultraviolet light under the reaction conditions, as shown by the appearance of isocyanate bands in the infrared at *ca.* 4.4 μ. The infrared lamps used produce light down to *ca.* 400 nm, sufficient to excite the azo compounds with λ_{max} (n → π*) at *ca.* 440 nm, but not to decompose the diazetidinones: **11e**, λ_{max} 342 nm (ε 10,200); mixture of **11e** (22%) and **10e** (78%), λ_{max} 344 nm (ε 9500). The uv-photostable mixture of **10d** and **11d**, in comparison, had λ_{max} 268 nm (ε 13,300).

Preparation of Cis Azo Compounds.[45] The cis azo compounds **2a–d** were prepared by irradiation of solutions of the trans isomers, preferably in 10% pentane–90% benzene, using Rayonet 3500-A lamps. A G. E. UA3 mercury lamp was used in the case of **2f**. It proved impossible to isolate cis-**2e** in sufficient quantity for use, owing to rapid thermal reversion.[45] All operations after the photoisomerization were performed in a darkened room, under a red safe-light, and the materials were kept at about 0° at all times. The isomers were separated by chromatography on neutral alumina in a jacketed (0°) column, the eluents being assayed by tlc on silica gel plates. The trans isomer always eluted first, using pentane or benzene; after its elution was complete the cis isomer was eluted, using methylene chloride or ether. The cis isomers were recrystallized from pentane at −78°. The following data were obtained for the n → π* maxima of the cis isomers in benzene: **2a**, λ_{max} 440 nm (ε 1250); **2b**, 440 (1920); **2c**, 440 (1630); **2d**, 445 (1430); **2f**, 440 (1100).

Kinetic Studies. Solutions of **1** and **2a–f** in benzene, in the concentration range 5–50 × 10^{-5} *M*, were prepared by standard volumetric methods, and the rate of reaction was followed using a Cary 14 spectrophotometer at 440 nm, using the 0–0.1 A slide wire. The mixing time was kept as short as possible, *ca.* 7 sec, and the absorbance was monitored until no further change occurred. The data were plotted on the assumption of a second-order rate law, and gave reasonable straight lines in most cases. The data, given in Table II, are the averages of 4–12 runs each. Values more than three standard deviations from the average, if any, were rejected,[46] and new averages and standard deviations were determined and are reported in Table II. Some curvature was noted in the kinetic plots for **2f**, which reacted at about the limit of our ability to make measurements. The standard deviation is therefore quite high; however, **2f** unequivocally reacts faster than **2a**, **2c**, or **2d**.

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Registry No.—**1**, 525-06-4; **2a**, 108-16-6; **2b**, 15516-72-0; **2c**, 6720-28-1; **2d**, 6530-97-8; **2e**, 15516-73-1; **2f**, 51003-24-8; **3**, 28053-14-7; **4**, 51002-91-6; **5**, 28053-15-8; **6**, 51002-90-5; **7**, 28052-13-6; **9**, 51002-89-2; **10b**, 51002-88-1; **10c**, 51003-22-6; **10d**, 51003-23-7; **10e**, 51002-87-0; **10f**, 51003-94-2; **11b**, 51003-95-3; **11c**, 51003-96-4; **11d**, 51003-97-5; **11e**, 51003-98-6; **11f**, 51003-99-7; **14**, 4083-64-1; *N*-benzhydrylidene-*p*-cyanoaniline, 51004-00-3; *p*-cyanoaniline, 873-74-5; benzophenone, 119-61-9; 2-isopropyl-1,4,4-triphenyl-1,2-diazetidin-3-one, 51004-01-4; acetone phenylhydrazone, 103-02-6; benzophenone dimethylhydrazone, 24398-55-8; *p*-toluenesulfonamide, 70-55-3; chlorosulfonyl isocyanate, 1189-71-5; *p*-nitrophenyl isocyanate, 100-28-7.

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(47) Note Added in Proof. The regioselectivities reported here may alternatively be rationalizable by Houk's frontier orbital method [K. N. Houk, R. W. Strozier, and J. A. Hall, *Tetrahedron Lett.*, 897 (1974), and references therein].

1,3-Dipolar Cycloadditions of Nitrile Oxides with α- and β-Azidovinyl Ketones

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Three types of adducts (**2**, **3**, and **4**) were isolated from the reactions of α-azidovinyl ketones with nitrile oxides. They were characterized by ir, nmr, mass spectra, microanalyses, and chemical transformations. β-Azidovinyl ketones, on the contrary, reacted with benzonitrile oxides to give 4-acylisoxazoles (**14**) as the only products. In all the cases studied, the additions onto the C=C bonds were regiospecific and fully controlled by the azide function. The synthetic value of this observation is further demonstrated in this paper by the additions of benzonitrile oxide to α- and β-azidostyrene.

Several methods have been developed recently for the synthesis of α- and β-azidovinyl ketones in high yields.[1] This led us to explore their reactions with nitrile oxides. These 1,3-dipoles are known to add to C=C and C=O bonds, although the latter reactions are restricted to aldehydes and ketones activated by adjacent electron-withdrawing groups.[2] Cycloadditions of nitrile oxides with nonactivated carbonyl compounds such as acetaldehyde, acetone, etc., however, have been performed in the presence of boron trifluoride etherate as catalyst.[3] Starting with az-

Table I
Products Obtained from the Reaction of 1a–d with 2 Equiv of PhCNO

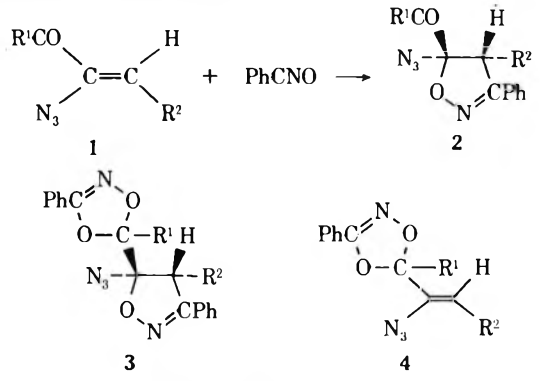
Starting azide (% unreacted)	Monoadduct 2 % by nmr	Monoadduct 2 % isolated	Bisadduct 3 % by nmr	Bisadduct 3 % isolated	Adduct 4 % by nmr	Adduct 4 % isolated
1a (36)	50	49	14	3.5		
1b (26)	14	14	60	(40)[a]		
1c (77)	11	*b*	12	*b*		
1d (61)	12	12	12	9	15	10

[a] Isolated from methanol as the ring-opened hemiketal (see discussion). [b] Not isolated but directly converted to the isoxazole **5c**.

idovinyl ketones we have observed that nitrile oxides can add to both dipolarophilic functions in the molecule. The results are described in this paper.

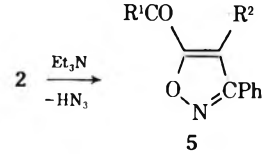
Results and Discussion

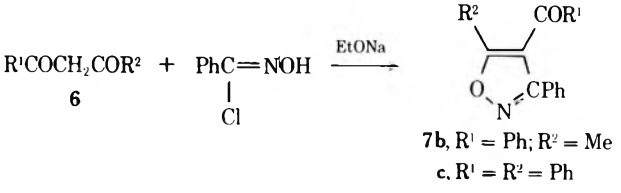
Treatment of α-azidovinyl ketones (**1a–d**) with benzonitrile oxide at room temperature gave both the monoadducts (**2a–d**) and bisadducts (**3a–d**) in addition to unreacted azide and diphenylfuroxan, the latter resulting from dimerization of the nitrile oxide. In one specific case compound **4** was also isolated together with **2** and **3**. The relative amounts of products were estimated from the nmr spectra of the crude mixtures by integration of the vinylic or methyl protons of **1a–d** and **4d**, and the ring protons (or ring methyl protons) of **2a–d** and **3a–d**. The results are summarized in Table I. The three types of adducts will now be discussed separately.



a, $R^1 = Me$; $R^2 = Ph$
b, $R^1 = Ph$; $R^2 = Me$
c, $R^1 = Ph$; $R^2 = Ph$
d, $R^1 = Ph$; $R^2 = m\text{-}NO_2C_6H_4$

The Δ^2-isoxazolines **2a–d** were characterized by spectral analyses (see Experimental Section). Although their stereochemistry is not proven, they are confidently considered to result from a stereospecific syn addition in conformity with the stereochemical course of all 1,3-dipolar cycloaddition reactions.[4] The regiochemistry of **2a–d** is of much more concern since the mode of addition of nitrile oxides



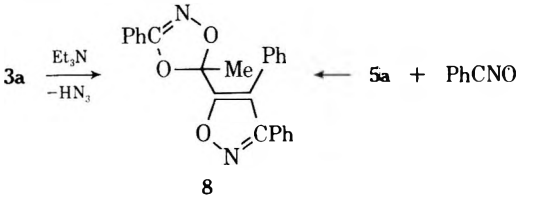


7b, $R^1 = Ph$; $R^2 = Me$
c, $R^1 = R^2 = Ph$

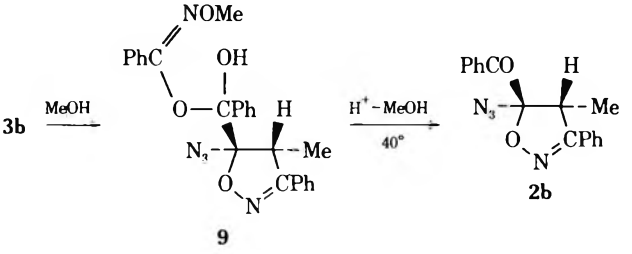
to C=C dipolarophiles could not be predicted with certainty.[2,4] Therefore, the adducts **2a–d** were converted to the isoxazoles **5a–d** upon treatment with triethylamine and then their data were compared with literature data.[5] Furthermore, **5b** and **5c** were compared with their regioisomers **7b** and **7c** and showed different spectral properties and melting points. The compounds **7b** and **7c** were prepared by the reaction of benzoylacetone (**6b**) and benzoylacetophenone (**6c**) with α-chlorobenzaldoxime in the presence of sodium ethoxide.[6]

A few comments on the stereo- and regiochemistry of **2** are in order here. It might be argued that the facile anti elimination of HN_3 from **2** provides evidence for the indicated stereochemistry. This argument, however, should be used with much reservation, since syn elimination of HN_3 is also a possible, although less favorable, pathway.[7] With respect to the regiochemical course of the addition, it is noteworthy to mention the results of Bianchi and coworkers.[5] These authors studied, *inter alia*, the addition of benzonitrile oxide with benzylideneacetone, ethylideneacetophenone, and chalcone, and obtained mixtures of 4- and 5-acylisoxazolines in ratios of respectively 59:41, 32:68, and 29:71. Our results now demonstrate that the introduction of an azide group in the α position of the α,β-unsaturated ketones makes the addition process regiospecific with exclusive formation of the 5-acylisoxazolines. This is not unexpected, since the azide function in vinyl azides has been reported[8] to exhibit a +M effect similar to the amine function in enamines, and should therefore manifest the same directional effect in 1,3-dipolar cycloadditions.[9]

In addition to the monoadducts **2a–d**, bisadducts **3a–d** were also formed in the reactions of benzonitrile oxide with α-azidovinyl ketones. The structures of **3a**, **3c**, and **3d** were established by microanalyses, spectroscopic data, and chemical evidence. They all exhibit typical ir absorptions at 2120–2130 (N_3 group) and 1630 cm^{-1} (C=N of the dioxazole ring).[10] Monoadduct **2a** could be transformed into bisadduct **3a** (40%) when treated with benzonitrile oxide. This indicates that the two adducts have the same regiochemistry about the C–C bond. Furthermore, elimination of HN_3 from **3a** by triethylamine at 55° furnished compound **8**, which was also obtained when **5a** was treated with benzonitrile oxide.



The reaction of **1b** with benzonitrile oxide also furnished the bisadduct **3b** in substantial amounts (see Table I, τ 8.65 for the ring methyl protons). During the isolation procedure, however, **3b** reacted with methanol to give the hemiketal **9**. Its nmr spectrum showed, *inter alia*, two methyl absorptions at τ 6.76 (s) and 9.50 (d, J = 8 Hz). The high chemical shift of the methyl group in the 4 position of the isoxazoline nucleus must be attributed to a shielding effect by the phenyl ring located on the exocy-



clic C=N bond. This has been verified with the aid of molecular models. That **9** had the same ring structure as **2b** was proven by its degradation into the latter under the influence of HCl.[11]

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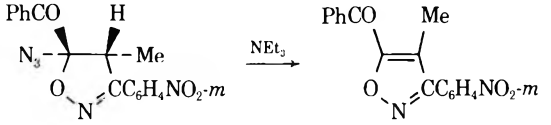
In only one case did benzonitrile oxide add onto the C=O bond of α-azidovinyl ketones to give **4** (see Table I). All attempts to convert this compound into **3** by addition of more benzonitrile oxide failed, an observation already made for other trisubstituted olefins.[2] This clearly demonstrated that the bisadducts **3a–d** are produced from **2a–d**, and not from **4**, in the course of the reactions. Since carbonyl compounds normally do not react with nitrile oxides, unless they are activated by electron-withdrawing substituents,[2] we explain our results by the −I effect of the azide function.[8] We further assume that the electron-withdrawing effect on the carbonyl group is increased in **2** by the presence of an isoxazoline nucleus.

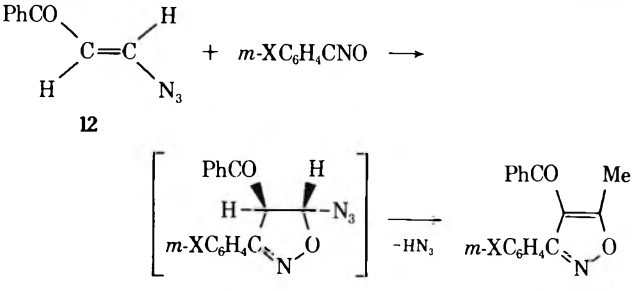
m-Nitrobenzonitrile oxide turned out to be much less reactive than benzonitrile oxide toward the α-azidovinyl ketones. It only reacted with **1b** and furnished the monoadduct **10** (33%) in addition to the corresponding furoxan. Treatment of **10** with triethylamine at 50° gave the isoxazole **11** (90%), which differed in all respects with its regioisomer prepared from benzoylacetone and *m*-nitrobenzonitrile oxide (see structure **7b**, *m*-$NO_2C_6H_4$ instead of Ph).

1b + *m*-$NO_2C_6H_4CNO$ ⟶



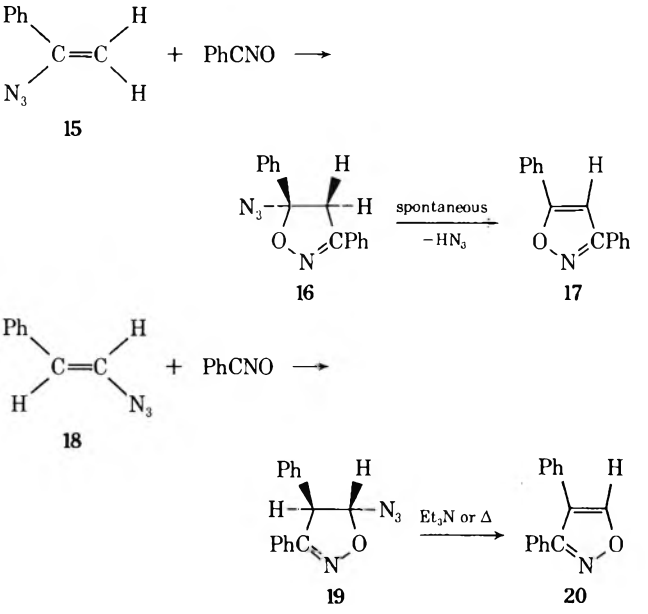
10 **11**

In contrast to the α-azidovinyl ketones **1a–d**, the β-azidovinyl ketone **12** reacted with benzonitrile oxide to give the known isoxazole **14a** directly. *m*-Nitrobenzonitrile oxide reacted similarly with **12** to give the new isoxazole **14b**. Apparently, the corresponding azidiosoxazolines **13** are formed first, but aromatize spontaneously to the isoxazoles **14a,b** by loss of HN_3. This probably occurs by a E1cB mechanism. The regiochemistry of the reaction is fully controlled by electronic factors. In this connection, it is interesting to mention that the regioisomers of **14a,b** can be obtained by an analogous reaction starting from benzonitrile oxides and β-chlorovinyl ketones.[12]



12 **13** **14a**, X = H; **b**, X = NO_2

From the reactions discussed above, it is evident that the azide group, like the amine group in enamines,[9] has a pronounced directional effect on cycloadditions. This property can be utilized for preparative work. For instance, the 5- and 4-phenylisoxazoles **17** and **20** can be readily prepared in separate reactions respectively from α- and β-azidostyrene. Isoxazoline **16** was first formed in reaction **15** ⟶ **17** and characterized by nmr, but it decomposed slowly to **17** at room temperature. Isoxazoline **19**, on the contrary, was stable at room temperature but could be transformed into **20** with triethylamine or upon heating in toluene. This is an example of syn elimination, which occurred much slower than the anti elimination of HN_3 from compounds **2a–d**.



15 **16** **17** **18** **19** **20**

Experimental Section

The vinyl azides **1a–d**, **12**, **15**, and **18** were prepared as reported.[13] In all the experiments described below, benzonitrile oxide was prepared from α-chlorobenzaldoxime and triethylamine in ether at 0°. The cold solution was then filtered into a dichloromethane (or ether) solution of the vinyl azide. *m*-Nitrobenzonitrile oxide was prepared by adding triethylamine (8.3 ml) dropwise to an ethanol solution (20 ml) of α-chloro-*m*-nitrobenzaldoxime (10 g) at −20°. The reaction mixture was then treated with water and the precipitate was collected by filtration and dried over P_2O_5, yield 8 g (97%), mp 81–82° (lit.[14] mp 82–83°).

Reaction of α-Azidobenzylideneacetone (1a) with Benzonitrile Oxide. Benzonitrile oxide (0.04 mol) was added to a solution of **1a** (0.02 mol) in CH_2Cl_2 (10 ml, dried over P_2O_5). The mixture was allowed to react at room temperature for a few hours and was then subjected to nmr analysis in order to determine the distribution of the reaction products (see Table I). Addition of *n*-pentane to the mixture caused the precipitation of unreacted azide and diphenylfuroxan (mp 117°). The solvent was removed and the residue was fractionally crystallized from ether–pentane to give consecutively **2a** and the more soluble **3a**.

3,4-Diphenyl-5-azido-5-acetyl-Δ²-isoxazoline (**2a**) was isolated in 49% yield: mp 89–89.5° ($CHCl_3$–CCl_4); ir (KBr) 2140 (N_3, s), 1730 cm^{-1} (CO, s); nmr ($CDCl_3$) τ 2.35–2.6 (m, 2 H), 2.6–3.0 (m, 8 H), 4.52 (s, 1 H), and 7.56 (s, 3 H); mass spectrum (70 eV) *m/e* (rel intensity) 306 (very small, $M\cdot^+$), 278 (very small, $M\cdot^+ - N_2$), 263 (12.5, $M\cdot^+ - HN_3$), 220 (6, 263 − MeCO·), 193 (9), 178 (5), 165 (5), 132 (100), 116 (6), 103 (31), 77 (21, Ph^+), 43 (34, CH_3CO^+). *Anal.* Calcd for $C_{17}H_{14}N_4O_2$ (306): C, 66.66; H, 4.57; N, 18.30. Found: C, 66.74; H, 4.55; N, 17.65.

3,4-Diphenyl-5-azido-5-(2-methyl-5-phenyl-1,3,4-dioxazolyl)-Δ²-isoxazoline (**3a**) was isolated in 3.5% yield: mp 155–156° (CCl_4–pentane); ir (KBr) 2120 (N_3, s), 1630 (C=N, w); nmr ($CDCl_3$) τ 1.62–1.84 (m, 2 H), 2.16–2.66 (m, 8 H), 5.34 (q, 1 H, *J* 8.1 (s, 3 H); mass spectrum *m/e* (rel intensity) 425 (very small, $M\cdot^+$), 397 (very small, $M\cdot^+ - N_2$), 382 (0.5, $M\cdot^+ - HN_3$), 220 (2), 193 (5), 178 (10), 165 (5), 162 (100), 132 (14), 116 (14), 105 (14), 103 (12), 89 (12), 77 (43), 43 (99.5). *Anal.* Calcd for $C_{24}H_{19}N_5O_3$ (425): C, 67.76; H, 4.47; N, 16.47. Found: C, 67.70; H, 4.30; N, 16.45.

Reaction of α-Azidoethylideneacetophenone (1b) with Benzonitrile Oxide. Azide **1b** (0.02 mol) was allowed to react with benzonitrile oxide (0.04 mol) in dry CH_2Cl_2 (10 ml) at room temperature for a few hours. After the reaction mixture had been analyzed by nmr (see Table I), the solvent was replaced by ether–pentane (40:10 ml) and diphenylfuroxan was isolated in 40% yield (1.87 g). The solvent was removed and the residue was dissolved in ether (10 ml) and then cooled at 5° to give 3-phenyl-4-methyl-5-azido-5-benzoyl-Δ²-isoxazoline (**2b**) in 14% yield: mp 69–69.5° (*n*-pentane); ir (KBr) 2120 (N_3, s), 1690 cm^{-1} (CO, s); nmr

($CDCl_3$) τ 1.62–1.84 (m, 2 H), 2.16–2.66 (m, 8 H), 5.34 (q, 1 H, J = 7 Hz), and 8.60 (d, 3 H, J = 7 Hz); mass spectrum m/e (rel intensity) no molecular ion, 278 (very small, $M^{\cdot+} - N_2$), 263 (2.5, $M^{\cdot+} - HN_3$) 201 (5, $M^{\cdot+}$ – PhCO), 158 (7), 131 (2.5), 130 (5), 115 (7), 105 (100), 103 (17), 89 (5), 77 (83.5). *Anal.* Calcd for $C_{17}H_{14}N_4O_2$ (306): C, 66.66; H, 4.57; N, 18.30. Found: C, 66.45; H, 4.55; H, 18.55.

The mother liquor was evaporated to dryness and the residual yellow oil was treated with MeOH (45 ml) to yield **9** (40%): mp 125–128° dec (MeOH); ir (KBr) 3350 (OH, br), 2140 cm^{-1} (N_3, s); nmr ($CDCl_3$, 100 MHz) 2.28–2.34 (m, 2 H), 2.36–2.68 (m, 13 H), 6.2 (q, 1 H, J = 7 Hz), 6.46 (s, OH exchangeable with D_2O), 6.76 (s, 3 H), and 9.50 (d, 3 H, J = 7 Hz); mass spectrum m/e (rel intensity) 264 (6), 201 (6), 158 (6), 137 (5), 105 (100), 77 (15.5). *Anal.* Calcd for $C_{25}H_{23}N_5O_4$ (457): C, 65.64; H, 5.03; N, 15.31. Found: C, 65.41; H, 5.15; N, 15.45.

When compound **9** was chromatographed over silica gel with chloroform as the eluent, it was quantitatively transformed into the isoxazoline **2b**. Similarly, when **7** (0.5 g) was heated at 40° in a MeOH–2 *N* H_2SO_4 solution (15 ml) for 4 days, decomposition into **2b** was observed by nmr. The mixture was neutralized with NaOH, extracted with $CHCl_3$, and dried over $MgSO_4$. After removal of the solvent, the residue was treated with ether (10 ml) and furnished **2b** in 80% yield.

Reaction of α-Azidochalcone (1c) with Benzonitrile Oxide. A solution of benzonitrile oxide (0.04 mol) and **1c** (0.02 mol) in CH_2Cl_2 or ether (10 ml) was stirred at 0° for 2 hr. The solvent was removed and the residual oil was first treated with ether–pentane (35:10 ml) and MeOH in order to remove most of the unreacted azide and diphenylfuroxan. The residue was then heated with an excess of NEt_3 (4 ml) in $CHCl_3$ (10 ml) at 50° for 24 hr. The solvent was replaced by MeOH and the solution was cooled. 3,4-Diphenyl-5-benzoylisoxazole (**5c**) was obtained in 10% yield: mp 166–167° (MeOH) (lit.[5] mp 167°); ir (KBr) 1665 cm^{-1} (CO, s); nmr ($CDCl_3$) τ 1.85–2.10 (m, 2 H) and 2.34–2.82 (m, 13 H); mass spectrum m/e (rel intensity) 325 (21, $M^{\cdot+}$), 297 (2, $M^{\cdot+}$ – CO), 220 (100), 192 (40), 178 (2), 165 (5), 105 (16), 89 (40), 77 (29). *Anal.* Calcd for $C_{22}H_{15}NO_2$ (325): C, 81.23; H, 4.61; N, 4.31. Found: C, 81.15; H, 4.55; N, 4.55.

Reaction of α-Azido-*m*-nitrobenzylideneacetophenone (1d) with Benzonitrile Oxide. Benzonitrile oxide (0.04 mol) was added to **1d** (0.02 mol) in dry CH_2Cl_2 (10 ml) at room temperature and the mixture was allowed to stand for a few hours. After analysis of the reaction mixture by nmr (see Table I), the solvent was replaced by ether–pentane to eliminate the unreacted azide and diphenylfuroxan. The solvent was partially evaporated (25 ml) to furnish a white precipitate of **4d** in 10% yield: mp 103–104° dec; ir (KBr) 2130 (N_3, s), 1640 (C=C, w), and 1625 cm^{-1} (C=N, w); nmr ($CDCl_3$) τ 1.42 (m, 1 H), 1.76–2.75 (m, 14 H), and 3.75 (s, 1 H); mass spectrum m/e (rel intensity) 413 (small, $M^{\cdot+}$), 224 (16.5), 122 (3.5), 119 (3.5), 115 (6), 105 (100), 103 (9.5), 91 (3.5), 77 (40.5). *Anal.* Calcd for $C_{22}H_{15}N_5O_4$ (413): C, 63.92; H, 3.63; N, 16.94. Found: C, 64.05; H, 3.50; N, 16.90.

The mother liquor was evaporated to dryness and the residue was fractionally crystallized from methanol to give **2d** and **3d**.

3-Phenyl-4-(*m*-nitrophenyl)-5-azido-5-benzoyl-Δ^2-isoxazoline (**2d**) was isolated in 12% yield: mp 100–103° dec ($CHCl_3$–pentane); ir (KBr) 2130 (N_3, s), 1672 cm^{-1} (CO, s); nmr ($CDCl_3$) τ 1.6–2.0 (m, 4 H), 2.2–2.8 (m, 10 H), and 3.93 (s, 1 H); mass spectrum m/e (rel intensity) no $M^{\cdot+}$, 370 (9.5, $M^{\cdot+} - HN_3$), 343 (2), 265 (100), 237 (24), 219 (4), 191 (12), 177 (31), 134 (7), 131 (12), 115 (2), 105 (98), 103 (14), 77 (60). *Anal.* Calcd for $C_{22}H_{15}N_5O_4$ (413): C, 63.92; H, 3.63; N, 16.94. Found: C, 63.75; H, 3.45; N, 17.15.

3-Phenyl-4-(*m*-nitrophenyl)-5-azido-5-(2,5-diphenyl-1,3,4-dioxazolyl)-Δ^2-isoxazoline (**3d**) was obtained in 9% yield: mp 184–186° ($CHCl_3$–MeOH); ir (KBr) 2135 (N_3, s), 1632 cm^{-1} (C=N, w); nmr ($CDCl_3$, 100 MHz) τ 1.80–1.95 (m, 1 H), 2.05–2.25 (m, 5 H), 2.40–2.8 (m, 13 H), and 4.70 (s, 1 H); mass spectrum m/e (rel intensity) no $M^{\cdot+}$, 370 (2.5, $M^{\cdot+}$ – PhCNO – HN_3), 265 (23), 237 (4), 224 (10), 191 (3), 177 (8), 134 (1.5), 131 (5), 119 (15), 115 (3), 105 (100), 103 (18), 77 (15). *Anal.* Calcd for $C_{29}H_{20}N_6O_5$ (532): C, 65.41; H, 3.76; N, 15.79. Found: C, 65.40; H, 3.65; N, 15.80.

3,4-Diphenyl-5-acetylisoxazole (5a). Compound **2a** (1 g) was heated with an excess of NEt_3 (0.7 ml) in dry benzene (15 ml) at 50° for 24 hr (monitored by nmr). The solvent was removed and the residual oil was treated with MeOH (5 ml) to give compound **5a** in quantitative yield: mp 134–134.5° (MeOH) (lit.[5] mp 135–136°); ir (KBr) 1700 cm^{-1} (CO, s); nmr ($CHCl_3$) τ 2.5–2.9 (m, 10 H) and 7.50 (s, 3 H); mass spectrum m/e (rel intensity) 263 (31.5, $M^{\cdot+}$), 220 (100, $M^{\cdot+}$ – MeCO), 193 (45), 131.5 (4.5, M^{2+}). *Anal.* Calcd for $C_{17}H_{13}NO_2$ (263): C, 77.56; H, 4.94; N, 5.32. Found: C, 77.20; H, 4.75; N, 5.25.

3-Phenyl-4-methyl-5-benzoylisoxazole (5b). Compound **2b** (0.5 g) was heated with NEt_3 (0.4 ml) in chloroform (5 ml) at 45°. After complete reaction, the solvent was removed and the residual oil was chromatographed over silica gel with chloroform as the eluent. Compound **5b** was obtained as a colorless oil in 74% yield: ir (neat) 1660 cm^{-1} (CO, s); nmr ($CDCl_3$) τ 1.80–2.0 (m, 2 H), 2.25–2.75 (m, 8 H), and 7.60 (s, 3 H); mass spectrum m/e (rel intensity) 263 (24, $M^{\cdot+}$), 234 (3, $M^{\cdot+}$ – HCO, m* at 208.2), 158 (100, $M^{\cdot+}$ – PhCO).

For comparison, compound **7b** was prepared from benzoylacetone and α-chlorobenzaldoxime in the presence of sodium ethoxide.[6b,c] The ir and nmr spectra of the two compounds showed a different absorption pattern.

3-Phenyl-4-(*m*-nitrophenyl)-5-benzoylisoxazole (5d). This compound was obtained by heating **2d** (0.4 g) with an excess of NEt_3 (0.3 ml) in chloroform (5 ml) at 55° for 5 days. The solvent was removed and the residue was chromatographed over silica gel with chloroform as the eluent to give a pale yellow oil (72%) which solidified on standing: mp 108–111° (MeOH); ir (KBr) 1650 cm^{-1} (CO, s); nmr ($CDCl_3$) τ 1.75–2.10 (m, 2 H) and 2.25–2.80 (m, 12 H); mass spectrum m/e (rel intensity) 370 (14, $M^{\cdot+}$), 265 (78, $M^{\cdot+}$ – PhCO), 238 (27, 265 – HCN), 237 (12, 265 – CO, m* at 211.9), 177 (100). *Anal.* Calcd for $M^{\cdot+}$ (determined by high-resolution exact-mass measurements): 370.09535. Found: 370.09557.

3,4-Diphenyl-5-(2-methyl-5-phenyl-1,3,4-dioxazolyl)isoxazole (8). Compound **3a** (0.06 g) was heated with an excess of NEt_3 (30 mg) in $CHCl_3$ (1 ml) at 55°. After complete reaction (19 days), the solution was saturated by addition of *n*-pentane and then cooled to give **8** in 66% yield: mp 118–119° (MeOH); ir (KBr) 1627 cm^{-1} (C=N); nmr ($CDCl_3$) τ 2.4–2.9 (m, 15 H) and 7.92 (s, 3 H); mass spectrum m/e (rel intensity) 382 (30, $M^{\cdot+}$), 263 (5, $M^{\cdot+}$ – PhCNO), 248 (2), 236 (8), 220 (100), 193 (35), 178 (1), 165 (3), 162 (7), 119 (7), 115 (3), 105 (43). *Anal.* Calcd for $M^{\cdot+}$ (determined by high-resolution exact-mass measurement): 382.131734. Found: 382.133624.

Reaction of α-Azidoethylideneacetophenone (1b) with *m*-Nitrobenzonitrile Oxide. A solution of **1b** (0.02 mol) and *m*-nitrobenzonitrile oxide (0.01 mol) in CH_2Cl_2 (10 ml) was stirred at 5° and then analyzed by nmr (64% unreacted **1b** and 36% **10**). Di(*m*-nitrophenyl)furoxan crystallized out at 5° in 20% yield, mp 188–189°. Addition of *n*-pentane to the mother liquor furnished 3-(*m*-nitrophenyl)-4-methyl-5-azido-5-benzoyl-Δ^2-isoxazoline (**10**) in 34% yield. This compound was purified by column chromatography on silica gel with $CHCl_3$ as the eluent: mp 120–122°; ir (KBr) 2120 (N_3, s), 1690 cm^{-1} (CO, s); nmr ($CDCl_3$, 100 MHz) τ 1.50–2.84 (m, 9 H), 5.35 (q, 1 H, J = 7 Hz), and 8.55 (d, 3 H, J = 7 Hz); mass spectrum m/e (rel intensity) no $M^{\cdot+}$, 308 (3, $M^{\cdot+}$ – HN_3), 246 (6, $M^{\cdot+}$ – PhCO), 203 (3), 176 (3), 175 (3), 115 (3), 105 (100). *Anal.* Calcd for $C_{17}H_{13}N_5O_4$ (351): C, 58.11; H, 3.70; N, 19.94. Found: C, 58.10; H, 3.55; N, 19.95.

3-(*m*-Nitrophenyl)-4-methyl-5-benzoylisoxazole (11). Compound **10** (0.5 g) was heated with an excess of NEt_3 (2.8 ml) in $CHCl_3$ (5 ml) at 50°. After complete reaction (24 hr by nmr), the solvent was removed and the residue was crystallized from $CHCl_3$–*n*-pentane to give **11** in 90% yield: mp 94–95° (MeOH); ir (KBr) 1655 cm^{-1} (CO, s); nmr ($CDCl_3$, 100 MHz) τ 1.4 (m, 1 H), 1.5–1.7 (m, 1 H), 1.75–2.0 (m, 3 H), 2.1–2.5 (m, 4 H), and 7.48 (s, 3 H); mass spectrum m/e (rel intensity) 308 (55, $M^{\cdot+}$), 280 (8, $M^{\cdot+}$ – CO, m* at m/e 254.5), 279 (10.5, $M^{\cdot+}$ – HCO·), 262 (9), 234 (10.5), 233 (18), 203 (8), 175 (5), 157 (18), 129 (16), 105 (100). *Anal.* Calcd for $C_{17}H_{12}N_2O_4$ (308): C, 66.23; H, 3.89; N, 9.09. Found: C, 66.00; H, 3.75; N, 9.15.

For comparison, the regioisomer of **11** (see structure **7b**, *m*-$NO_2C_6H_4$ instead of Ph) was prepared as follows. Sodium (0.03 mol) was dissolved in dry ethanol (15 ml) and the solution was cooled at 0°. After addition of benzoylacetone (0.02 mol), an ethanol solution (10 ml) of α-chloro-*m*-nitrobenzaldoxime (0.03 mol) was added slowly with stirring. The mixture was stirred at room temperature for 5 hr, the precipitated NaCl was filtered, and the solvent was removed under reduced pressure. The yellow residue was washed with water, extracted with chloroform (50 ml), and dried over $MgSO_4$. Crystallization from EtOH–H_2O (60%) furnished 3-(*m*-nitrophenyl)-4-benzoyl-5-methylisoxazole in 45% yield, mp 73–74°. The two regioisomers showed a different pattern in ir, nmr, and mass spectrum. *Anal.* Calcd for $C_{17}H_{12}N_2O_4$ (308): C, 66.23; H, 3.89; N, 9.09. Found: C, 66.25; H, 3.90; N, 9.00.

Reaction of β-Azidovinyl Phenyl Ketone (12) with Benzoni-

trile Oxide. A solution of **12** (0.01 mol) and benzonitrile oxide (0.02 mol) in CH_2Cl_2 (10 ml) was stirred at room temperature in the dark. Then *n*-pentane was added and 3-phenyl-4-benzoylisoxazole (**14a**) was isolated in 60% yield: mp 84–84.5° (MeOH) (lit.[6c] mp 83–84°); ir (KBr) 3125 (=CH, w), 1650 cm^{-1} (CO, s); nmr ($CDCl_3$) τ 1.29 (s, 1 H) and 2.09–2.84 (m, 10 H); mass spectrum *m/e* (rel intensity) 249 (100, $M\cdot^+$), 220 (25, $M\cdot^+ - HCO\cdot$). *Anal.* Calcd for $C_{16}H_{11}NO_2$ (249): C, 77.10; H, 4.41; N, 5.62. Found: C, 77.00; H, 4.25; N, 5.55.

Further addition of *n*-pentane to the mother liquor furnished a mixture of unreacted azide and diphenylfuroxan.

Reaction of β-Azidovinyl Phenyl Ketone (12) with *m*-Nitrobenzonitrile Oxide. A solution of **12** (0.01 mol) and *m*-nitrobenzonitrile oxide (0.02 mol) in dry CH_2Cl_2 (10 ml) was stirred at room temperature in the dark for 18 hr. Then *n*-pentane was added dropwise to the reaction mixture in order to precipitate di(*m*-nitrophenyl)furoxan (37%). The mother liquor was evaporated to dryness and the residue was extracted with *n*-pentane to remove the unreacted azide. The residue from this manipulation was crystallized from MeOH (25 ml) to give 3-(*m*-nitrophenyl)-4-benzoylisoxazole (**14b**) in 23% yield: mp 80–82° (CCl_4); ir (KBr) 3150 (=CH, w), 1655 cm^{-1} (CO, s); nmr ($CDCl_3$, 100 MHz) τ 1.10 (s, 1 H), 1.35 (m, 1 H), 1.6–1.75 (m, 2 H), 1.8–2.0 (m, 2 H), and 2.05–2.60 (m, 4 H); mass spectrum *m/e* (rel intensity) 294 (39, $M\cdot^+$), 277 (22.5, $M\cdot^+ - HO\cdot$, m* at 260.9), 265 (2, $M\cdot^+ - HCO$), 247 (8), 220 (4), 219 (5.5), 217 (1), 189 (7), 143 (6.5), 115 (3), 105 (100). *Anal.* Calcd for $C_{16}H_{10}N_2O_4$ (294): C, 65.30; H, 3.40. Found: C, 65.05; H, 3.20. *Anal.* Calcd for $M\cdot^+$ (determined by high-resolution exact-mass measurement): 294.064051. Found: 294.064206.

Reaction of α-Azidostyrene (15) with Benzonitrile Oxide. Benzonitrile oxide (0.02 mol) was added to a solution of **15** (0.01 mol) in dry ether (5 ml) at room temperature. After a reaction period of 3 hr, the mixture was analyzed by nmr and showed a complete conversion of **15** into a mixture of **16** [88%, ring protons at τ 6.46 (d, $J \cong 2.5$ Hz)] and **17** [12%, ring proton at τ 3.20 (s)]. When this mixture was allowed to stand at room temperature for an additional 1 hr, the reaction **16** → **17** was finished. The yellow residue was dissolved in ether (10 ml) to remove most of the diphenylfuroxan and the solvent was then replaced by methanol (10 ml) in order to crystallize 3,5-diphenylisoxazole (**17**), yield 64%, mp 136–137° (MeOH) (lit.[6b,15] mp 141°).

Reaction of β-Azidostyrene (18) with Benzonitrile Oxide. An ether solution (5 ml) of **18** (0.01 mol) and benzonitrile oxide (0.02 mol) was stirred at room temperature for a few hours and then analyzed by nmr (30% **18** and 70% **19**). The yellow oil was treated with ether (15 ml) to remove diphenylfuroxan (1.2 g). After removal of the solvent, the oil was chromatographed over basic Al_2O_3 (activity I) with *n*-pentane (30 ml) and chloroform (30 ml) as eluents to give respectively unreacted **18** and **19** as a pale yellow liquid: yield 66%; ir (neat) 2120 cm^{-1} (N_3, s); nmr ($CDCl_3$) τ 2.10–2.80 (m, 10 H), 4.29 (d, 1 H, J = 1.5 Hz), and 5.50 (d, 1 H, J = 1.5 Hz); mass spectrum *m/e* (rel intensity) 264 (very small, $M\cdot^+$), 221 (100, $M\cdot^+ - HN_3$). Compound **19** (0.77 g) in $CHCl_3$ (6 ml) was heated with an excess of NEt_3 (0.84 ml) for 25 days at 45° (monitored by nmr). The solvent was then removed and the dark brown oil was chromatographed over silica gel with $CHCl_3$ as the eluent to give 3,4-diphenylisoxazole (**20**) as a colorless oil (82%) which solidified on standing: mp 88.5–89.5° (ether) (lit.[16] mp 91°); ir (KBr) 3115 cm^{-1} (=CH, w); nmr ($CDCl_3$) τ 0.92 (s, 1 H) and 2.4–2.8 (m, 10 H); mass spectrum *m/e* (rel intensity) 221 (100, $M\cdot^+$). Similarly, when **19** (0.83 g) was heated in dry toluene (5 ml) at 100° for 1 month (monitored by nmr) and then worked up in the same manner as above, isoxazole **20** was obtained in 92% yield.

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Registry No.—**1a**, 26309-09-1; **1b**, 26309-10-4; **1c**, 26309-08-0; **1d**, 51002-98-3; **2a**, 51002-99-4; **2b**, 51003-00-0; **2d**, 51003-01-1; **3a**, 51003-54-1; **3d**, 51003-55-5; **4d**, 51002-97-2; **5a**, 1631-96-5; **5b**, 51003-56-6; **5c**, 1167-72-2; **5d**, 51003-57-7; **7b**, 14677-93-1; **8**, 51003-58-8; **9**, 51003-59-9; **10**, 51002-96-1; **11**, 51003-60-2; **12**, 13850-37-8; **14a**, 19688-06-3; **14b**, 51003-61-3; **15**, 16717-64-9; **16**, 51003-62-4; **17**, 2039-49-8; **18**, 18756-03-1; **19**, 51002-95-0; **20**, 7467-78-9; benzonitrile oxide, 873-67-6; α-chlorobenzaldoxime, 698-16-8; triethylamine, 121-44-8; *m*-nitrobenzonitrile oxide, 7007-35-4; α-chloro-*m*-nitrobenzaldoxime, 33512-94-6; di(*m*-nitrophenyl)furoxan, 51003-63-5; benzoylacetone, 93-91-4; 3-(*m*-nitrophenyl)-4-benzoyl-5-methylisoxazole, 51003-64-6.

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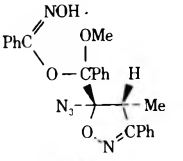
(11) A referee suggested that structure i instead of **9** would better account for the cleavage of **3b** in MeOH. We have considered this alternate structure in detail, but are excluding it on the basis of the high nmr singlet absorption for OH (τ 6.46, exchangeable with D_2O). Indeed, tertiary alcohols are known to absorb in this region, whereas oximes give rise to absorptions (usually broad) at much lower field ($0 < \tau < 3$ ppm); see, for instance, "Varian NMR Catalog," Vol. 2, 1963, Spectrum 397 *vs.* 585. In addition, our compound does not show the color test with $FeCl_3$ or $Cu(OAc)_2$ characteristic for hydroxamic acids; see, for instance, H. Henecka and P. Kurtz in "Houben-Weyl VIII: Methoden der Organische Chemie," Georg Thieme Verlag, Stuttgart, 1952, p 685.



i

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Studies of *N*-(α-Chlorobenzylidene)carbamoyl Chloride. I. Preparation of *N*-(α-Chlorobenzylidene)carbamoyl Chloride and Its Reaction with Sodium Azide

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N-(α-Chlorobenzylidene)carbamoyl chloride, $C_6H_5C(Cl)=NCOCl$ (1), is obtained in good yield by chlorination of C_6H_5CSNCO. The reaction of 1 with NaN_3 in anhydrous glyme gave 5-phenyltetrazole, benzonitrile, 2,5-diphenyl-*s*-triazolo[3,4-*b*]-1,3,4-oxadiazole (**5a**) and a product tentatively considered to be 2,5-diphenyl-1,3,4-oxadiazolo[2,3-*e*]-1,2,3,4,6-pentazepine.

Two methods have been available for the preparation of *N*-(α-chlorobenzylidene)carbamoyl chloride (1) having two reactive chlorine atoms in the molecule: one is based on the reaction of benzoyl isocyanate with phosphorus(V) chloride[2] and the other, the reaction of benzonitrile with phosgene in the presence of hydrogen chloride.[3] However, the former must be carried out under drastic conditions (in refluxing chlorobenzene for 48 hr), and the latter gives a low yield of 1 because of a side reaction yielding a *s*-triazine derivative.

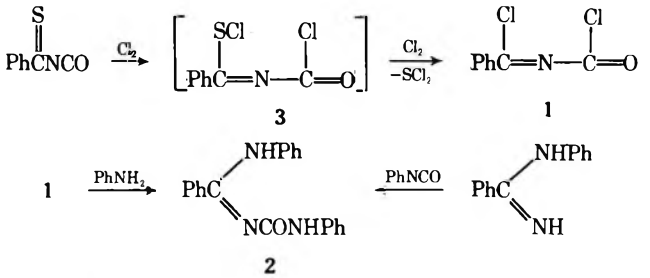
Carbamoyl chloride 1 can be expected to be useful as a precursor for the synthesis of heterocyclic compounds.[4] Recently, Yanagida, *et al.*,[5] have reported some cyclization reactions of 1 with nucleophiles, including sodium azide. These reports prompted us to describe our findings of a new, convenient preparative method for the preparation of 1 and of its reaction with sodium azide.

From our previous work on the cycloaddition reactions of benzoyl and thiobenzoyl isocyanates with a variety of compounds having a C=N bond,[6-9] the reactivity of thiobenzoyl isocyanate in 1,4 additions was found to be somewhat higher than that of benzoyl isocyanate. Thus, it might be expected that thiobenzoyl isocyanate could easily react with chlorine to form 1.

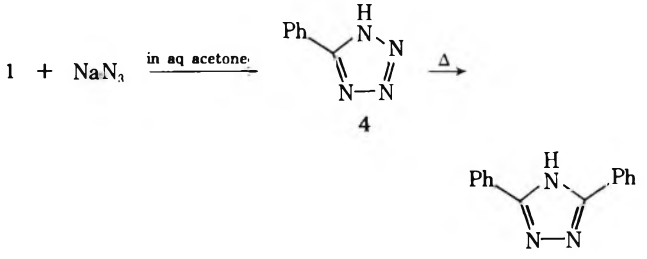
The chlorination of thiobenzoyl isocyanate with chlorine gas at room temperature afforded the expected carbamoyl chloride 1 in a good yield. The structure of 1 was confirmed by the spectral data, microanalysis, and chemical conversion. The reaction of 1 with aniline gave *N*-phenyl-*N'*-anilinoformylbenzamidine (2), which was identical with an authentic sample prepared from *N*-phenylbenzamidine and phenyl isocyanate.

Although the exact pathway for the formation of 1 is not clear, it might be viewed as proceeding *via* an initial formation of *N*-(α-chlorosulfinylbenzylidene)carbamoyl chloride (3), followed by further chlorination with the concurrent elimination of sulfinyl chloride as shown in Scheme I.

Scheme I



As reported by Yanagida, *et al.*,[5] the reaction of 1 with sodium azide in aqueous acetone gave 5-phenyltetrazole (4), which was thermally converted to 3,5-diphenyl-1,2,4-triazole.[10] It is evident that water is involved in the formation of 4, because the evolution of carbon dioxide was observed during the reaction. Yanagida, *et al.*,[5] described that this reaction did not occur under anhydrous conditions. However, we found that in *anhydrous* 1,2-dimethoxyethane (glyme) 1 reacted with sodium azide to give different products from 4.



The reaction of 1 with 2 mol of sodium azide in glyme at room temperature afforded novel products 5 and 6 in 52 and 13% yields, accompanied by small amounts of 4 and benzonitrile.

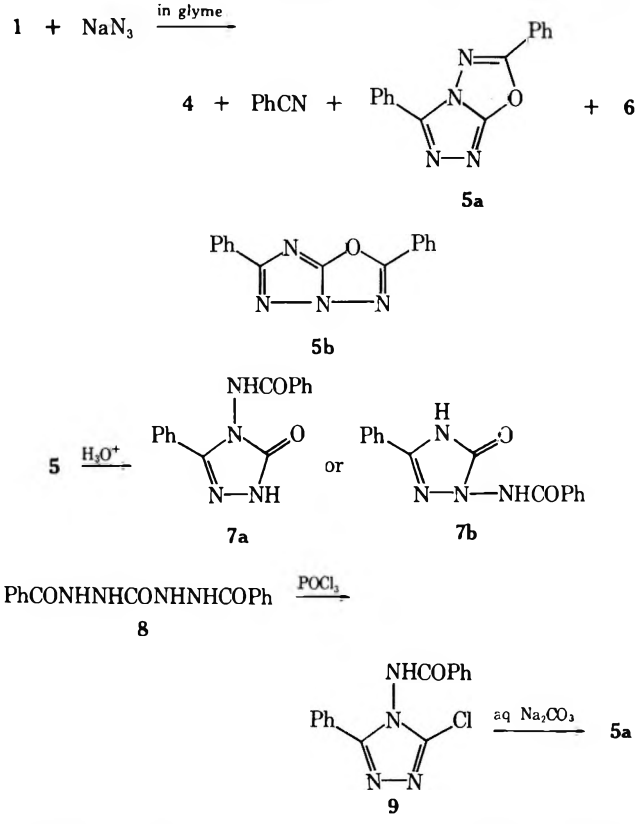
The molecular formula of 5 agreed with that of a compound arising from the diazide by the elimination of 2 mol of nitrogen, followed by the addition of benzonitrile. The ir spectrum of 5 did not show any bands ascribable to NH and C=O absorptions. Hydrolysis of 5 with dilute hydrochloric acid afforded a product 7, whose structure was assumed to be either 4-benzoylamino-3-phenyl-Δ^2-1,2,4-triazolin-5-one (7a) or the 1-benzoylamino isomer (7b) from the spectral data. On the basis of these observations and the mode of formation of 5, either of two isomers, 2,5-diphenyl-*s*-triazolo[3,4-*b*]-1,3,4-oxadiazole (**5a**) or 2,6-diphenyl-*s*-triazolo[3,2-*b*]-1,3,4-oxadiazole (**5b**), is thought possible for the structure of 5 (Scheme II).

Kanaoka[11] reported the preparation of the sulfur analog of **5a**, 2-alkyl- (or aryl-) 5-phenyl-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazole, from methyl benzoyldithiocarbazinate. It was found by Yoshida and Asai[12] that the reaction of isonicotinylhydrazine with carbon disulfide gave small quantities of 4-isonicotinylamino-3-pyridyl-Δ^2-1,2,4-triazoline-5-thione *via* 1,5-diisonicotinylthiocarbazide. The 1,2,4-triazoline-5-thione corresponds to a sulfur analog of 7a.

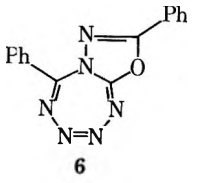
In order to elucidate the structure of 5, 5a was prepared by modification of the above methods. Treatment of 1,5-dibenzoylcarbohydrazide (8) with phosphorus oxychloride afforded 4-benzoylamino-5-chloro-3-phenyl-1,2,4-triazole (9), whose structure was confirmed by the result of microanalysis and spectral data. Cyclization of 9 with aqueous sodium carbonate gave 5a, which was identical with 5.

On the other hand, the molecular formula of a minor product 6 agreed with that of an adduct of the diazide and benzonitrile with the elimination of 1 mol of nitrogen. On the basis of its spectral data and mode of formation, 6 is

Scheme II



tentatively assigned as 2,5-diphenyl-1,3,4-oxadiazolo[2,3-*e*]-1,2,3,4,6-pentazepine. Although **6** was quite stable under the reaction conditions, thermal decomposition of **6** did not give **5a**, but afforded resinous materials.

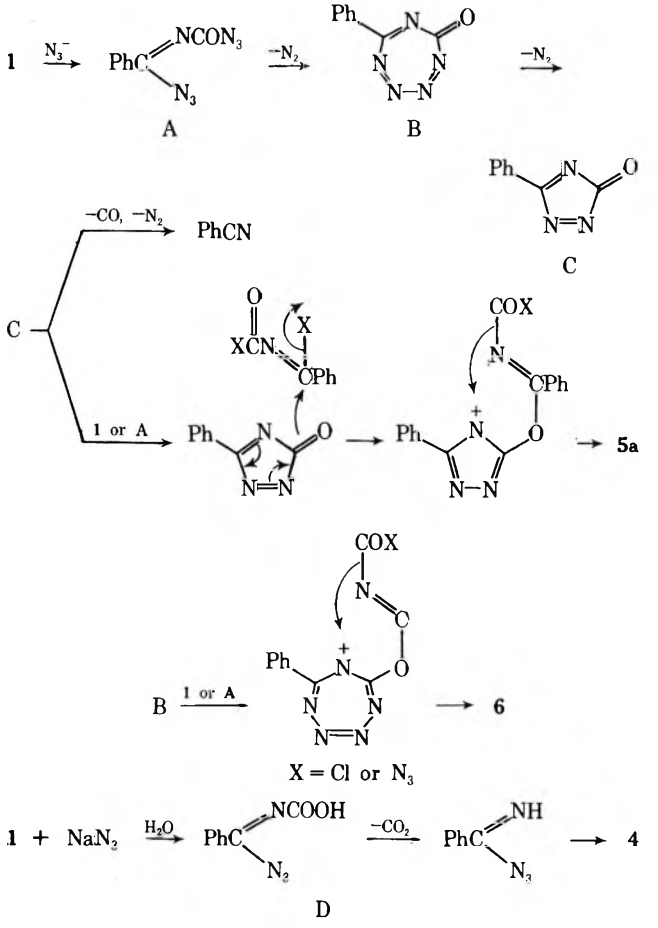


Although the exact pathway of the reaction of **1** with sodium azide under anhydrous conditions is not clear, it might be viewed as proceeding *via* initial formation of diazide A. This is followed by cyclization with the concurrent elimination of nitrogen to form 1,2,3,4,6-pentazepin-7-one B, because no insertion products derived from potential nitrene intermediates from A were formed. Then, B is converted to *s*-triazolone C with the elimination of nitrogen.[13] Recently, it has been reported that the oxidation of 5-substituted *s*-triazolin-3-ones with lead tetraacetate led to the formation of the intermediate *s*-triazolones which in the absence of 1,3-dienes decomposed to nitriles, carbon monoxide, and nitrogen.[14] The formation of benzonitrile in the reaction can be viewed as arising from *s*-triazolone C.

No crossover products were formed in the reaction in the presence of *p*-methoxybenzonitrile. Therefore, the pathways for the formation of **5** and **6** *via* the reactions of C and B with benzonitrile can be excluded. Thus, the reactions of C and B with **1** or diazide A give the novel products **5** and **6** as shown in Scheme III.

On the other hand, under the influence of water **1** reacts competitively with sodium azide and water. In general, the carbamoyl chlorine atom is more reactive than the imidoyl chlorine atom in **1**.[15] Thus, water would attack the former and sodium azide would react with the latter to form intermediate D, followed by cyclization with the

Scheme III



elimination of carbon dioxide to lead to the formation of **4**.

Experimental Section[16]

***N*-(α-Chlorobenzylidene)carbamoyl Chloride (1).** Into a reddish-violet solution of thiobenzoyl isocyanate[17] generated *in situ* from 10 g of 2-phenylthiazoline-4,5-dione[18] in 40 ml of dry chlorobenzene was introduced dry chlorine gas at room temperature for about 5.5 hr, during which time the solution turned to pale yellow. After removal of the solvent, the residue was distilled *in vacuo* to give 7.5 g (71% based on 2-phenylthiazoline-4,5-dione used) of carbamoyl chloride **1**: bp 99–100° (1 mm) [lit. bp 75–80° (0.02 mm),[2] 85–90° (1 mm)[3]]; ir (neat) 1770, 1750 (sh), 1640, 1045, 920, 780, 750, 690 cm^{-1}; mass spectrum *m/e* 205, 203, 201 (M^+), 168, 166 ($M^+ - Cl$), 140, 138 ($M^+ - Cl - CO$), 103 ($PhCN^+$).

Anal. Calcd for $C_8H_5NOCl_2$: C, 47.56; H, 2.50; N, 6.93. Found: C, 47.81; H, 2.46; N, 6.95.

The reaction of **1** with 2 equiv of aniline in diethyl ether at room temperature afforded a 72% yield of *N*-phenyl-*N'*-anilinoformylbenzamidine (**2**) as colorless needles (from MeOH), mp 175–175.5° (lit. mp 179–180°,[19] 159–172°[5]). This compound was identical with an authentic sample[19] prepared from *N*-phenylbenzamidine and phenyl isocyanate.

Reaction of 1 with Sodium Azide. A. In Aqueous Acetone. To a solution of 0.65 g (0.01 mol) of sodium azide in 10 ml of aqueous acetone (containing 2 ml of water) was added 1.0 g (4.95 mmol) of **1** under water cooling. The reaction mixture was stirred at room temperature for 1 hr and then concentrated *in vacuo* to leave a residue. The residue was washed with hot acetone and the washings were again concentrated *in vacuo* to leave crystals. Recrystallization from dioxane afforded 0.53 g (73%) of 5-phenyltetrazole (**4**) as colorless plates: mp 212.5–213° dec (lit.[20] mp 212° dec); ir (KBr) 3020–2800 (NH), 1610 cm^{-1} (C=N).

Heating of 0.1 g of **4** at 230–240° for 15 min afforded 35 mg (47%) of 3,5-diphenyl-1,2,4-triazole as colorless needles, mp 185–186° (lit.[10] mp 187–189°).

B. In Glyme. To a suspension of 0.65 g (0.01 mol) of sodium azide in 25 ml of dry glyme was added 1.0 g (4.95 mmol) of **1** under water cooling at 10°. The reaction mixture was stirred at room temperature for 9 hr. The precipitate was filtered and ex-

tracted with hot benzene. The benzene extract was evaporated *in vacuo* to leave crystals. Recrystallization from petroleum ether (bp 60–75°) gave 0.34 g (52%) of 2,5-diphenyl-s-triazolo[3,4-*b*]-1,3,4-oxadiazole (**5a**) as colorless prisms: mp 179–180° dec; ir (KBr) 1600, 1550, 1460, 1380, 1150, 1050, 960, 768, 730, 700, 680, cm^{-1}; mass spectrum *m/e* 262 (M^+), 245, 234 ($M^+ - N_2$), 206 ($234^+ - N_2$ or CO), 192 ($234^+ - NCO$), 145 ($234^+ - PhC$), 117 ($PhCN_2^+$), 105 ($PhCO^+$), 103 ($PhCN^+$), 77 (Ph^+).

Anal. Calcd for $C_{15}H_{10}N_4O$: C, 68.69; H, 3.84; N, 21.37. Found: C, 68.84; H, 3.56; N, 21.59.

The glyme filtrate was concentrated *in vacuo* below 50° to leave resinous materials, which were chromatographed on silica gel to give trace amounts of 4 and 95 mg (13%) of 2,5-diphenyl-1,3,4-oxadiazolo[2,3-e]-1,2,4,6-pentazepine (**6**). The formation of benzonitrile was confirmed by gas chromatography of the glyme filtrate.

6 had mp 124–125° dec [from petroleum ether (bp 60–70°)] and was obtained as colorless plates: ir (KBr) 1600, 1550, 1500, 1460, 1350, 1300, 1170, 1080, 980, 790, 755, 730, 700 cm^{-1}; mass spectrum *m/e* 262 ($M^+ - N_2$ or CO), 145, 117, 105, 103, 77.

Anal. Calcd for $C_{15}H_{10}N_6O$: C, 62.06; H, 3.47; N, 28.95. Found: C, 62.18; H, 3.26; N, 28.71.

Hydrolysis of 5a. A solution of 0.5 g of **5a** in 30 ml of ethanol was refluxed with 20 ml of 1 *N* hydrochloric acid for 9 hr, and then the mixture was neutralized with aqueous sodium carbonate. The precipitate was filtered and recrystallized from acetone to give 0.35 g (66%) of 4-benzoylamino-3-phenyl-Δ^2-1,2,4-triazolin-5-one (**7a**) as colorless prisms: mp 259.5–260° dec; ir (KBr) 3300–3000 (NH), 1745, 1670 cm^{-1} (C=O); nmr (DMSO-d_6) δ 7.4–8.05 (m, 10, aromatic protons), 11.64, 12.22 (each s, 1, NH); mass spectrum *m/e* 280 (M^+), 161 ($M^+ - PhNCO$), 119, 118 ($161^+ - HNCO$), 105 ($PhCO^+$, base peak); uv max (EtOH) 267 nm (log ϵ 4.0).[21]

Anal. Calcd for $C_{15}H_{12}N_4O_2$: C, 64.27; H, 4.32; N, 19.99. Found: C, 64.02; H, 4.14; N, 19.79.

Preparation of 5a. After a solution of 1.0 g of 1,5-dibenzoylcarbohydrazide (**8**)[22] in 10 ml of phosphorus oxychloride was heated at 80–90° for 2 hr, the reaction mixture was poured into ice–water. The precipitate was filtered and recrystallized from benzene to afford 0.29 g (29%) of 4-benzoylamino-5-chloro-3-phenyl-1,2,4-triazole (**9**) as colorless needles: mp 152.5–153° dec; ir (KBr) 3400 (broad, NH), 1640 cm^{-1} (C=O); mass spectrum *m/e* 300, 298 (M^+).

Anal. Calcd for $C_{15}H_{11}N_4OCl$: C, 60.31; H, 3.71; N, 18.75. Found: C, 60.54; H, 3.64; N, 18.63.

A solution of 0.17 g of **9** in 20 ml of acetone–water mixture (10:1 v/v) was stirred with 1.0 g of sodium carbonate at room temperature for 4 hr. The reaction mixture was neutralized with dilute hydrochloric acid to precipitate a solid, which on recrystallization from petroleum ether (bp 60–75°) gave 0.11 g (74%) of colorless prisms, mp 179–180° dec. This compound was identical with the product **5**.

Registry No.—**1**, 4547-71-1; **2**, 33655-23-1; **4**, 18039-42-4; **5a**, 32550-72-4; **6a**, 51003-52-2; **7**, 3658-32-0; **8**, 51003-53-3; thiobenzoyl isocyanate, 3553-61-5.

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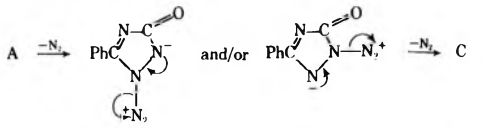

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Studies on *N*-(α-Chlorobenzylidene)carbamoyl Chloride. II.[1] Reaction of *N*-(α-Chlorobenzylidene)carbamoyl Chloride with Active Methylene Compounds

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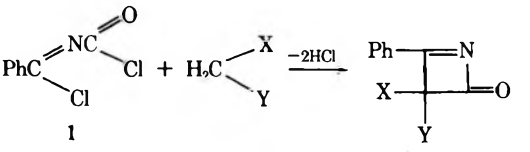
The reaction of *N*-(α-chlorobenzylidene)carbamoyl chloride (**1**) with active methylene compounds has been investigated. In general, the imidoyl chlorine atom in **1** reacts faster with active methylene compounds in the presence of NEt_3. An azetinone intermediate (**7**) is proposed as an initial product in the reaction with ethyl cyanoacetate (**2**) in the presence of 2 equiv of NEt_3. The reactions of **1** with acenaphthenone (**13**) and dimedone (**18**) give oxazin-2-one (**14a**) and oxazin-4-one derivatives (**19**), respectively. On the other hand, **1** reacts with **13** in the presence of metallic sodium to yield a pyridine derivative (**17**).

In the preceding paper,[1] we have reported a convenient synthesis of *N*-(α-chlorobenzylidene)carbamoyl chloride (**1**), which is useful as a precursor for the synthesis of heterocycles.[1-3] It could be expected that **1** might react with active methylene compounds to form azetinones, and fur-



1

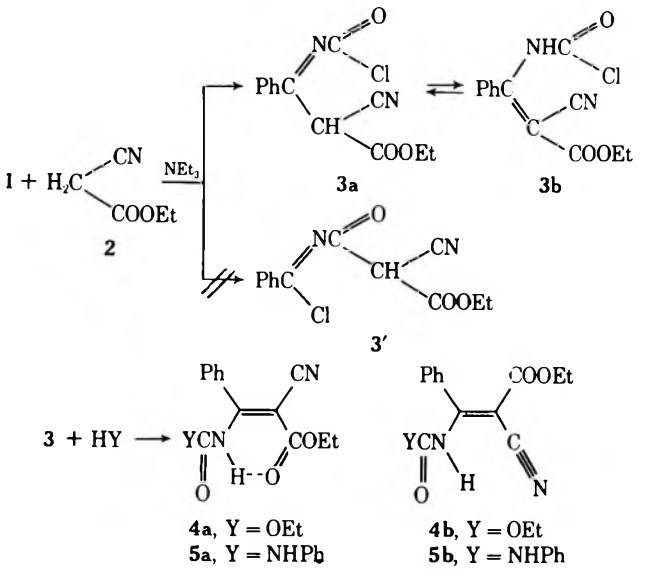
thermore, we were interested in studying which chlorine in 1 is more reactive. These considerations prompted us to investigate the reaction of 1 with active methylene compounds.

Results and Discussion

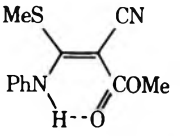
Reaction with Ethyl Cyanoacetate (2). In order to determine which chlorine in 1 reacts faster with 2, the reaction of 1 with 1 equiv of 2 in the presence of equimolar triethylamine (NEt_3) was carried out in ether at room temperature; an unstable, oily product 3 whose ir spectrum showed bands at 3280 (NH), 2200 (C≡N), 1745, and 1710 cm^{-1} (C=O) was obtained and it could not be purified. Treatment of 3 with ethanol or aniline afforded ethyl α-cyano-β-(*N*-ethoxycarbonylamino)acrylate (4) or -β-phenyl-β-(3-phenylureido)acrylate (5).

In view of the formation of 4 and 5 from 3, it is evident that the imidoyl chlorine is more reactive than the carbamoyl chlorine under the conditions, and the initial oily product is 3, which would predominantly exist in the form 3b on the basis of its ir spectrum, but not 3′ (Scheme I).

Scheme I

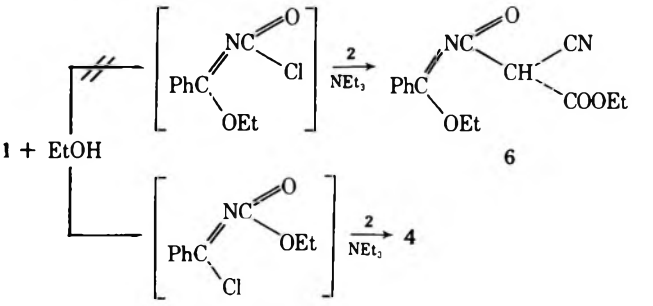


Shvo and Belsky[4] have investigated the thermal isomerization of conjugated ketene mercaptoaminals involving rotation about a C=C double bond. They clarified that methyl β-anilino-β-methylmercapto-α-cyanoacrylate exists in the following configuration on the basis of its nmr



and ir spectroscopic studies. The ir spectrum (CCl_4) of 4 exhibited the hydrogen-bonded NH and C=O absorption bands at 3240 and 1690 cm^{-1}, besides the nonbonded C=O absorption band at 1775 cm^{-1} (these absorption bands were independent of concentration). Furthermore, the nmr spectrum of 4 showed one signal ascribable to NH even at −60°.[5] These results can be reconciled only with the configuration 4a depicted in Scheme I, since the linear nitrile group in 4b is not in the appropriate geometrical disposition for internal hydrogen bonding. Similarly, it was deduced that 5 exists in the same configuration 5a as 4 does.

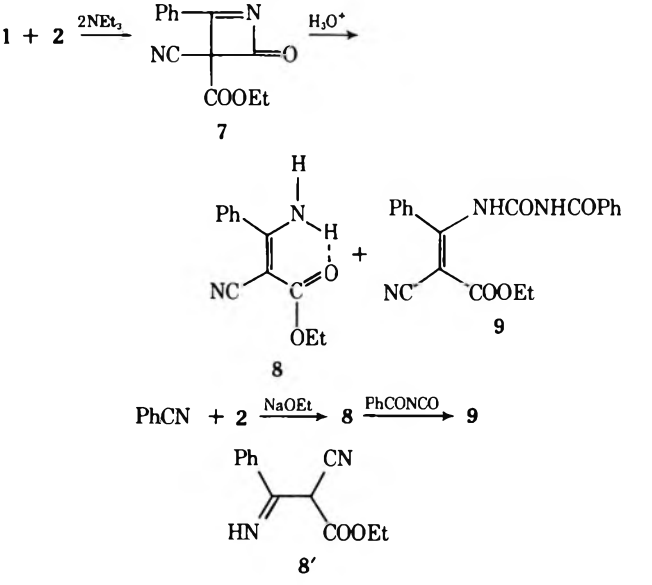
It was thus reasoned that, if the imidoyl chlorine in 1 is more reactive, the reaction of 1 with ethanol would yield the imidate, which should condense with 2 to give the isomeric compound 6. Thus, 1 was initially treated with 1 equiv of ethanol, followed by a mixture of 2 and NEt_3. However, contrary to expectation, it was found that 4 was isolated rather than 6. This suggests that the carbamoyl



chlorine in 1 reacts faster with ethanol in the absence of NEt_3. On the basis of these observations, the NEt_3 might initially react with the carbamoyl chlorine to form a kind of salt which would be less reactive than the imidoyl chlorine, if the NEt_3 is present from the start in the reaction system.

If 2 equiv of NEt_3 is used as a dehydrochlorinating agent, it would be expected that azetinone 7 would be formed from the reaction of 1 with 2. When 2 equiv of NEt_3 was added to a mixture of equimolar amounts of 1 and 2, an unstable, oily product was obtained, together with triethylammonium chloride in an almost quantitative yield.

Scheme II

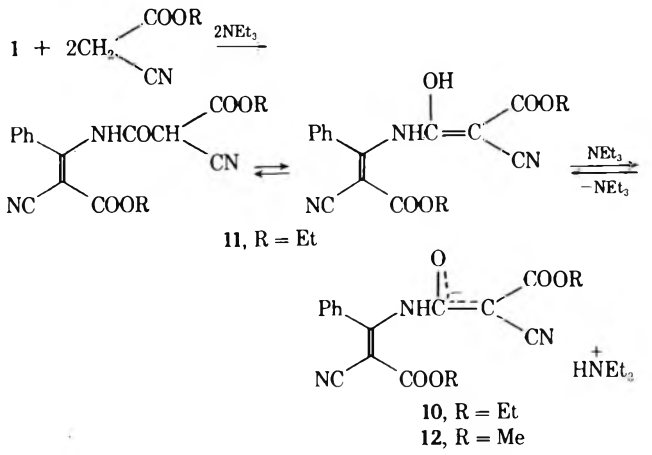


The oily product was deduced as the expected azetinone 7 on the basis of the following evidence. Its ir spectrum showed C=O absorption bands at 1800 and 1745 cm^{-1}. Chromatography of the oily product on alumina afforded ethyl α-cyano-β-amino-β-phenylacrylate (8) and α-cyano-β-phenyl-β-(3-benzoylureido)acrylate (9). The compounds 8 and 9 were also formed by hydrolysis of the oily product with hydrochloric acid in ethanol.[6] The formation of 8 from 7 can be easily understood in terms of the hydrolytic cleavage of the azetinone ring with the subsequent decarboxylation, but the pathway for the formation of 9 is not clear, since 1 did not react with 8 even in the presence of NEt_3.

The structures of 8 and 9 were confirmed on the basis of their spectral data and of comparison with authentic samples prepared from the reaction of benzonitrile with 2[7] and of the reaction of 8 with benzoyl isocyanate, respectively. Although Atkinson, *et al.*,[7] reported that the product from the reaction of benzonitrile with 2 was ethyl α-cyano-β-imino-β-phenylpropionate (8′), its. ir and nmr spectra supported strongly that the product is the enamine as depicted in Scheme II. The ir spectrum in CCl_4 showed absorption bands ascribable to nonbonded NH (3520), bonded NH (3260), and C=O (1680 cm^{-1}) (These bands were independent of concentration), and the nmr spectrum exhibited signals due to single ethyl and two NH groups even at −60°.

On the other hand, when a mixture of equimolar amounts of 1 and 2 was added to a solution of 2 equiv of NEt_3 in ether, a product 10 was obtained as yellow needles. The molecular formula of 10 agreed with that of the compound derived from NEt_3 and 1:2 condensation product of 1 and 2. In fact, the reaction of 1 with 2 equiv of 2 in the presence of 3 equiv of NEt_3 afforded 10 in a good yield. Treatment of 10 with hydrochloric acid gave 1:2 condensation product 11 as colorless needles, which was converted into 10 on treatment with NEt_3. Structures of 10 and 11 as shown in Scheme III were confirmed on the basis of their spectral data. The absence of methine proton and the appearance of NH and OH in the nmr spectrum of 11 in deuteriochloroform ($CDCl_3$) suggests that 11 exists exclusively in the enol form in the solvent.

Scheme III

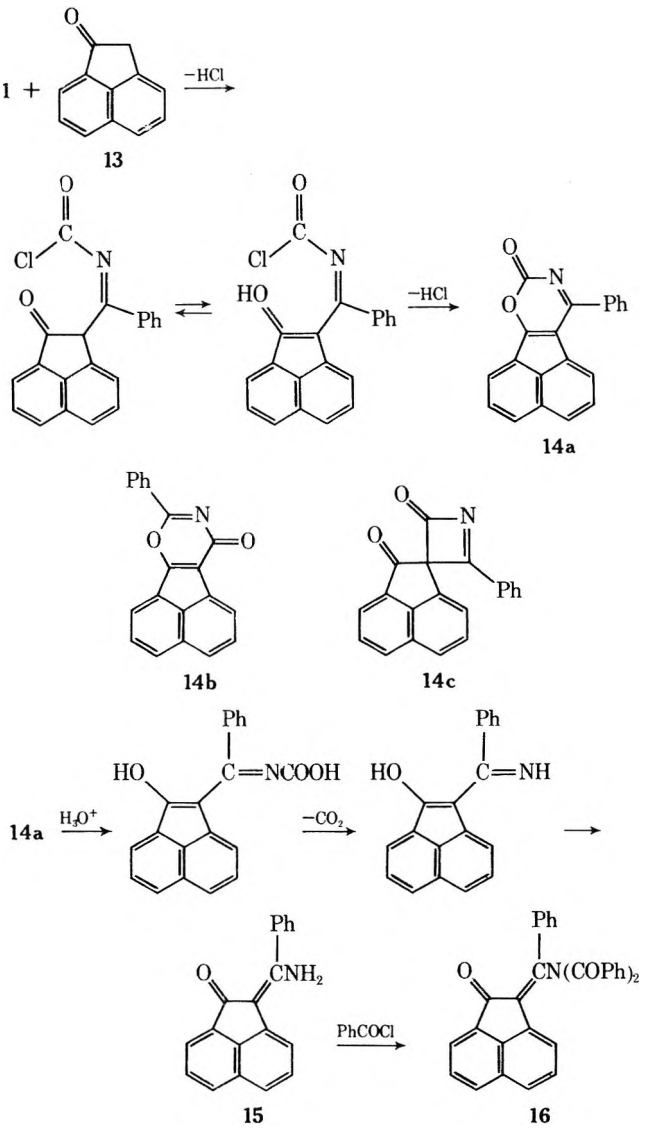


Similarly, 1 reacted with methyl cyanoacetate and NEt_3 under the same conditions to form salt 12 of the type 10.

Reaction with Acenaphthenone (13). In the reaction of 1 with 13, the formation of oxazinones 14a and 14b would be expected, besides azetinone derivative 14c. When 1 was treated with 1 equiv of 13 in the presence of 2 equiv of NEt_3, a product 14 was formed whose molecular formula agreed with that of the compound derived from a 1:1 adduct of 1 and 13 by the elimination of 2 mol of hydrogen chloride. Since the ir spectrum of 14 showed the single carbonyl absorption band at 1735 cm^{-1}, azetinone 14c could be excluded from possible structures for 14.

Although the spectral data of 14 did not permit a clear assignment as to whether 14a or 14b would be more reasonable for 14, the formation of 2-(1′-aminobenzylidene)-acenaphthenone (15), which was converted into the dibenzoyl derivative 16 by acidic hydrolysis, indicated that 14 is 10-phenylacenaphtho[1,2-e]-2*H*-1,3-oxazin-8-one (14a), but not the 8-phenyl derivative 14b. The formation of 15 from 14a can be easily rationalized by an initial hydrolytic cleavage of the C–O bond of the oxazinone ring, followed by decarboxylation as shown in Scheme IV.

Scheme IV



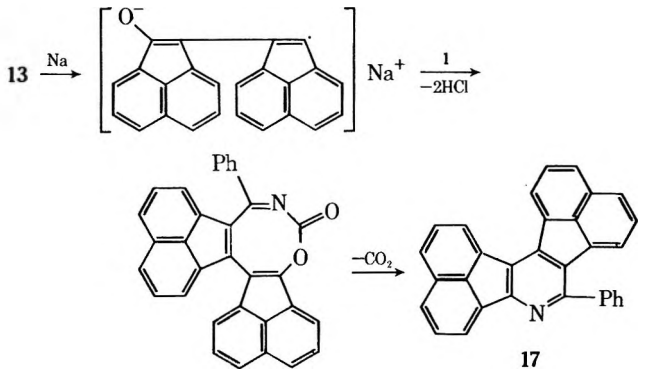
It is known that 13 is exclusively in the keto form.[8] Consequently, the formation of 14a can be also understood by an initial reaction of the imidoyl chlorine atom in 1 with the active methylene group in 13, and then subsequent ring closure to the oxazinone *via* the enol tautomer (Scheme IV).

On the other hand, the reaction of 1 with 13 in the presence of metallic sodium afforded 2-phenyldiacenaphtho[1,2-*b*:1′,2′-*d*]pyridine (17), besides tarry materials. The structure of 17 was established by its spectral data as well as by comparison with an authentic sample.[9]

When metallic sodium was added to a solution of 13 in ether, the colorless solution changed to a violet color. It has been reported that benzophenone gives a violet metal ketyl intermediate with sodium amalgam.[10] Although the exact pathway of formation of 17 is not clear, it may be viewed as proceeding *via* metal ketyl intermediate as shown in Scheme V.

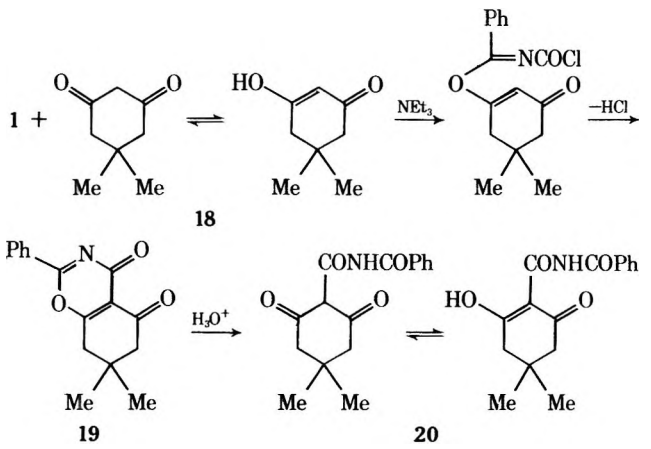
Reaction with 5,5-Dimethylcyclohexane-1,3-dione (18). It is well known that dimedone (18) exists predominantly in the enol form.[11] Therefore, it was expected that, in the presence of NEt_3, the imidoyl chlorine of 1 would initially react with the enolic hydroxyl group of 18, leading to the formation of 4*H*-1,3-oxazinone derivative 19. In fact, the reaction of 1 with 18 in the presence of NEt_3

Scheme V



gave the expected 4*H*-1,3-oxazinone derivative **19**. The structure of **19** was confirmed by its spectral data as well as by the result of hydrolysis. Hydrolysis of **19** with hydrochloric acid afforded 2-benzoylcarbamoyl-5,5-dimethylcyclohexane-1,3-dione (**20**) in a good yield. It was clarified by the nmr spectrum that **20** exists in the enol form as **18** does (Scheme VI).

Scheme VI



Experimental Section[12]

Reaction with Ethyl Cyanoacetate (2). In the Presence of Equimolar NEt_3. A. A solution of NEt_3 (0.5 g, 4.95 mmol) in diethyl ether (15 ml) was added, drop by drop, to a solution of carbamoyl chloride **1**[1] (1.0 g, 4.95 mmol) and **2** (0.56 g, 4.95 mmol) in diethyl ether (15 ml). The reaction mixture was stirred at room temperature for 1 hr and then filtered to give 0.67 g (98.5%) of triethylamine hydrochloride. To the filtrate was added ethanol (0.25 g, 5.4 mmol) and the resulting mixture was stirred at room temperature for 2 hr to yield crystals. Filtration and recrystallization from ethanol gave 0.63 g (44%) of ethyl α-cyano-β-(*N*-ethoxycarbonylamino)acrylate (**4**) as colorless needles: mp 151.5–153.5°; ir (KBr) 3200 (NH), 2235 (C≡N), 1780, 1760 (sh), 1680 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.20, 1.39 (each t, 3, CH_2CH_3, J = 7 Hz), 4.10, 4.35 (each q, 2, CH_2Me, J = 7 Hz), 7.5 (m, 5, aromatic protons), 11.31 (broad, 1, NH, exchanged with D_2O); mass spectrum m/e (rel intensity) 288 (M^+, 30), 242 (M^+ − EtOH, 58), 216 (242^+ − OEt, 100), 197 (242^+ − CO, 40), 171 (197^+ − CO, 58), 116 (38), 104 (60), 77 (38).

Anal. Calcd for $C_{15}H_{15}N_2O_4$: C, 62.49; H, 5.59; N, 9.72. Found: C, 62.43; H, 5.46; N, 9.85.

B. Similarly, treatment of the filtrate obtained from the same reaction as in A with aniline (0.5 g, 5.3 mmol) in place of ethanol at room temperature for 30 min gave 0.43 g (26%) of ethyl α-cyano-β-phenyl-β-(3-phenylureido)acrylate (**5**) as colorless needles: mp 173–173.5°; ir (KBr) 3260, 3160 (NH), 2235 (C≡N), 1720 (sh), 1700, 1680 cm^{-1} (sh) (C=O); nmr ($CDCl_3$) δ 1.40 (t, 3, CH_2CH_3, J = 7 Hz), 4.45 (q, 2, CH_2Me, J = 7 Hz), 7.45–8.0 (m, 10, aromatic protons), 8.73, 13.3 (each broad, 1, NH, exchanged with D_2O).

Anal. Calcd for $C_{19}H_{17}N_3O_3$: C, 68.05; H, 5.11; N, 12.53. Found: C, 67.93; H, 4.98; N, 12.34.

C. Initially, **1** (1.0 g, 4.95 mmol) was treated with ethanol (0.25 g, 5.4 mmol) in diethyl ether (15 ml) at room temperature for 10 hr. A solution of **2** (0.56 g, 4.95 mmol) and NEt_3 (0.5 g, 4.95 mmol) in diethyl ether (15 ml) was added, drop by drop, to the above mixture and the resulting mixture was then stirred at room temperature for 2 hr to precipitate crystals. Crystals were collected by filtration and washed with water. Recrystallization of insoluble crystals from ethanol afforded 0.52 g (36%) of **4**.

In the Presence of 2 Equiv of NEt_3. A. A solution of **2** (1.33 g, 11.8 mmol) and NEt_3 (2.4 g, 23.7 mmol) in diethyl ether (20 ml) was added, drop by drop, to a solution of **1** (2.4 g, 11.8 mmol) in diethyl ether (10 ml), and the reaction mixture was then stirred at room temperature for 4 hr. Filtration gave 3.0 g of triethylamine hydrochloride. The filtrate was concentrated *in vacuo* to leave a brown, oily product **7**, which was chromatographed on alumina.

Crystals were obtained from the elution with benzene–chloroform (1:1 v/v) and recrystallized from diethyl ether to afford 0.84 g (33%) of ethyl α-cyano-β-amino-β-phenylacrylate (**8**) as colorless needles: mp 125–125.5°; ir (KBr) 3320, 3180 (NH), 2210 (C≡N), 1665 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.34 (t, 3, CH_2CH_3, J = 7 Hz), 4.28 (q, 2, CH_2Me, J = 7 Hz), 7.4–7.75 (m, 5, aromatic protons), 5.85, 9.45 (each broad, 1, NH, exchanged with D_2O); mass spectrum m/e (rel intensity) 216 (M^+, 79), 187 (M^+ − Et, 65), 171 (M^+ − OEt, 83), 143 (171^+ − CO and/or 187^+ − CO_2, 65), 127 (143^+ − NH_2, 71), 117 (143^+ − CN, 74), 104 (100), 89 (76), 77 (65).

Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.72; H, 5.66; N, 12.96.

The compound **8** was identical with an authentic sample prepared from the reaction of **2** with benzonitrile in the presence of sodium ethoxide.[7]

On the other hand, crystals were obtained from the elution with methanol and recrystallized from ethanol to give 0.28 g (6.5%) of ethyl α-cyano-β-phenyl-β-(3-benzoylureido)acrylate (**9**) as colorless needles, which was identical with an authentic sample prepared from **8** and benzoyl isocyanate: mp 172.5–173.5° dec; ir (KBr) 3220, 3150 (NH), 2220 (C≡N), 1740 (sh), 1710, 1700, 1690 (sh), 1670 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.40 (t, 3, CH_2CH_3, J = 7 Hz), 4.45 (q, 2, CH_2Me, J = 7 Hz), 7.4–8.0 (m, 10, aromatic protons), 8.73, 13.38 (each broad s, 1, NH, exchanged with D_2O); mass spectrum m/e (rel intensity) 363 (M^+, 54), 318 (M^+ − OEt, 25), 290 (318^+ − CO, 13), 247 (290^+ − HNCO, 57), 242 (M^+ − $PhCONH_2$, 43), 216 (242^+ − CN, 80), 197 (242^+ − OEt, 81), 188 (216^+ − CO_2, 89), 171 (197^+ − CO, 92), 144 (188^+ − MeCHO, 51), 116 (144^+ − CO, 57), 105 ($PhCO^+$, 100), 89 (40), 77 (60).

Anal. Calcd for $C_{20}H_{17}N_3O_4$: C, 66.11; H, 4.72; N, 11.57. Found: C, 66.34; H, 4.65; N, 11.49.

B. A solution of **7** (obtained from the reaction under the same conditions) in ethanol (10 ml) was stirred with concentrated hydrochloric acid (5 ml) at room temperature for 12 hr, during which time crystals precipitated. Filtration and recrystallization from ethanol afforded 0.36 g (8.3%) of **9**. The filtrate was neutralized with aqueous sodium hydroxide and then extracted with diethyl ether. The ether extract was evaporated to leave crystals, which on crystallization from diethyl ether gave 0.89 g (35%) of **8**.

In the Presence of 3 Equiv of NEt_3. A solution of **1** (0.5 g, 2.47 mmol) and **2** (0.6 g, 5.3 mmol) in diethyl ether (30 ml) was added, drop by drop, to a solution of NEt_3 (0.75 g, 7.4 mmol) in diethyl ether (20 ml), and the reaction mixture was then stirred at room temperature for 5 hr, during which time crystals appeared. Crystals were collected by filtration and washed with water to leave yellow crystals. Recrystallization from ethanol–diethyl ether afforded 0.76 g (67%) of salt **10** as yellow needles: mp 127.5–128.5° dec; ir (KBr) 3200 (NH), 3000–2800 (NH^+), 2250, 2225 (C≡N), 1740 (sh), 1720 (sh), 1700, 1670, 1635 cm^{-1} (C=O); nmr ($CDCl_3$)[13] δ 1.01 (t, 9, NCH_2CH_3), 1.28, 1.32 (each t, 3, OCH_2CH_3), 2.5–3.0 (m, 6, NCH_2Me), 4.25, 4.36 (each q, 2, OCH_2Me), 7.41 (s, 5, aromatic protons), 9.60, 13.15 (each broad, 1, NH).

Anal. Calcd for $C_{24}H_{32}N_4O_5$: C, 63.14; H, 7.07; N, 12.21. Found: C, 62.91; H, 6.87; N, 12.25.

Treatment of Salt 10 with Hydrochloric Acid. A suspension of **10** (70 mg) in 1 *N* hydrochloric acid (20 ml) was stirred at room temperature for 1 hr, and crystals were filtered and washed with water. Recrystallization from diethyl ether gave 40 mg (73%) of the enol **11** as colorless needles, which on treatment with NEt_3 was converted into **10**: mp 92–93° dec; ir (KBr) 3080 (NH), 2210, 2190 (C≡N), 1730 (sh), 1710 (sh), 1690 (sh), 1640, 1630 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.35, 1.39 (each t, 3, CH_2CH_3), 4.31, 4.45

(each q, 2, CH_2Me), 7.52 (s, 5, aromatic protons), 10.0, 12.45 (each 1, OH or NH, exchanged with D_2O).

Anal. Calcd for $C_{18}H_{17}N_3O_5$: C, 60,84; H, 4.82; N, 11.83. Found: C, 61.07; H, 4.92; N, 11.76.

Reaction with Methyl Cyanoacetate. The reaction of **1** (0.5 g, 2.47 mmol) with methyl cyanoacetate (0.6 g, 6 mmol) in the presence of NEt_3 (0.75 g, 7.4 mmol) in diethyl ether at room temperature for 5 hr afforded 0.7 g (66%) of salt **12** as yellow needles: mp 157–159° dec; ir (KBr) 3180 (NH), 3000–2800 (NH^+), 2190, 2180 (C≡N), 1700, 1650. 1620 cm^{-1} (C=O); nmr ($CDCl_3$)[13] δ 1.02 (t, 9, NCH_2CH_3), 2.5–3.05 (m, 6, NCH_2Me), 3.80, 3.91 (each s, 3, OCH_3), 7.43 (s, 5, aromatic protons), 9.60, 13.18 (each broad, 1, NH).

Anal. Calcd for $C_{22}H_{28}N_4O_5$: C, 61.66; H, 6.59; N, 13.08. Found: C, 61.49; H, 6.69; N, 12.78.

Reaction with Acenaphthenone (13) in the Presence of NEt_3. A solution of **1** (0.5 g, 2.47 mmol) and **13** (0.4 g, 2.4 mmol) in diethyl ether (30 ml) was stirred with NEt_3 (0.5 g, 4.95 mmol) at room temperature for 2 hr, during which time crystals precipitated. Crystals were collected by filtration and washed with water to leave yellow crystals Recrystallization from benzene–petroleum ether (bp 45–65°) gave 0.2 g (27%) of 10-phenylacenaphtho[1,2-*e*]-2*H*-1,3-oxazin-8-one (**14a**) as yellow needles: mp 180–180.5° dec; ir (KBr) 1735 (C=O), 1710 cm^{-1} (C=N); nmr ($CDCl_3$) δ 7.25–8.4 (m, aromatic protons); mass spectrum *m/e* (rel intensity) 297 (M^+, 87), 296 (100), 269 (M^+ − CO, 7), 255 (M^+ − NCO, 7), 240 (269^+ − CO − H, 17), 226 (269^+ − HNCO, 17), 138 (241^+ − PhCN, 25).

Anal. Calcd for $C_{20}H_{11}NO_2$: C, 80.79; H, 3.73; N, 4.71. Found: C, 80.97; H, 3.99; N, 4.58.

Hydrolysis of 14a. After a suspension of **14a** (0.2 g) in 15% hydrochloric acid (20 ml) was stirred at room temperature for 4 hr, filtration gave crystals, which were washed with water and chromatographed on alumina. From the elution with chloroform yellow crystals were obtained. Recrystallization from benzene–petroleum ether (bp 50–65°) afforded 0.18 g (98.7%) of 2-(1′-aminobenzylidene)acenaphthenone (**15**) as yellow needles: mp 143–144° dec; ir (KBr) 3440, 3260 (NH), 1635 cm^{-1} (C=O); nmr ($CDCl_3$) δ 5.0, 9.9 (each broad, 1, NH, exchanged with D_2O), 7.0–8.15 (m, 11, aromatic protons); mass spectrum *m/e* (rel intensity) 271 (M^+, 82), 270 (100), 254 (270^+ − NH_2, 30), 243 (271^+ − CO, 15) 226 (154^+ − CO, 12), 136 (20), 120 (20).

Anal. Calcd for $C_{19}H_{13}NO$: C, 84.11; H, 4.83; N, 5.16. Found: C, 83.91; H, 5.10; N, 5.25.

Benzoylation of 15. After a solution of **15** (0.2 g, 0.74 mmol) in pyridine (2 ml) was heated with benzoyl chloride (0.28 g, 2 mmol) at 80° for 15 min, the reaction mixture was poured into water, giving yellow crystals. Recrystallization from benzene–petroleum ether (bp 45–60°) afforded 0.19 g (53.7%) of dibenzoyl compound **16** as yellow needles: mp 188° dec; ir (KBr) 1710, 1670 cm^{-1} (C=O); mass spectrum *m/e* 479 (M^+).

Anal. Calcd for $C_{33}H_{21}NO_3$: C, 82.56; H, 4.41; N, 2.92. Found: C, 82.39; H, 4.31; N, 3.04.

Reaction with 13 in the Presence of Metallic Sodium. When metallic sodium (0.46 g, 0.02 g-atom) was added to a solution of **13** (1.4 g, 8.3 mmol) in diethyl ether (30 ml), the colorless solution changed to a violet color. The violet solution was stirred with **1** (1.0 g, 4.95 mmol) at room temperature for 10 hr to yield a brown solid, which was extracted with hot benzene. The extract was concentrated *in vacuo*, and a residue was chromatographed on alumina using benzene as an eluent to give yellow crystals. Recrystallization from benzene afforded 0.2 g (20%) of 2-phenyldiacenaphtho[1,2-*b*:1′,2′-*d*]pyridine (**17**), mp 287°, as yellow needles, which was identical with an authentic sample obtained from the pyrolysis of acenaphthenone *N*-benzoylhydrazone[9] [*Anal.* Calcd for $C_{31}H_{17}N$: C, 92.31; H, 4.22; N, 3.47. Found: C, 92.24; H, 3.97; N, 3.25. Mass spectrum *m/e* 403 (M^+)].

Reaction with 5,5-Dimethylcyclohexane-1,3-dione (18). A solution of **1** (0.5 g, 2.47 mmol) and **18** (0.35 g, 2.5 mmol) in diethyl ether (30 ml) was stirred with NEt_3 (0.5 g, 4.95 mmol) at room temperature for 2 hr, during which time crystals appeared. Crystals were collected by filtration and washed with water. Recrystallization from benzene–petroleum ether (bp 45–65°) afforded 0.2 g (30%) of 4*H*-1,3-oxazinone derivative **19** as yellow needles: mp 184–184.5°; ir (KBr) 1715, 1660, 1640 cm^{-1} (C=O, C=N); nmr ($CDCl_3$) δ 1.20 (s, 6, CH_3), 2.50, 2.85 (each s, 2, CH_2), 7.5–7.7 (m, 3, aromatic protons), 8.15–8.35 (m, 2, aromatic protons); mass spectrum *m/e* (rel intensity) 269 (M^+, 100), 254 (M^+ − Me, 10), 166 (M^+ − PhCN, 20), 165 (50), 151 (254^+ − PhCN, 65), 138 (166^+ − CO, 74), 104 (40), 103 (70).

Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.62; H, 5.89; N, 5.29.

Hydrolysis of 19. After a suspension of **19** (0.2 g) in 15% hydrochloric acid (20 ml) was stirred at room temperature for 2 hr, crystals were collected by filtration and washed with water. Recrystallization from diethyl ether afforded 0.18 g (84.5%) of 2-benzoylcarbamoyl-5,5-diemethylcyclohexane-1,3-dione (**20**) as yellow prisms: mp 149–150.5° dec; ir (KBr) 3175 (NH), 1720, 1650, 1625 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.13 (s, 6, CH_3), 2.47, 2.62 (each s, 2, CH_2), 7.5–7.72 (m, 3, aromatic protons) 8.0–8.2 (m, 2 aromatic protons), 13.2 16.92 (each broad, 1, NH or OH, exchanged with D_2O); mass spectrum *m/e* (rel intensity) 287 (M^+, 95), 272 (M^+ − Me, 10), 259 (M^+ − CO, 15) 231 (259^+ − CO, 38), 203 (231^+ − CO, 26), 167 (272^+ − PhCO, 26), 105 (100).

Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.88; H, 5.96; N, 4.88. Found: C, 67.17; H, 5.84; N, 4.97.

Registry No.—**1**, 4547-71-1; **2**, 105-56-6; **4**, 51003-09-9; **5**, 51003-10-2; **7**, 51002-93-8; **8**, 39491-78-6; **9**, 51003-08-8; **10a**, 51003-04-4; **10b**, 51003-06-6; **11**, 51003-07-7; **12**, 2235-15-6; **13a**, 51003-25-9; **14**, 51003-26-0; **15**, 51003-27-1; **16**, 51003-28-2; **17**, 23952-27-4; **18**, 126-81-8; **19**, 51003-29-3; **20**, 51003-30-6.

References and Notes

(1) Part I: O. Tsuge, M. Yoshida, and S. Kanemasa, *J. Org. Chem.*, **39**, 1226 (1974).
(2) E. Degener, H. G. Schmelzer, and H. Hotschmidt, *Angew. Chem.*, **78**, 981 (1966).
(3) S. Yanagida, M. Yokoe, M. Ohoka, and S. Komori, *Bull. Chem. Soc. Jap.*, **44**, 2182 (1971).
(4) Y. Shvo and I. Belsky, *Tetrahedron*, **25**, 4649 (1969).
(5) In the nmr spectra in $CDCl_3$ at −20, −50, and −60°, the NH signal appeared as a singlet at δ 11.40, 11.45, and 11.47, respectively.
(6) Hydrolysis of **3** under the same conditions gave **4** as a sole product.
(7) E. F. J. Atkinson, H. Ingham, and J. F. Thorpe, *J. Chem. Soc., London, Trans.*, **91**, 579 (1907).
(8) O. Tsuge, M. Tashiro, and I. Shinkai, *Bull. Chem. Soc. Jap.*, **42**, 181 (1969).
(9) O. Tsuge, K. Hokama, and M. Koga, *Yakugaku Zasshi*, **89**, 789 (1969).
(10) J. F. Garst, D. Walmsley, and W. R. Richards, *J. Org. Chem.*, **27**, 2924 (1962).
(11) C. L. Angell and R. L. Werner, *Aust. J. Chem.*, **6**, 294 (1953).
(12) All melting points are uncorrected. The nmr spectra were determined at 60 MHz with a Hitachi R-20 nmr spectrometer with TMS as an internal reference. The mass spectra were obtained on a Hitachi RMS-4 mass spectrometer with a direct inlet and an ionization energy of 70 eV.
(13) It has been found that the difference of chemical shift between methyl and methylene protons in the nmr spectrum of NEt_3 in $CDCl_3$ was 1.50 ppm, while that between methyl and methylene protons in triethylamine hydrochloride was 1.75 ppm. The difference of chemical shift between methyl and methylene protons in the NEt_3 group in **10** and **12** was found to be 1.75 ppm.

Phosgene Immonium Salts. XIII. Dichloromalonyl Cyanines and 3,5-Bis(dimethylamino)pyrazoles

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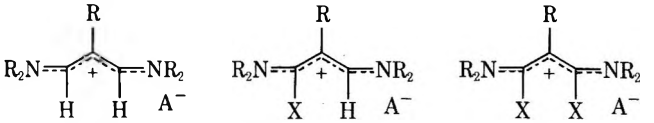
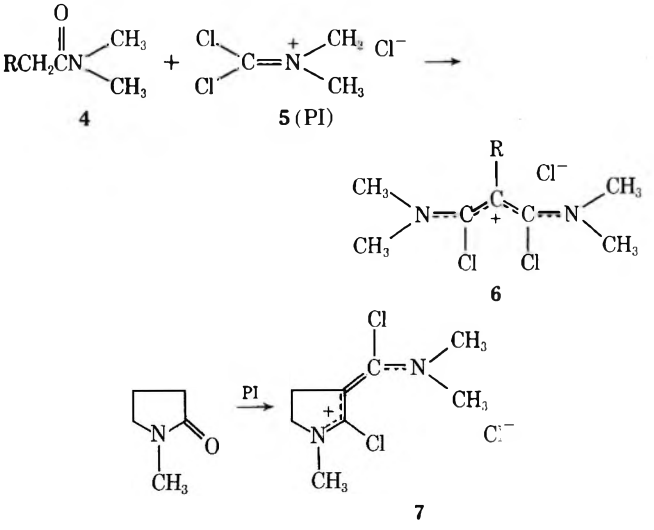
The chloromalonyl cyanine derivatives, **6**, were synthesized by the reaction of α-substituted *N,N*-dialkylacetamides with phosgene immonium chlorides. The biselectrophilic system in **6** is of general applicability to the synthesis of aminated heterocyclic systems. As the first example, the reactions of a variety of hydrazines with **6** are described. The corresponding 3,5-bis(dialkylamino)pyrazoles, **9**, are formed in good yield.

Cyanines (trimethinium salts) of the general structure **1** are well-known compounds, and have been widely used in synthesis. Vinylogous guanidinium salts **2a**[1] and the corresponding chloro derivatives **2b**[2] are also readily available, but previous efforts to obtain cyanines **3** at the oxidation level of malondiamide have been unsuccessful. Reactions of malondiamide with alkyl sulfates[3] or trialkyloxonium salts[4] give only monoactivated derivatives. Attempts to convert N,N′-tetrasubstituted malondiamides to bis(amide chlorides) (**3**, X = Cl) with a $TiCl_4$–dialkylamine complex furnished ill-defined products believed to be chelates;[5] with $POCl_3$, only one amide chloride function is introduced.[6] The use of phosphorus halides for these reactions would be expected to give the monoamide chloride, since reactions of this type are extremely sensitive to electron-attracting substituents. Although malondithioamides[7] and bis(dialkylamino)dithiolium compounds[8] have found some use in the synthesis of bis(dialkylamino)heterocycles, their general availability is limited.



1 **2a**, X = NR_2; **b**, X = Cl **3a**, X = NR_2; **b**, X = OR

As a source of synthon **3** we have developed a general and convenient preparation of the dichloromalonylcyanines **6**[9] by condensation of the powerfully electrophilic phosgene immonium (PI) salts **5** with N,N-disubstituted amides. Amides without α hydrogen are readily converted to amide chlorides by the PI reagent.[10] With monosubstituted acetamides, further condensation to the malonyl cyanines **6** occurs even at low temperatures and with deficient amounts of the PI salt. *N*-Methylpyrrolidine gives the cyclic analog **7**.

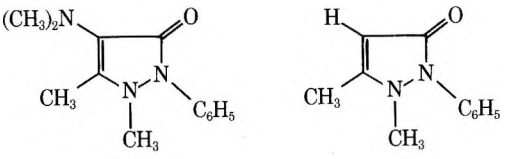


4 **5** (PI) **6** **7**

The method is quite general and leads to cyanines **6** with R = alkyl, aryl, halo, and alkoxy substituents; the reaction fails with bulky groups such as *tert*-butyl and R_3N^+–. The cyanines that have been prepared are listed in Table I. For characterization the cyanines were hydrolyzed with aqueous bicarbonate to the N,N-tetrasubstituted malondiamides.

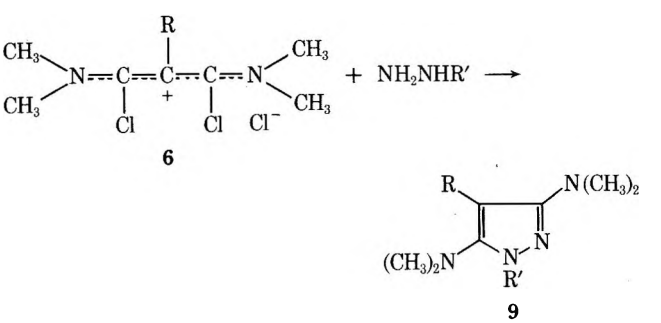
The dichloromalonylcyanines are stable yellow solids, soluble in chloroform but insoluble in ether. The extended charge delocalization in these compounds is reflected in their spectral properties. For the unsubstituted cyanine (**6**, R = H), the uv absorption maximum is at 346 nm; alkyl substitution causes a bathochromic shift of 42 nm, and groups that can exert a positive mesomeric effect (OR, Cl, C_6H_5, etc.) cause a further shift of 20–30 nm. As expected for the completely delocalized cyanine structure, the four NCH_3 groups give rise to a single CH_3 resonance at δ 3.4–3.7 ppm in the nmr spectra of **6**. The ir spectra of **6** shows no absorption from 1600 to 1800 cm^{-1}; a characteristic band appears at 1550 cm^{-1}.

The synthetic utility of the malonyl cyanines is borne out by their conversion to a variety of malonic acid derivatives and 1,3-bis(dialkylamino) heterocycles.[10] A particularly effective application is the reaction with hydrazines to give a variety of 4-substituted-3,5-bis(dialkylamino)pyrazoles. A limited number of 3,5-bis(amino)pyrazoles have been obtained by various condensation routes,[7,8,11] but these routes are of limited scope. The enhanced activity of aminopyrine **8a** compared to antipyrine **8b** exemplifies the potential value of the dialkylamino pharmacophore.[12]



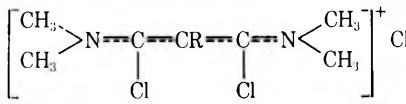
8a **8b**

The malonyl cyanines **6** were condensed directly with a variety of hydrazines in refluxing chloroform or dichloromethane. Bis(dimethylamino)pyrazoles **9** were obtained in

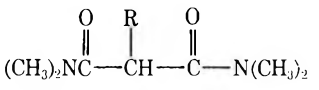


6 **9**

Table I
Dichloromalonyl Cyanines 6 and Malondiamides 10[a]



6

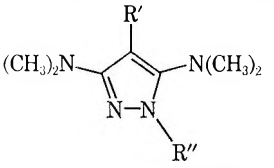


10

R	Registry no.	Yield, %	Uv max (CH_2Cl_2)	Malondiamide mp, °C	Registry no.
H	34057-61-9	91	346		
CH_3	50859-92-2	90		69–70	50859-98-8
C_2H_5	34057-62-0	88	388	75–76	33564-08-8
C_6H_5	34057-63-1	90	397	149[b]	33564-09-9
Cl	34112-12-4	88	410	92	33564-10-2
OCH_3	50859-93-3	95	406	63	50859-99-9
OC_2H_5	50859-94-4	98	409	76	50860-00-9
$OCH(CH_3)_2$	50859-95-5	92	407	53	50860-01-0
OC_6H_5	50859-96-6	99	406	116	50860-02-1
$OCOCH_3$	50859-97-7	60	392	82 (0.04 mm)[c]	50860-03-2

[a] Satisfactory analytical data (±0.4% for C, H) were obtained for malonyldiamides. [b] Lit. mp 150°: R. Burguda, *C. R. Acad. Sci.*, **258**, 1532 (1964). [c] Boiling point.

Table II
3,5-Bis(dimethylamino)pyrazoles 9



Registry no.	Compd	R′	R″	Yield, %	λ_{max} (EtOH[e]), nm (ε)	Mp or bp, °C (mm)
50860-04-3	**9a**	H	CH_3	82[c]	244 (8800)[f]	118 (0.4)
50860-05-4	**b**	H	C_6H_5	92[c]	290 (7000)	120 (0.3)
50860-06-5	**c**[a]	H	C_6H_5	90[c]	292 (8800)	125 (0.3)
50860-07-6	**d**	H	$CO_2C_2H_5$	72[c]	260 (13,700)	84 (petroleum ether) 126 (0.4)
50860-08-7	**e**	H	2,4-$(NO_2)_2C_6H_3$	89[c]		159–160 (MeOH)
50860-09-8	**f**	C_6H_5	$CO_2C_2H_5$	72[c]	280 (12,000)	130 (0.4)
50860-10-1	**g**	Cl	C_6H_5	85[c]	280 (9600)	130 (0.4)
50860-11-2	**h**	OCH_3	$CO_2C_2H_5$	92[d]	273 (10,300)	115–120 (0.4)
50860-12-3	**i**	OCH_3	$SO_2C_6H_5$	90[d]	270 (6500)[g]	76 (EtOH)
50860-13-4	**j**	OCH_3	C_6H_5	82[d]	284 (11,400)	68 (CCl_4)
50860-14-5	**k**	OC_2H_5	$CO_2C_2H_5$	95[d]	275 (13,800)	115–120 (0.4)
50860-15-6	**l**	OC_2H_5	$SO_2C_6H_5$	95[d]	274 (7800)	86 (Ether)
50860-16-7	**m**	OC_2H_5	C_6H_5	86[d]	288 (10,500)[g]	51 (Petroleum ether)
50860-17-8	**n**	O-*i*-C_3H_7	C_6H_5	78[d]	289 (11,500)[g]	89 (Ether)
50860-18-9	**o**	OC_6H_5	$CO_2C_2H_5$	98[d]	275 (7600)	72 (Ether)
50860-19-0	**p**	OC_6H_5	$SO_2C_2H_5$	73[d]	274 (9600)[g]	112 (MeOH)
50860-20-3	**q**	OC_6H_5	C_6H_5	93[d]	277 (15,500)[h]	90 (MeOH)
50860-21-4	**r**	OC_6H_5	H	32[b,d]	240 (8270)	160 (Ether)
50860-22-5	**s**	OC_6H_5	CH_3	78[d]	243 (7200)	125 (0.4)

[a] Bis(diethylamino) analog of **9**. [b] Obtained as a by-product (maximum yield) in the reaction to form **9**. [c] Condensation was carried out in $HCCl_3$. [d] Condensation was carried out in CH_2Cl_2. [e] Or as otherwise indicated. [f] $CHCl_3$. [g] CH_2Cl_2. [h] CH_3OH.

70–90% yield (Table II). The use of bases such as tertiary amines was not required, and their use resulted in lower yields. The pyrazoles were liberated from the hydrochlorides by aqueous base. In one condensation of benzenesulfonyl chloride, cleavage to give the unsubstituted pyrazole and the sulfonyl chloride was observed. With 1,1-dimethylhydrazine, dealkylation occurred to give the 1-methylpyrazole.

Experimental Section

Melting points were taken in open capillary tubes and were uncorrected. Boiling points recorded for molecular distillations were of the oven temperatures. The uv spectra were recorded on a Unicam SP1800 spectrometer, ir spectra were obtained using a Perkin-Elmer 237, and nmr spectra were recorded on a Varian T60 spectrometer at room temperature with TMS as internal standard.

Malonyl Cyanines and Their Hydrolysis Products. The same general procedure was used for all the malonyl cyanines. Phosgene immonium chloride (0.2 mol) and the amide (0.1 mol) were combined in chloroform or dichloromethane (100 ml), and the mixture was refluxed until all the phosgene immonium chloride had dissolved and HCl evolution had ceased. The reaction was protected by a drying tube ($CaCl_2$) at all times. The solvent was removed under vacuum, and the residue was washed with several portions of dry ether until all of the dimethylcarbamoyl chloride was removed. The cyanines, which in most instances crystallized upon stirring with ether, were characterized by hydrolysis to the corresponding malondiamide. The cyanines were soluble in chloroform or dichloromethane, but were insoluble in ether. The nmr spectra contained a single NCH_3 peak at 3.6–3.7 ppm.

The malonyl cyanines (0.05 mol) were dissolved in water (20 ml), and solid potassium carbonate was added until the yellow color of the cyanine disappeared and the solution remained basic. The mixture was extracted with ether, the organic extract was dried ($CaCl_2$), and the ether was evaporated. The resulting residues were crystallized from ether–petroleum ether (bp 40–60°).

1-Dimethylamino-1,3-dichloro-3-methylamino(*N*-2-ethylene)-trimethinium Chloride (7). *N*-Methylpyrrolidone (2.5 g, 25 mmol) and phosgene immonium chloride (8.1 g, 50 mmol) were refluxed in 50 ml of dry chloroform until all solid had dissolved. The solvent was then removed to give 6.01 g (98%) of **7** as a dense oil: nmr ($CDCl_3$) δ 4.39 (2 H, t, J = 10 Hz), 3.43 (9 H, s), 3.40 (2 H, t); uv (CH_2Cl_2) λ_{max} 381 nm (ϵ 5500).

3-(*N,N*-Dimethylcarbamoyl)-*N*-methyl-2-pyrrolidone. The cyanine **7** (6.00 g, 24.7 mmol) was dissolved in 20 ml of chloroform and stirred with 5 ml of water and an excess of $NaHCO_3$ for 1 hr. The organic phase was collected, dried over $MgSO_4$, and evaporated. Distillation gave 3.6 g (87%) of **7**: bp 114° (0.5 mm); nmr ($CDCH_3$) δ 3.27 (3 H, s), 3.00 and 2.88 (6 H, 2 s), and a complex second-order pattern between 2.0 and 4.0 ppm (4 H); mass spectrum *m/e* 170 (M^+), 142, 126, 98.

General Procedure for Pyrazole Formation. The cyanine **6** (0.01 mol) and the hydrazine (0.011 mol) were combined in chloroform or dichloromethane (75 ml) and the reaction mixture was refluxed until the yellow color of the cyanine disappeared. The reaction mixture was filtered and the solvent was evaporated under reduced pressure. Aqueous potassium hydroxide (2 *N*) was added to liberate the free pyrazole, and the resulting mixture was extracted with dichloromethane (5 × 100 ml). The organic phase was dried (Na_2SO_4), the solvent was evaporated, and the crude pyrazole was purified either by crystallization or by molecular distillation; characteristics of the pyrazoles are given in Table I. The nmr spectra of all 1-substituted 3,5-bis(dimethylamino)pyrazoles had two six-proton singlets at 2.6–2.7 and 2.8–2.9 ppm; 4-unsubstituted compounds had a one-proton singlet at 5.2–5.3 ppm; peaks due to substituents were present at the expected positions in all spectra; all pyrazoles gave satisfactory analytical data (±0.3% for C and H or ±0.003 Daltons by mass spectrum). The general procedure above gave only poor yields of **9s**. For this reason **9s** was made by two alternate procedures:

Procedure 1. Methyl hydrazine (0.01 mol) in dioxane (50 ml) was slowly added to the phenoxycyanine **6** (R = OC_6H_5) (0.01 mol) in CH_2Cl_2 (25 ml) with stirring at −8°. The reaction mixture was stirred overnight, the precipitated salts were filtered off, and the organic solvent was evaporated under suction. The residue was dissolved in a minimal amount of water, and 2 *N* KOH was added to liberate the free pyrazole. The aqueous mixture was extracted with ether (5 × 100 ml), the ethereal solution was dried (Na_2SO_4), and the solvent was evaporated. The resulting residue was distilled horizontally to give 2.04 g (78%) of **9s**.

Procedure 2. The phenoxycyanine (0.01 mol) in $CHCl_3$ (50 ml) and *N,N*-dimethylhydrazine (0.02 mol) in $CHCl_3$ (25 ml) were combined slowly with stirring at 0°. After 1 hr the solution was refluxed until the yellow color of the cyanine disappeared. The dimethylhydrazine hydrochloride was filtered off and the solvent was evaporated under suction. The residue was dissolved in a minimal amount of water and 2 *N* KOH was added to liberate the free pyrazole. Further work-up was carried out as in procedure 1 to give 1.25 g (48%) of **9s**.

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Registry No.—**4** (R = H), 127-19-5; **4** (R = CH_3), 758-96-3; **4** (R = C_2H_5), 760-79-2; **4** (R = C_6H_5), 18925-69-4; **4** (R = Cl), 2675-89-0; **4** (R = OCH_3), 4128-76-1; **4** (R = OC_2H_5), 24475-96-5; **4** [R = $OCH(CH_3)_2$], 50860-23-6; **4** (R = OC_6H_5), 10397-59-8; **4** (R = $OCOCH_3$), 13831-28-2; **5**, 33842-02-3; **7**, 50860-24-7; NH_2NHR' (R' = CH_3), 60-34-4; NH_2NHR' (R' = C_6H_5), 100-63-0; NH_2NHR' (R' = $CO_2C_2H_5$), 4114-31-2; NH_2NHR' [R' = 2,4-$(NO_2)_2C_6H_3$], 119-26-6; NH_2NHR' (R' = $SO_2C_6H_5$), 80-17-1; NH_2NHR' (R' = $SO_2C_2H_5$), 37984-88-6; NH_2NHR' (R' = H), 302-01-2; *N*-methylpyrrolidone, 872-50-4; 3-(*N,N*-dimethylcarbamoyl)-*N*-methyl-2-pyrrolidone, 50932-75-7.

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Hydrogen Cyanide Chemistry. VII. Diiminosuccinonitrile Condensation with Diaminomaleonitrile[1]

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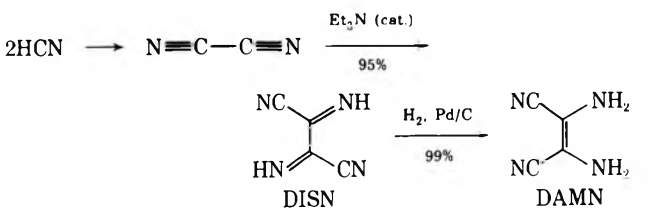
Diiminosuccinonitrile (DISN) condenses with diaminomaleonitrile (DAMN) to give tetracyanopyrazine, aminotricyanopyrazine, and 2,3-diamino-5,6-dicyanopyrazine. By choice of conditions any one of these tetrafunctional pyrazines can be the major product; linear 1:1 and 2:1 adducts are formed under other conditions and the 1:1 adduct can be cyclized to the pyrazines. DISN reacts with 1 mol of water to form an intermediate, probably iminooxalyl cyanide, which condenses with DAMN to give 2-amino-3-hydroxy-5,6-dicyanopyrazine. Two moles of water hydrolyze DISN to oxalyl cyanide, which condenses with DAMN to give tetracyanopyrazine under acidic conditions and 1,4,5,6-tetrahydro-5,6-dioxo-2,3-dicyanopyrazine under neutral conditions.

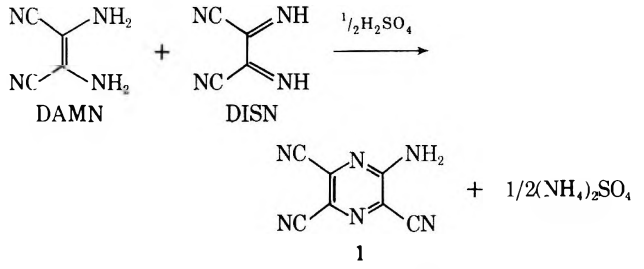
Diiminosuccinonitrile (DISN) and diaminomaleonitrile (DAMN) are now readily available research chemicals derived from hydrogen cyanide.[2] We have previously shown that nucleophiles displace either ammonia or hydrogen cyanide from DISN under varying conditions.[3] This behavior is further exemplified by the reactions of DISN with DAMN by which various tetrasubstituted pyrazines



and acyclic adducts can be selectively prepared in good yield.

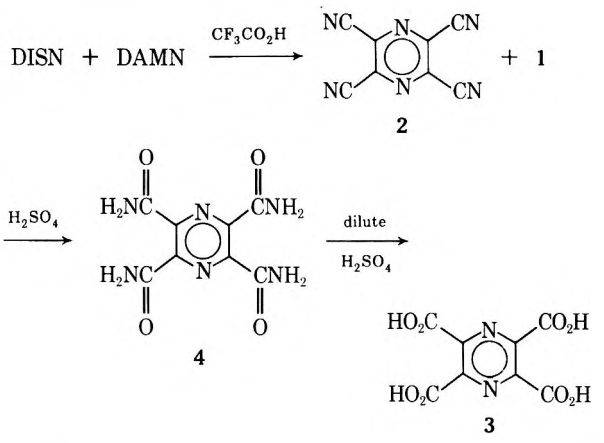
Results

When equimolar amounts of DISN and DAMN are mixed in tetrahydrofuran, no immediate reaction occurs. However, addition of 0.5 mol of sulfuric acid to this solution induces an exothermic reaction and ammonium sulfate precipitates. Filtration and removal of the solvent give aminotricyanopyrazine (1) as light-yellow crystals in 95% yield. Structure assignment of 1 is based on analysis, infrared and mass spectra, and its chemistry which will be discussed later. The *p*-toluenesulfonic acid salt of DAMN also reacts with DISN, giving 1 in good yield.

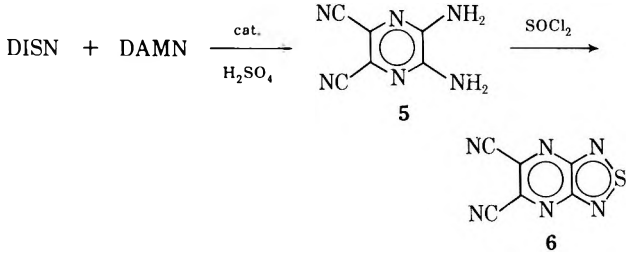


1

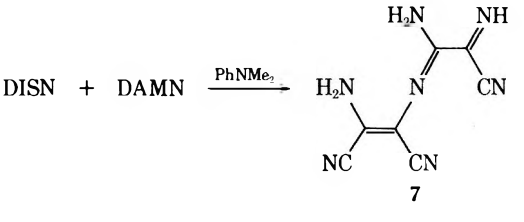
When a powdered mixture of DISN and DAMN is added to trifluoroacetic acid, an exothermic reaction occurs followed by precipitation of white crystals of tetracyanopyrazine (2) in 60% yield; by evaporation of the filtrate, a mixture of 1 and 2 is recovered in approximately 25% yield. The structure of tetracyanopyrazine (2) was confirmed by its hydrolysis to the known pyrazinetetracarboxylic acid (3).[4] Stepwise hydrolysis with concentrated sulfuric acid initially gave pyrazinetetracarboxamide (4) in over 90% yield followed by further hydrolysis to 3 in aqueous acid.

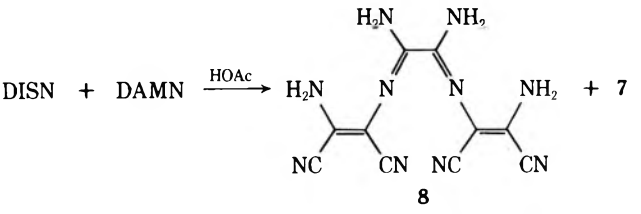


The addition of only a catalytic amount of sulfuric acid to an equimolar solution of DISN and DAMN in tetrahydrofuran or acetonitrile yields yet another new pyrazine. When the acid is added, an immediate exothermic reaction occurs and a yellow precipitate forms. Within the next 30 sec the precipitate redissolves, the reaction temperature again rises, and crystals begin to form. After 30 min the crystals are collected, giving 2,3-diamino-5,6-dicyanopyrazine (5) in 60–70% yield. The 2,3 orientation of the amino groups in 5 was confirmed by formation of 5,6-dicyano[1,2,5]thiadiazolo[3,4-*b*]pyrazine (6) upon treatment of 5 with thionyl chloride.

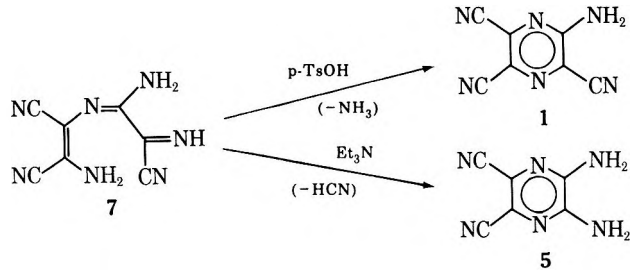


The condensation of DISN and DAMN using a basic catalyst such as *N,N*-dimethylaniline gives 1,4-diamino-1,2,5-tricyano-3,6-diazahexatriene (7) in 70% yield. Addition of acetic acid to a solution of DISN and DAMN in tetrahydrofuran also gives adduct 7; however, the major product from this reaction is a very insoluble 2:1 DAMN–DISN adduct which is thought to be 1,4,5,8-tetraamino-1,2,7,8-tetracyano-3,6-diazaoctatetraene (8).

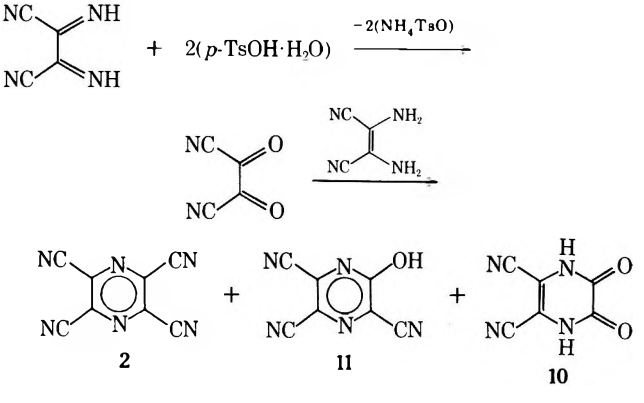




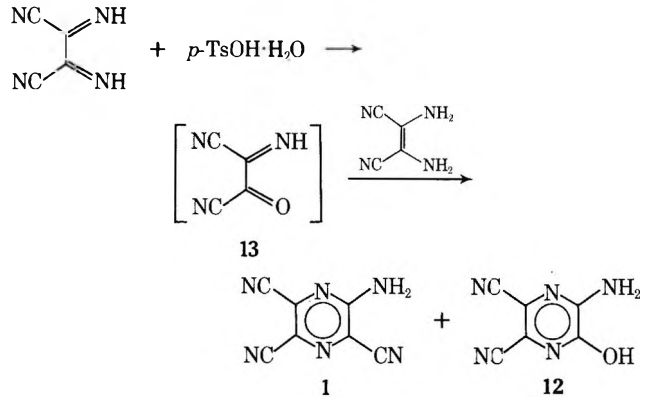
The structure of 7 was confirmed by its facile cyclization to two of the previously obtained pyrazines. Thus, treatment of 7 with 1 equiv of anhydrous *p*-toluenesulfonic acid gives 1 nearly quantitatively. Triethylamine, however, affords 2,3-diamino-5,6-dicyanopyrazine (5).



In addition to the compounds obtained by the direct condensation of DISN with DAMN, we have isolated three other pyrazines when water is added to the DISN prior to the addition of DAMN. Addition of 2 equiv of *p*-toluenesulfonic acid monohydrate to a solution of DISN in THF forms oxalyl cyanide (9).[3] If DAMN is added to this solution, the isolated products are tetracyanopyrazine (2, 25%), 2,3-dioxo-1,2,3,4-tetrahydro-5,6-dicyanopyrazine[5] (10, 34%), and hydroxytricyanopyrazine (11, 5%).



Addition of 1 equiv of *p*-toluenesulfonic acid monohydrate to a solution of DISN, followed by addition of DAMN, yields aminotricyanopyrazine (**1**, 31%) and 2-amino-3-hydroxy-5,6-dicyanopyrazine (**12**, 22%). Although we were unable to isolate α-iminooxalyl cyanide (**13**), we feel that it must be the initially formed intermediate in this reaction.



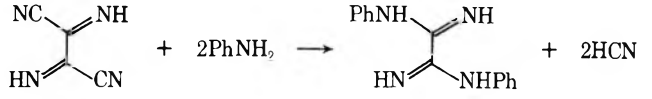
13

1 **12**

Discussion

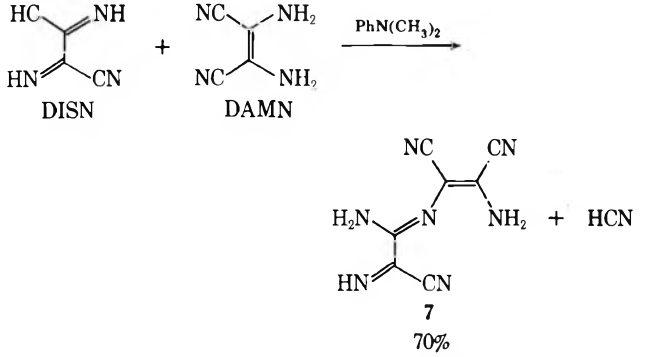
The condensation of DISN with o-phenylenediamine to give amino- and cyano-substituted quinoxalines was reported in a previous paper in the series.[3] The condensation of DISN with DAMN is analogous and has been examined more thoroughly, especially with regard to the control of product formation under acid catalysis. A detailed mechanistic interpretation is not possible without extensive experimental investigation, but the control achieved through acid catalysis can be rationalized in the following way.

Under neutral or basic conditions DISN reacts with amines with cyanide displacement,[3] as shown, for example, with aniline.



DISN

Attack by the weakly basic amine groups of DAMN is very slow under neutral conditions but is mildly base catalyzed by bases such as tertiary amines which are compatible with DISN.



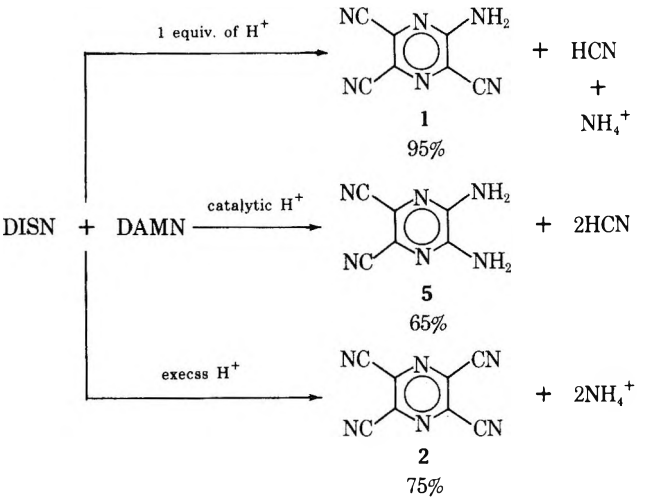
DISN DAMN

7

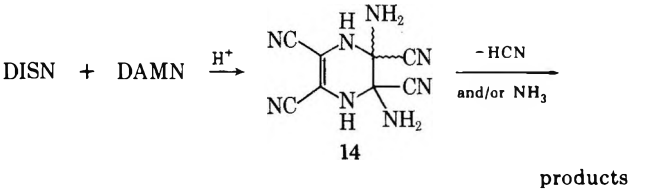
70%

The condensation of DISN and DAMN is strongly acid catalyzed, presumably because of protonation of DISN. In addition, an acidic medium promotes the loss of ammonia from the intermediates. This latter effect has provided a means for controlling the reaction so that any one of the three possible pyrazines **1**, **2**, and **5** can be made the major product.

These three sets of reaction conditions undoubtedly influence not only the overall outcome of the reaction, but



also the sequence of events leading to products in such a way that no one unifying mechanism can be written. The discussion is greatly simplified, however, by assuming that the cyclic intermediate **14** is formed rapidly under acid catalysis. However, ammonia and/or hydrogen cyanide could be lost from acyclic intermediates that can cyclize to pyrazine products. Various acid–base equilibria are obviously involved and the amount of acid present would have significant influence on equilibria.



14

products

In the case of the reaction utilizing a catalytic amount of acid which produces mainly 2,3-diamino-5,6-dicyanopyrazine by loss of 2 mol of hydrogen cyanide, the primary function of the acid is to catalyze the addition of the amino groups of DAMN to DISN.

Even at this low acid concentration some loss of ammonia occurs, leading to aminotricyanopyrazine **1**. In this acid-catalyzed case presumably the small amount of acid would be consumed when ammonia is eliminated so that cyclization must occur before loss of ammonia (note that ammonium salts do not catalyze the condensation of DISN and DAMN); however, this does not rule out acyclic intermediates which have lost hydrogen cyanide.

The reaction of DAMN with oxalyl cyanide and α-iminooxalyl cyanide can be rationalized in a manner analogous to the DISN reactions, but with these more reactive and less basic compounds the catalytic role of the acid in the initial addition is less important. Also acid has less effect in influencing loss of water from the intermediates as compared to the loss of ammonia in the DISN reactions.

Experimental Section

The infrared spectra were obtained on a Perkin-Elmer Model 21 spectrometer, the uv spectra on a Cary Model 14, and the mass spectra on a Du Pont CEC 21-110B high-resolution double-focusing instrument. All reactions were conducted under nitrogen.

2-Amino-3,5,6-tricyanopyrazine (1). To a vigorously stirred solution of 10.0 g (0.0095 mol) of DISN and 10.0 g (0.093 mol) of DAMN in 200 ml of THF at 30° was added all at once 3.7 g (0.068 equiv) of sulfuric acid. The temperature rose immediately to 55° and a precipitate of $(NH_4)_2SO_4$ formed. The reaction mixture was stirred for 18 hr, filtered, and stripped to dryness, and the resulting solid was washed with ether to give 15.0 g (95.5%) of **1** as a yellow powder. Recrystallization from chloroform gave light-yel-

low needles: mp 225° dec; ir (KBr) 3420, 3340, 3230, 2240, 1630, 1550, and 1480 cm^{-1}; uv (CH_3CN) 207 nm (ϵ 17,000), 225 (11,300), 285 (21,300), 375 (6700); mass spectrum *m/e* 170.0338 (calcd *m/e* 170.0341).

Anal. Calcd for $C_7H_2N_6$: C, 49.41; H, 1.19, N, 49.40. Found: C, 49.48, 49.78; H, 1.49, 1.30; N, 49.20, 49.48.

Tetracyanopyrazine (2). A powdered mixture of 64.2 g (0.60 mol) of DISN and 64.8 g (0.60 mol) of DAMN was added in portions over 20 min to 900 ml of trifluoroacetic acid. The temperature rose from 27° to 48° during the addition. The resulting mixture was warmed to 70° and filtered to give 63.8 g (59%) of tetracyanopyrazine (as a white powder) after washing with 30 ml of CF_3CO_2H and 2 × 300 ml of water. Removal of the CF_3CO_2H from the filtrate gave, after washing with water, 26.9 g of a mixture of 1 and 2. Recrystallization of 2 from benzene gave white plates: mp 274–276°; ir (KBr) 2250, 1175, and 1158 cm^{-1}; uv (CH_3CN) 213 nm (ϵ 34,500), 253 (13,300), 295 (6900), 302 (7050), 313 sh (5500); mass spectrum *m/e* 180.0172 (calcd *m/e* 180.0184).

Anal. Calcd for C_8N_6: C, 53.33; N, 46.67. Found: C, 53.14; N, 46.80

Pyrazinetetracarboxamide (4). Tetracyanopyrazine (660 mg, 3.66 mmol) was stirred in 10 ml of concentrated H_2SO_4 for 3 days, then poured into ice water. The precipitated white tetramide, 4, was washed with water and acetone, collected, and dried, 920 mg (99%), mp 390–391° dec. Recrystallization of the product from water gave colorless prisms: mp 390–391° dec; ir (KBr) 3490, 3290, 3200, 1690, 1613, and 1595 cm^{-1}; uv (H_2O) 223 nm (ϵ 11,800), 282 (8250), 325 sh (890).

Anal. Calcd for $C_8H_8O_4N_6$: C, 38.10; H, 3.20; N, 33.30. Found: C, 37.83; H, 3.34; N, 33.40.

Pyrazinetetracarboxylic Acid (3). Pyrazinetetracarboxamide 4 was heated at reflux in 5 *N* sulfuric acid for 2 days, giving a 91.4% yield of pyrazinetetracarboxylic acid (3), mp 198–199° dec.[6]

The tetramethyl ester of 3 was prepared, mp 181.5–182.8° (lit.[8] mp 184°).

2,3-Diamino-5,6-dicyanopyrazine (5). To a solution of 70 g (0.66 mol) of DISN and 60 g (0.55 mol) of DAMN in 1500 of acetonitrile partially immersed in a water bath at 25° was added (all at once) 2.5 ml of concentrated sulfuric acid. The pot temperature rose immediately to 36° and a yellow precipitate formed. Over the next 30 sec the precipitate redissolved, the temperature rose to 44°, and crystals of 5 began to form. The reaction temperature dropped to 30° over 10 min, the solution was then stirred for 30 min and cooled to −10°, and the solid was collected by filtration and washed with a little CH_3CN to give 71 g of crude product. This solid was washed with 200 ml of water to remove $(NH_4)_2SO_4$, rinsed with CH_3CN, and dried in a vacuum oven at 100° to give 63 g (71%) of 5 as a light tan powder. Recrystallization from acetonitrile gave white plates: mp 332° dec; ir (KBr) 3460, 3400, 3320, 3160, 2230, 1675, 1630, 1560, 1520, and 1505 cm^{-1}; uv (CH_3CN) 227 nm (ϵ 25,050), 317 (17,450); mass spectrum *m/e* 160.0502 (calcd *m/e* 160.0497).

Anal. Calcd for $C_6H_4N_6$: C, 45.00; H, 2.52; N, 52.48. Found: C, 45.06; H, 2.32; N, 52.35.

5,6-Dicyano[1,2,5]thiadiazolo[3,4-*b*]pyrazine (6). A solution of 16.0 g (0.10 mol) of 5 and 21.6 ml (0.328 mol) of $SOCl_2$ in 500 ml of CH_3CN was heated at gentle reflux for 22 hr. The resulting orange solution was evaporated at reduced pressure, leaving 18.7 g of crude 6 which was recrystallized from CH_3CN, 16.8 g (89.5%), as yellow prisms: mp 268° dec: ir (KBr) 2235, 1520, 900–800 cm^{-1}; uv (CH_3CN) 213 nm (ϵ 24,900), 335 (18,500), 342 (20,200), 348 (21,800).

Anal. Calcd for C_6N_6S: C, 38.29; N, 44.66. Found: C, 38.26; N, 44.80.

3,6-Diamino-2,5,6-tricyano-1,4-diaza-1,3,5-hexatriene (7). To a 3-l., three-necked flask equipped with a condenser, mechanical stirrer, and addition funnel was added 6.0 g (5.55 mmol) of DAMN and 2.0 ml of *N,N*-dimethylaniline in 400 ml of acetonitrile. The solution was brought to reflux under nitrogen with stirring and dropwise addition of 300 ml of an acetonitrile solution containing 8.0 g (7.5 mmol) of DISN was begun. The addition required 2.25 hr. After refluxing overnight 50 g of SilicAR was added and the slurry was evaporated to dryness. The dry solid was washed repeatedly with diethyl ether, which removed 5.75 g (55%) of tan solid. Recrystallization from acetonitrile gave 7 as yellow crystals: mp 204° dec; ir (KBr) 3460, 3320, 3260, 2240, 2200, 1650, 1620, 1605, 1590, 1560 cm^{-1}; uv (CH_3CN) 295 nm (ϵ 13,400), 385 (12,800); nmr (DMSO-d_6) δ 6.55 (broad singlet, 2 H), 7.30 (broad singlet, 2 H), 13.85 (singlet, 1 H); mass spectrum *m/e* 187.0610 (calcd *m/e* 187.0606).

Anal. Calcd for $C_7H_5N_7$: C, 44.92; H, 2.69; N, 52.39. Found: C, 44.97; H, 2.60; N, 52.10.

2,3-Diamino-5,6-dicyanopyrazine (5) *via* Cyclization of 7. A solution of 5.75 g (3.1 mmol) of 7 and 2 ml of triethylamine in 300 ml of acetonitrile was refluxed for 20 hr. SilicAR (50 g) was added and the solution was evaporated to dryness. The dry solid was washed repeatedly with diethyl ether, which removed 1.73 g (35%) of 5, identified by its infrared spectrum.

Aminotricyanopyrazine (1) from the Acid-Catalyzed Cyclization of 3,6-Diamino-2,5,6-tricyano-1,4-diaza-1,3,5-hexatriene (7). The water of hydration was removed from 0.505 g (2.66 mmol) of *p*-toluenesulfonic acid monohydrate by azeotropic distillation in 3 ml of benzene. The dry benzene solution was diluted with 10 ml of anhydrous tetrahydrofuran and 0.500 g (2.66 mmol) of 7 was added. After stirring at room temperature for 45 min the slurry was filtered and the collected solid was washed with tetrahydrofuran and dried, yielding 0.50 g (2.64 mmol) of the ammonium salt of *p*-toluenesulfonic acid. Evaporation of the filtrate to dryness gave the theoretical amount of 1, identified by its infrared spectrum.

1,4,5,8-Tetraamino-1,2,7,8-tetracyano-3,6-diazaoctatetraene (8). A solution containing 5.0 g of DISN, 5.0 g of DAMN, and 10 ml of glacial acetric acid in 100 ml of tetrahydrofuran was stirred at room temperature for 18 hr. Removal of the solvent and collection of the resulting product with an ether rinse gave a dark powder. This material was slurried with 500 ml of acetonitrile and filtered to give 4.35 g (69.5%) of crude 8. Tetraamine 8 is very insoluble in most organic solvents and can be recrystallized only with considerable product loss by dissolution in dimethylformamide, treatment with Darco, and reprecipitation with water to give a yellow-brown powder: mp 249° dec; ir (KBr) 3410, 3305, 3175, 2250, 2200, 1610, 1510 cm^{-1}; uv (CH_3CN) 235 nm (ϵ 10,450), 292 (13,200), 362 (21,800); mass spectrum *m/e* 268; *m/e* for $M^+ - HCN$ 241.0825 (calcd *m/e* for $C_9H_7N_9$ 241.0825).

Anal. Calcd for $C_{10}H_8N_{10}$: C, 44.77; H, 3.00; N, 52.22. Found: C, 45.22; H, 3.15; N, 52.07.

Reaction of DAMN with Oxalyl Cyanide. To a stirred solution of 40.0 g (0.376 mol) of DISN in 600 ml of THF under N_2 was added dropwise at room temperature (1.5-hr addition) a solution of 152 g (0.80 mol) of *p*-toluenesulfonic acid monohydrate in 500 ml of THF. Stirring at room temperature was continued for 2 hr. The precipitated ammonium tosylate was then removed by filtering the solution under N_2 into another flask. To the orange-colored filtrate was added 20 g (0.185 mol) of powdered DAMN (15 min) followed by stirring at 50° for 3 days. The solution was filtered (removing additional $^+NH_4OTs^-$) and preabsorbed on 150 g of SilicAR CC7 which was subsequently chromatographed on another 300 g of SilicAR. Elution with benzene removed crude tetracyanopyrazine, which was recrystallized twice from benzene, giving 8.47 g (25.4%) of white leaflets, mp 274–276. Elution with $CHCl_3$ gave a dark, viscous oil which solidified on standing overnight and was recrystallized from benzene, affording 1.62 g (5.1%) of hydroxytricyanopyrazine (11) as tan prisms, mp 165–168°. Ether removed the known dioxopyrazine **10**, which was recrystallized from water, yielding 10.28 g (34.2%) of white needles, mp 278° (lit.[5] mp 270° dec). Spectral data of 11 follow: ir (KBr) 3160, 2260, 1690, 1560, and 1545 cm^{-1}; uv (CH_3CN) 206 nm (ϵ 17,900), 257 (9850), 300 (5200), 328 (7400), 385 (1760); mass spectrum *m/e* 171.0170 (calcd *m/e* 171.0181).

Anal. Calcd for C_7HON_5: C, 49.12; H, 0.59; N, 40.93. Found: C, 48.91; H, 0.60; N, 41.41.

Reaction of DAMN with α-Iminooxalyl Cyanide. To a stirred solution of 21.2 g (0.20 mol) of DISN in 400 ml of CH_3CN–ether (50:50) under N_2 was added dropwise at room temperature (1-hr addition) a solution of 37.0 g (0.20 mol) of *p*-toluenesulfonic acid monohydrate in 400 ml of CH_3CN–ether (50:50). Stirring at room temperature was continued for an additional 1 hr and the reaction mixture was filtered under N_2 into another flask. Powdered DAMN (10.8 g, 0.10 mol) was added to the filtrate (10 min) and this solution was stirred at 50° for 3 days, filtered, preabsorbed on 100 g of SilicAR CC7, and chromatographed. Elution with $CHCl_3$ removed 1, which has recrystallized from $CHCl_3$, giving 5.36 g (31.5%) of light-yellow needles, mp 225° dec. Elution with CH_3CN gave an orange solid which was recrystallized from acetone, yielding 12 as pale-yellow needles: 3.58 g (22.2%); mp 300° dec; ir (KBr) 3430, 3340, 2780, 2270, 1685, 1625, 1595, and 1530 cm^{-1}; uv (CH_3CN) 225 nm (ϵ 14,400), 313 (16,600), 324 (17,500), 338 (10,700); mass spectrum *m/e* 160.0330 (calcd *m/e* 160.0338).

Anal. Calcd for $C_6H_3ON_5$: C, 44.72; H, 1.88; N, 43.47. Found: C, 44.66; H, 1.93; N, 43.75.

Registry No.—**1**, 33420-45-0; **2**, 33420-37-0; **3**, 43193-60-8; **4**, 22051-80-5; **5**, 36023-58-2; **6**, 50921-36-3; **7**, 36023-60-6; **8**, 36023-59-3; **9**, 36086-83-6; **11**, 36023-63-9; **12**, 36023-62-8; **13**, 41245-87-8; DISN, 28321-79-1; DAMN, 1187-42-4.

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Synthesis of Adamantane Derivatives. XXV.[1] Synthesis and Reactions of 1- and 2-Adamantyl Isocyanides

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1- (**4**) and 2-adamantyl isocyanide (**11**) were prepared by the reactions of the corresponding amines with dichlorocarbene using a phase-transfer method and/or by dehydration of *N*-1-adamantylformamide. **4** was very stable in the atmosphere while **11** was converted rapidly to *N*-2-adamantylformamide (**13**) by the atmospheric moisture. Some simple derivatives of **4** and **11** such as 1-(1-adamantyl)- (**5**) and 1-(2-adamantyl)tetrazole (**12**), 1-(1-adamantyl)-2,4-dithioxo-1,2,3,4-tetrahydrotriazine (**6**), and *N*-adamantyl-*N'*-pentamethyleneformamidine (**7**) were prepared. Thermal rearrangements of **4** and **11** to the corresponding nitriles **8** and **14** were compared with that of *tert*-butyl isocyanide. The relative rate of the rearrangement for gas phase at 200° was 1.0:0.22:0.24 for *t*-BuNC, **4**, and **11**. The rate of the rearrangement of **4** in diglyme at 200° was 11 times faster than that of **11** and the formation of considerable amounts of adamantane was observed.

Adamantyl isocyanides have not been described in the extensive literature on adamantane chemistry.[2,3] This paper describes the facile preparation of 1- and 2-adamantyl isocyanides and some of their fundamental chemical and thermal behaviors.

Results and Discussion

Preparation and Properties of 1- and 2-Adamantyl Isocyanides. 1-Adamantyl isocyanide (**4**) was prepared in 61% yield by dehydration with triphenylphosphine–carbon tetrachloride–triethylamine[4] of *N*-1-adamantylformamide (**2**), which was obtained by the Ritter reaction on 1-adamantanecarboxylic acid (**1b**)[5] or 1-adamantyl bromide (**1a**), and/or by heating **1a** in formamide. It was also prepared by the Hofmann carbylamine reaction of 1-adamantanamine (**3**) in 40% yield by using a 3-molar excess of dichlorocarbene, which was generated from $CHCl_3$ and *t*-BuOK in *n*-hexane.[6] The yield of **4** was improved up to 54% in the carbylamine reaction by using benzyltriethylammonium chloride, a phase-transfer catalyst.[7,8] 1-Adamantyl isocyanide (**4**) formed colorless crystals, mp 185–186°, and had no foul odor but a rather fragrant one. The structure was indicated by ir (KBr) absorption at 2150 cm^{-1} ($\nu_{N\equiv C}$), mass spectral ion peaks at *m/e* (rel intensity) 161 (M^+, 5), 135 (95), and 41 (100), and nmr ($CDCl_3$) signals at δ 3.30–1.85 (broad s, 9 H) and 1.80–1.56 (unsymmetrical s, 6 H).

2-Adamantyl isocyanide (**11**) was prepared by the carbylamine reaction of 2-adamantanamine (**10**). *N*-2-Adamantylformamide (**13**) was not chosen as the starting material because it was not obtained by the conventional formylation of **10** with formic acid. The yield of **11** in the carbylamine reaction was raised from 40% to 76% by application of the phase-transfer technique[7] (50% aqueous KOH–C_6H_6–benzyltriethylammonium chloride). Colorless crystals of **11** were obtained, mp 186–188°, having a similar odor to **4** and ir (KBr) absorption at 2140 cm^{-1} ($\nu_{N\equiv C}$), mass spectral ion peaks at *m/e* (rel intensity) 161 (M^+, 34), 135 (94), and 106 (100), and nmr ($CDCl_3$) signals at δ 3.41 (broad s, 1 H) and 2.35–1.30 (m, 14 H).

The 1 isomer **4** was very stable and was largely recovered even after stirring in $CHCl_3$–H_2O in the presence of a catalytic amount of sulfuric acid for 3 days at room temperature. In contrast the 2 isomer **11** was very sensitive to atmospheric moisture and was converted rapidly to formamide **13**.

Both **4** and **11** afforded the corresponding 1-substituted tetrazole derivatives **5** and **12** in 92 and 54% yields, re-

Scheme I

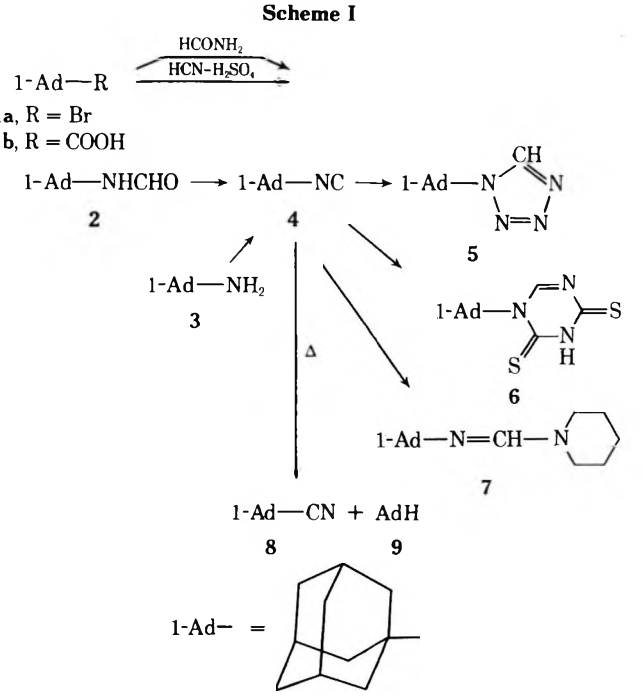


Table I
Thermal Rearrangement Products of 4 and 11 at 200°

Isocyanide	Solvent	Reaction time, hr	Recovered isocyanide, %[a]	Product, %[a] Nitrile	Adamantane	Others[b]
4	None[c]	4.0	61	35	Trace	4
4	Diglyme	1.5	4	56	40	Trace
11	None[c]	4.0	40	28	1	31[d]
11	Diglyme	2.0	70	20	8	2
t-BuNC[e]	None[c]	1.5	55	45		

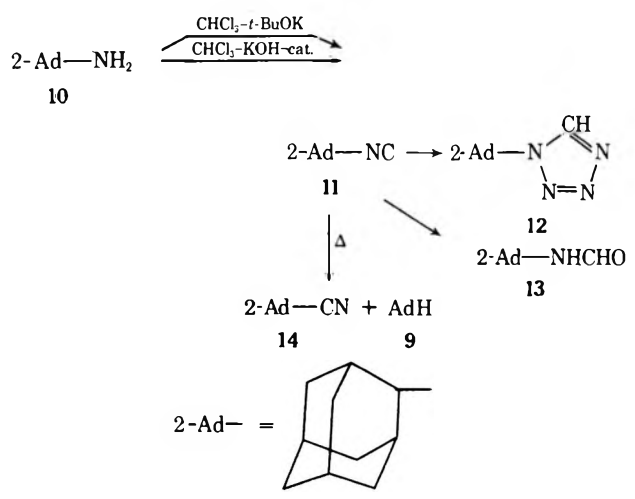
[a] Glpc analysis. [b] Unidentified. [c] In a sealed tube at *ca.* 30 mm. [d] This was largely adamantan-2-one and decreased to 4–6% in argon atmosphere. [e] *Cf.* ref 13.

Table II
First-Order Rate Constants of Thermal Rearrangement of 4, 11, and *t*-BuNC

Isocyanide	Solvent	Temp, °C[c]	$k_1 \times 10^5$, sec^{-1}	k_1^{rel} at 200°	E_a, kcal/mol	Log *A*	ΔS^*, eu/mol
t-BuNC[a]	None[b]	200	11.2	1.0	32.0	10.83	−9.9
		180	2.50				
4	None[b]	200	2.42	0.22	26.8	7.766	−23.9
		180	0.695				
	Diglyme	200	50.6	4.52	17.3	4.697	−38.0
		180	22.5				
		170	16.4				
11	None[b]	200	2.68[d]	0.24			
	Diglyme	200	4.60	0.41			

[a] *Cf.* ref 13. [b] In a sealed tube at *ca.* 30 mm. [c] Temperature accuracy and constancy were within ±0.7°. [d] An approximate value because of extensive side reactions.

Scheme II



spectively, on treatment with hydrazoic acid in dry chloroform.[9] The 2,4-dithioxo-1,2,3,4-tetrahydrotriazine derivative 6 was obtained in 85% yield on treatment of 4 with thiocyanic acid, and 4 was converted to *N*-1-adamantyl-*N'*-pentamethyleneformamidine (7) in 30% yield by refluxing with piperidine in the presence of cuprous chloride.[10] These conversions are summarized in Schemes I and II.

Thermal Rearrangement of 4 and 11. Although the thermal rearrangement of isocyanides to cyanides has long been known, only relatively recently was the reaction shown to proceed *via* a true unimolecular process with the stereochemical integrity maintained at the migrating carbon atom.[11-13] The rearrangement has also been studied theoretically by the "extended Hückel"[14] and the MINDO/2 methods[15] for methyl isocyanide. The first method suggests that the reaction path for a methyl group is an approximate semicircle around the center of the CN bond, with the CN bond lengthening and the methyl group flattening as it shifts, always keeping the same face toward CN. The second method predicts that the rearrangement involves a stable triangular intermediate with the properties of a π complex rather than an ion pair. The relative rates of the rearrangement of methyl, ethyl, isopropyl, isobutyl, and *tert*-butyl isocyanides are shown to be 5.6:7.8:2.6:2.6:1.0 by Casanova, *et al.*[13] This sequence is in accordance with that expected for an entropy-controlled rather than for an enthalpy-controlled reaction, except for the methyl substituent. In view of the above features of the isocyanide–cyanide rearrangement, it would be of interest to compare the thermal behavior of 4 and 11 with those of simple alkyl isocyanides.

The rearrangement of 4 proceeded smoothly on heating at 200° under reduced pressure (*ca.* 30 mm), affording the nitrile 8.[16] However, that of 11 to nitrile 14[17] was contaminated with considerable amounts of adamantan-2-one as a by-product.[18] In diglyme, considerable amounts of adamantane were produced as a by-product from both 4 and 11. However, no trace of protoadamantane and 4-protoadamantene[2a] was produced from 11. These data are summarized in Table I. The rearrangement was followed by glpc periodically at 200 and 180°, and the observed rate constants for 4, 11, and *t*-BuNC[19] are summarized in Table II. From an Arrhenius plot of log *k* *vs.* $1/T$, activation parameters for the rearrangement were calculated and the results are shown also in Table II.

The fact that 4 rearranges slower than *t*-BuNC might imply that the reaction is actually entropy controlled, as postulated by Casanova, *et al.*,[13] which is supported by the larger negative entropy of activation for 4 than for *t*-BuNC. Furthermore, the only slightly faster rearrangement of *t*-BuNC compared to 4 contrasts with the 10^3 faster solvolysis rate of *tert*-butyl than of 1-adamantyl derivatives, in which the relative reactivity is dependent on the ready formation of cations.[20] Therefore, the isocyanide–cyanide rearrangement should be regarded as a process proceeding *via* an almost neutral intermediate; *i.e.*, the charge separation developed at the transition state should be negligible. The observed somewhat higher reactivity of 11 than 4 is in accordance with the reactivity sequence reported for a series of alkyl isocyanides,[13] though the rate constant for 11 should be regarded as a very approximate value because of the considerable side reactions. The results in diglyme are of interest because a con-

siderable rate enhancement as well as the formation of a considerable amount of adamantane was observed; these results are quite different from those reported for aromatic isocyanide.[13] The large negative value of ΔS^* suggests a strong solvation at the transition state. Furthermore, **4** rearranges 11 times faster than **11**. These facts indicate that the reaction proceeding *via* an ion-pair or a cationic intermediate is involved in a polar solvent such as diglyme. The formation of adamantane might be explained by an initial formation of adamantyl cation followed by hydride abstraction from the solvent or the substrate.

Experimental Section[21]

***N*-1-Adamantylformamide (2). A.** A powdered mixture of 1-adamantyl bromide (**1a**, 1.43 g, 20 mmol) and sodium cyanide (6.5 g, 0.13 mol) was added to a stirred sulfuric acid (95%) (100 ml) at room temperature in 2 hr (*Caution!* the reaction should be carried out under a good hood). After stirring was continued for 2 days at room temperature, the mixture was poured onto crushed ice (0.5 kg), neutralized with 20% sodium hydroxide, and extracted with methylene chloride (5 × 80 ml). The combined extracts were dried (Na_2SO_4) and evaporated to give crude **2**, which was recrystallized from *n*-hexane–CH_2Cl_2 to afford **2** (2.68 g, 75%), mp 140–141° (lit.[4] mp 139–140°).

B. A mixture of **1a** (3.0 g, 13.1 mmol) in formamide (11.4 g, 253 mmol) was refluxed for 15 hr. The cooled solution was diluted with chloroform (50 ml)–water (50 ml). The organic layer was separated, washed with water (4 × 50 ml), and dried (Na_2SO_4). Removal of the solvent and recrystallization of the residue gave **2** (1.54 g, 62%).

1-Adamantyl Isocyanide (4). A. From 2. A mixture of **2** (0.90 g, 5.9 mmol), triphenylphosphine (1.57 g, 6.0 mmol), carbon tetrachloride (0.77 g, 5.0 mmol), and triethylamine (0.55 g, 5.0 mmol) in chloroform (10 ml) was heated at 60° for 3 hr. After removal of the solvent, the residue was chromatographed on a silica gel column eluting with methylene chloride. The isocyanide **4** was obtained from the first fraction and was recrystallized from light petroleum (bp 40–60°) to give analytically pure **4** (0.59 g, 61%), mp 179–180° (sealed tube).

Anal. Calcd for $C_{11}H_{15}N$: C, 81.93; H, 9.38; N, 8.69. Found: C, 81.67; H, 9.51; N, 8.90.

B. From 1-Adamantanamine (3). A mixture of **3** (150 mg, 1.0 mmol), benzyltriethylammonium chloride (20 mg), and benzene (8 ml) in 50% aqueous potassium hydroxide (9 ml) was stirred vigorously for 30 min at room temperature, and to the resulting emulsion chloroform (179 mg, 1.5 mmol) in benzene (3 ml) was added in 15 min under ice cooling. After stirring was continued for 1 hr under ice cooling and for 4 hr at room temperature, the mixture was diluted with water (10 ml) and the organic layer was separated. The water layer was extracted with benzene (20 ml) and the organic layer was combined with the benzene extracts, washed with water (3 × 10 ml), and dried (Na_2SO_4). Removal of the solvent and sublimation of the residue at 80° (30 mm) afforded the isocyanide **4** (87 mg, 54%). The reaction of **3** with dichlorocarbene (3-molar excess) generated from $CHCl_3$–*t*-BuOK in *n*-hexane gave **4** in 40% yield.

1-(1-Adamantyl)tetrazole (5). To an anhydrous hydrazoic acid solution prepared from sodium azide (1.8 g, 27 mmol), water (1 ml), sulfuric acid (1.32 g, 13.5 mmol), and chloroform (20 ml, dried over Na_2SO_4)[22] was added **4** (0.5 g, 31 mmol). The resulting solution was warmed at 40° for 1 day and the excess hydrazoic acid and the solvent were removed to afford a solid residue (632 mg) which was washed with ether to give pure tetrazole **5** (589 mg, 91%): mp 123–126° (sealed tube); ir (KBr) 3140, 3120, 2920, 2850, 1455, 1345, 1185, and 1105 cm^{-1}; uv (EtOH) λ_{max} 274 nm (ϵ 3) as a shoulder; nmr ($CDCl_3$) δ 8.60 (s, 1 H), 2.40–2.10 (s, 9 H), and 1.90–1.65 (s, 6 H); mass spectrum *m/e* (rel intensity) 204 (M^+, 53), 179 (57), 149 (51), and 135 (100).

Treatment of **4** with hydrazoic acid in ether in the presence of a catalytic amount of sulfuric acid according to the Zimmerman and Olofson procedure[9] afforded crystalline compounds, mp 134–137 and/or 175–178° dec depending on the reaction conditions, both in 90% yield. These as yet unidentified compounds seem to be dimeric.

1-(1-Adamantyl)-2,4-dithioxo-1,2,3,4-tetrahydrotriazine (6). To a stirred mixture of **4** (161 mg, 1.0 mmol), potassium thiocyanate (292 mg, 3.0 mmol), ether (5 ml), and water (3 ml) was added potassium hydrogen sulfate (409 mg, 3.0 mmol) in water (3 ml) under ice–salt bath cooling. After stirring for 30 min, the mixture was diluted with water (100 ml) and extracted with chloroform (4 × 20 ml). The combined extracts were dried (Na_2SO_4) and evaporated to afford yellowish crystals (295 mg), which were recrystallized from MeOH–C_6H_6 to give **6** as faintly yellowish needles (237 mg, 85%): mp 184–187° dec; ir (KBr) 3200, 1600, and 1105 cm^{-1}.

Anal. Calcd for $C_{13}H_{17}N_3S_2$: C, 55.90; H, 6.14; N, 15.05. Found: C, 55.97; H, 6.11; N, 15.01.

***N*-1-Adamantyl-*N'*-pentamethyleneformamidine (7).** A mixture of **4** (161 mg, 1.0 mmol) and cuprous chloride (15 mg, 0.15 mmol) in piperidine (1.0 ml, 10 mmol) was refluxed for 4 hr. After removal of the excess piperidine by distillation, methylene chloride (5 ml) was added and an insoluble material was removed by filtration. The filtrate was chromatographed on a silica gel column, eluting with chloroform to afford **7** (74 mg, 30%) after recrystallization from *n*-hexane: mp 104–107°; ir (KBr) 1655 cm^{-1} (C=N); nmr ($CDCl_3$) δ 3.80 (s, 1 H) and 2.75–1.90 (m, 25 H); mass spectrum *m/e* (rel intensity) 246 (M^+, 95), 245 (M − 1, 100), 189 (80), 179 (90), 162 (40), 135 (60), and 111 (40).

Anal. Calcd for $C_{16}H_{26}N_2$: C, 77.99; H, 10.64; N, 11.37. Found: C, 77.91; H, 10.85; N, 11.24.

In the above reaction, when the reaction mixture stood for 2 days at room temperature, a cuprous chloride complex, mp 235–237°, was obtained as an insoluble portion in methylene chloride. Its structure was not clarified.

2-Adamantanamine (10). Adamantanone oxime (2.5 g, 15 mmol) was reduced with lithium aluminum hydride (2.5 g, 66 mmol) in tetrahydrofuran (50 ml) by refluxing for 2 days. The usual work-up and recrystallization from *n*-hexane–CH_2Cl_2 afforded amine **10** as colorless crystals (1.84 g, 81%): mp 100–103;[23] ir (KBr) 3320 (NH), 1620, 1550, and 1460 cm^{-1}; nmr ($CDCl_3$) δ 3.0 (s, 1 H), 2.6–2.3 (s, 2 H), and 2.2–1.35 (broad s, 14 H).

Anal. Calcd for $C_{10}H_{17}N$: C, 79.40; H, 11.34; N, 9.26. Found: C, 79.45; H, 11.01; N, 9.54.

2-Adamantyl Isocyanide (11). A. A mixture of **10** (100 mg, 0.66 mmol), benzyltriethylammonium chloride (10 mg), benzene (5 ml), and 50% aqueous potassium hydroxide (8 ml) was vigorously stirred for 30 min at 30°. To the resulting emulsified mixture was added chloroform (80 mg, 0.67 mmol) in benzene (3 ml) under ice cooling in 1 hr, and the stirring was continued for 2 hr at the same temperature and for a further 2 hr at 30°. The benzene layer was separated, washed with water, dried (Na_2SO_4), and evaporated to give crude isocyanide **11**, which was purified by sublimation at 80° (30 mm) to afford pure **11** (81 mg, 76%), mp 178–180° (sealed tube).

Anal. Calcd for $C_{11}H_{15}N$: C, 81.93; H, 9.38; N, 8.69. Found: C, 82.20; H, 9.41; N, 8.70.

B. To an ice-cooled and stirred mixture **10** (302 mg, 2.0 mmol) and potassium *tert*-butoxide (1.12 g, 10 mmol) in *n*-hexane (10 ml) was added chloroform (1.0 g, 8.3 mmol) during 1 hr under nitrogen, and stirring was continued for 2 hr at the same temperature and for 1 hr at 25°. The organic layer was separated after dilution of the mixture with water, washed with water, and dried (Na_2SO_4). Removal of the solvent gave crude isocyanide **11** (200 mg), which was purified on a silica gel column, eluting with methylene chloride, followed by sublimation to give pure **11** (113 mg, 35%).

1-(2-Adamantyl)tetrazole (12). **11** (161 mg, 1.0 mmol) was treated with a chloroform solution of hydrazoic acid prepared from sodium azide (0.6 g, 9 mmol) as above. The crude product was purified by preparative tlc (silica gel, $CHCl_3$) to afford tetrazole **12** (110 mg, 54%) as colorless crystals: mp 130–135°; ir (KBr) 3080, 1475, 1455, and 1100 cm^{-1}; nmr ($CDCl_3$) δ 8.70 (s, 1 H), 4.60 (broad s, 1 H), 2.9–2.5 (broad s, 2 H), and 2.4–1.6 (m, 12 H); mass spectrum *m/e* (rel intensity) 204 (M^+, 10), 190 (14), 179 (8.6), 178 (26), 149 (13), and 135 (100).

***N*-2-Adamantylformamide (13).** On standing in the atmosphere at room temperature, **11** was converted almost quantitatively to the formamide **13**: mp 164–166°; ir (KBr) 3320, 1660, and 1540 cm^{-1}; nmr ($CDCl_3$) δ 7.0–6.6 (broad s, 1 H), 5.95 (s, 1 H), 4.15 (broad d, J = 7.5 Hz, 1 H), and 2.2–1.6 (m, 14 H); mass spectrum *m/e* (rel intensity) 179 (M^+, 98), 135 (100), 94 (99), and 80 (80).

Anal. Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.92; H, 9.66; N, 7.54.

Kinetic Measurement. Samples of isocyanides (*ca.* 2 mg) were transferred into glass tubes (50 × 6 mm i.d.) and sealed under *ca.* 30 mm. The sealed samples were heated at 200 ± 0.7 or 180 ± 0.7° as described in Table II, removed at intervals of time, and quenched in a water bath. The samples were analyzed after dilution with 0.3 ml of acetone on a 1-m Silicone SE-30 and/or Apie-

zon grease L column. For kinetic runs in diglyme, samples of isocyanides (15 mg) were dissolved in freshly purified diglyme (0.5 ml), heated in a sealed tube, and analyzed at intervals directly by glpc. The peak area factors were calculated according to the chromatographic results of known authentic mixtures of the cyanide and isocyanide. The rate constants were calculated as ln [area (RNC) + area (RCN)]/area (RNC) = kt. For the case of the formation of adamantane the area of RCN was corrected by summing the area of adamantane. The results are shown in Table II.

Registry No.—**1a**, 768-90-1; **2**, 3405-48-9; **3**, 768-94-5; **4**, 22110-53-8; **5**, 50987-38-7; **6**, 50987-39-8; **7**, 50987-40-1; **10**, 13074-39-0; **11**, 50987-41-2; **12**, 50987-42-3; **13**, 24161-71-5; adamantanone oxime, 4500-12-3.

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Vilsmeier–Haack Cyclizations. Synthesis of 2-Substituted 3-Dimethylamino-5,6-methylenedioxyindenes and the Corresponding Indanones

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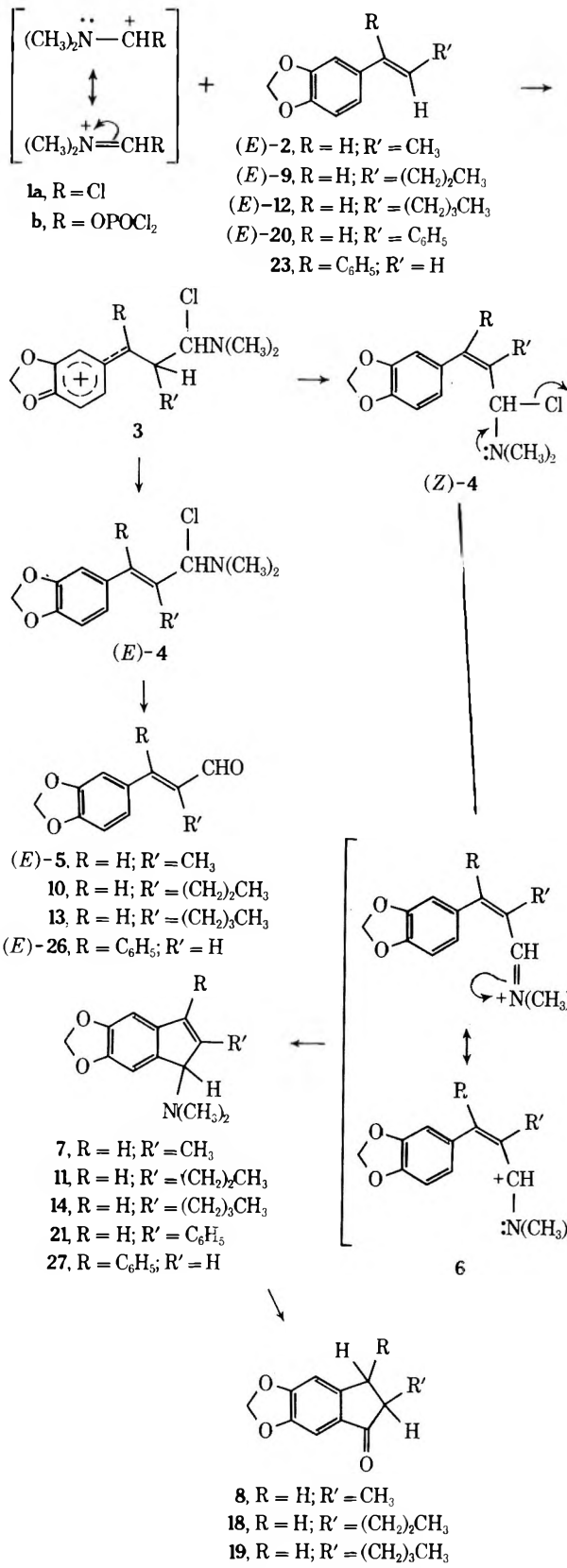
In the presence of the Vilsmeier–Haack reagent, suitably activated styrene analogs afford previously unreported 2-substituted 3-dimethylamino-5,6-methylenedioxyindenes. The indenes were hydrolyzed to the corresponding indanones. This constitutes a new synthesis of indanones. Cinnamaldehydes are also obtained under Vilsmeier–Haack conditions. Reaction conditions and electronic and other structural requirements which govern the formation of cinnamaldehydes and aminoindenes are discussed. Selected cinnamaldehydes were shown to have the *E* configuration by X-ray crystallography. Aminoindenes result from cyclization of Vilsmeier–Haack intermediates (**4**) having the *Z* configuration while aldehydes result from Vilsmeier–Haack intermediates (**4**) having the *E* configuration.

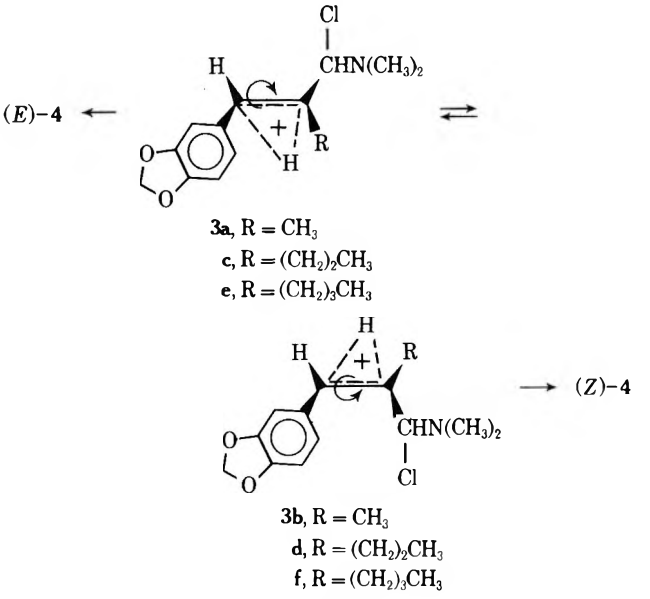
Formylation of π-excessive heteroaromatic and activated benzenoid compounds under Vilsmeier–Haack conditions[2] [$POCl_3$, $(CH_3)_2NCHO$] affords aldehydes.[3-13] Formylation of styrenes affords cinnamaldehydes.[13-15] Definitive studies indicate that the electrophile is **1a**[16] rather than **1b**.[15] Thus, (*E*)-1-(3,4-methylenedioxyphenyl)-prop-1-ene[17] (**2**) gives **3** (R = H; R′ = CH_3), which should lose a proton and provide varying quantities of intermediates (*E*)-**4** (R = H; R′ = CH_3) and (*Z*)-**4** (R = H; R′ = CH_3). Hydrolysis of these should yield (*E*)-**5** and (*Z*)-**5**. However, the product appears to be stereochemically homogeneous.[15] Nevertheless, analogs of (*Z*)-**4** suitably activated toward electrophilic aromatic substitution may be expected to undergo cyclization *via* **6** formed by anchimerically assisted dissociation of chloride. If sufficiently general, this would represent a facile synthesis for the previously unreported 3-dimethylamino-1-indene system (**7**). This, in turn, would serve as precursor for 2-substituted 1-indanones such as **8**, since treatment of **7** with aqueous hydroxide would isomerize the allylamine double bond and would effect hydrolysis of the resulting enamine.[18]

In this report we describe Vilsmeier–Haack cyclizations leading to aminoindenes (*cf.* **7**) which undergo hydrolysis to indanones (*cf.* **8**) which are desired as intermediates for the synthesis of potential prostaglandin analogs.

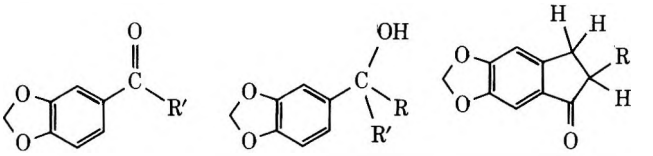


Results and Discussion

Schmidle and Barnett[15] obtained **5** in 27% yield by adding **2** to the cooled (20°) Vilsmeier-Haack reagent, warming to 55°, maintaining the temperature during the exothermic reaction, and finally heating at 75–80° for 1 hr (method I). The *E* configuration was assigned to **5**.[15] Under these conditions we isolated **5** in 48% yield. No aminoindene (**7**) was detected. The *E* configuration for **5** was substantiated by X-ray crystallography. However, when the reagent-olefin mixture was immediately heated on a steam bath for 3 hr (method II), **2** afforded 47% of **7** and 23% of (*E*)-**5**. The remainder of the reaction mixture contained starting olefin. The application of first principles of conformational analysis to the formation of (*E*)-**4** and (*Z*)-**4** from **3** (R = H; R′ = CH_3) provides an explanation for the change in steric course of the reaction leading to (*E*)-**4** at lower temperatures and to a mixture of (*E*)-**4** and (*Z*)-**4** at higher temperatures. Thus, at lower temperatures, minimization of nonbonded repulsions in **3** requires that product (**4**) develop mainly from **3a** (Ar/Me), the thermodynamically more stable intermediate, to give (*E*)-**4** rather than from **3b** (Ar/ClCHNMe$_2$) which leads to (*Z*)-**4**.[19,20] At higher temperatures the relative population of **3b** increases at the expense of **3a** and the product (**4**) contains more (*Z*)-**4** than at lower temperatures. In line with this, method I yields 48% of aldehyde **10** but no indene **11** from olefin (*E*)-**9** while method II affords 71 and 70% of indenes **11** and **14** but, in contrast to treatment of **2** at elevated temperatures, no aldehydes **10** and **13** from olefins (*E*)-**9** and (*E*)-**12**. Thus, the steric bulk of the *n*-propyl and *n*-butyl groups (**3c–f**) reinforces the thermal effects by increasing the relative populations of **3d** and **3f** relative to **3c** and **3e**, lowers the yield of aldehyde precursor [*cf.* (*E*)-**4**], and increases the yield of indene precursor [*cf.* (*Z*)-**4**] relative to that obtained from **2**.

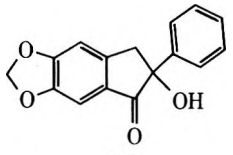


Starting olefin [(*E*)-**9**] was prepared in 95% yield by dehydration of **16**, which was obtained in 66% yield by treatment of **15** with *n*-butyllithium. The homolog [(*E*)-**12**] was prepared by dehydration of **17** obtained by treatment of **15** with *n*-pentylmagnesium bromide. Vinyl proton coupling of 15.5 Hz established the *E* stereochemistry of **2**, **9**, and **12**. The aminoindenes (**7**, **11**, **14**) were characterized by conversion to the respective indanones (**8**, **18**, **19**). The nmr spectra (Table I, Experimental Section) are in agreement with the assigned structures. Additional evidence for the structural assignment was obtained from the nmr spectra of the hydrochloride salts of the aminoindenes (**7**,



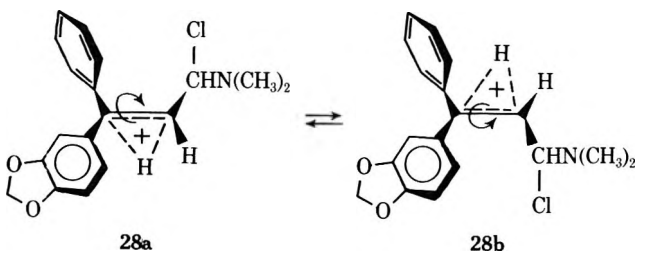
11, 14) (Table II, Experimental Section). Integration of the complex proton resonance multiplets between δ 3.0 and 0.5 ppm accounted for the alkyl and dimethylamino substituents at positions 2 and 3 for each compound. No signals were observed downfield to the aromatic proton resonances H_4 and H_7. The broad singlets observed at different δ values for H_1 and H_3 define the position of the indene double bond.

To further investigate the scope of these cyclizations, (*E*)-**20**[21,22] was subjected to conditions of method II. The indene **21** was obtained in 16% yield, although the yield could be increased to 25% if (*E*)-**20** was added directly to the previously heated (steam bath) Vilsmeier-Haack reagent. Recovery of starting olefin averaged 70%. The indene **21** was characterized by its nmr spectrum (Table II, Experimental Section). The hydrochloride salts of indenes **7**, **11**, and **14** afforded indanones **8**, **18** and **19**. **21** as the free base afforded 2-hydroxyindan-1-one **22** which like-



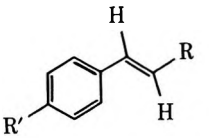
22

ly results from both hydrolysis and air oxidation in the alkaline medium.[23] This compound was identified by its nmr and mass spectra (Experimental Section). Unlike ketones **8**, **18**, and **19**, **22** did not form a 2,4-dinitrophenylhydrazone.[24] Both hydrogen-bonded[25] OH stretching (3435 cm^{-1}) and C=O stretching (1685 cm^{-1}) were observed in the infrared spectrum (mull). In contrast to the behavior of **20**, **23** prepared by dehydration of **24** obtained by treatment of **25** with phenylmagnesium bromide afforded a 70% yield of aldehyde **26** but no aminoindene **27**. The *E* geometry for **26** was established by X-ray crystallography. The crystal conformation of **26** provides an explanation for the steric course of this reaction. Since there is a greater propensity for resonance interaction between the methylenedioxyphenyl ring system and the α,β-unsaturated aldehyde moiety, these groups are more nearly coplanar (25°) than are the phenyl and α,β-unsaturated aldehyde groups (63°). In the intermediate carbonium ion (**28**) the methylenedioxyphenyl and the contiguous ethyl units should more closely approach coplanarity, while the phenyl and the methylenedioxyphenethyl units should more closely approach 90°. Accordingly, **28a**, which leads to aldehyde **26**, is more thermodynamically stable than **28b**, which leads to indene, since the effective steric bulk of the phenyl moiety in **28a** is smaller than that of the methylenedioxyphenyl group of **28b** in the direction of the $ClCHN(CH_3)_2$ unit.

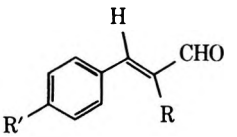


28a **28b**

That activation of the aromatic ring toward electrophilic substitution is a necessary condition for Vilsmeier-Haack cyclizations is indicated by the following. Both methods I and II afford **30** in 42% yield in addition to starting olefin **29** and polymer. No indene could be isolated. Specifically, the effect must be electromeric (*cf.* **6**), since **31** affords **32**

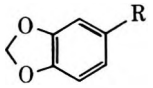


29, R = H; R′ = H
31, R = H; R′ = OCH_3



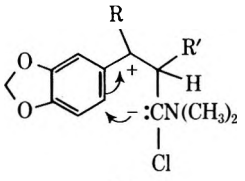
30, R = H; R′ = H
32, R = H; R′ = OCH_3

in 68% yield but no indene was isolated.[15] On the other hand, both inductomeric and electromeric effects influence aldehyde formation in the expected manner (*cf.* **3**, **28**), $OCH_3 > CH_3 > H$.[15] Furthermore, when the exocyclic double bond was isolated from the methylenedioxyphenyl unit, no aldehyde or cyclic products could be detected; 85% of starting olefin **33** and about 5% basic polymer were recovered.



33, R = $CH_2CH{=}CH_2$
34, R = $CH_2CH_2CH_3$

Formylation of the aromatic ring of these styrenes has not been observed. This is not surprising, since the vinyl substituent is expected to deactivate the ring toward electrophilic attack. While this does not argue well for the intermediacy of **6**, the cyclization (**4** → [**6**] → **7**) may be a concerted process. The fact that **33** and **34** fail to afford aldehydes also suggests an element of steric hindrance (*cf.* ref 12) inherent as well in the styrenes. In addition, initial attack on the ring system fails to explain why the *n*-propyl and *n*-butyl analogs **9** and **12** afford higher yields of indenes (**11**, **14**) than **2** and why **23** affords no indene at all (*cf.* **20** → **21**). Attack of the vinyl group by carbene[26] [$(CH_3)_2NCCl$] has also been rejected based on the acidity of the medium. In addition, nucleophilic cyclization through the conjugate base of **3** (**35**) produced in this process lacks precedent.



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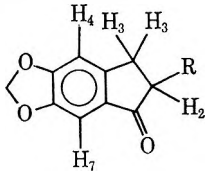
Finally, recalling that **29** and **31** give **30** and **32** but no indene, this route suggests no decisive role for O(3) and requires a more general scope than can be demonstrated for cyclizations under Vilsmeier-Haack conditions.

In summary, Vilsmeier-Haack cyclization of styrenes to form indenes is facilitated by para-substituents exerting +I or +E effects and requires meta-substituents capable of strong +E effects. Cyclization is promoted by increasing the size of β-alkyl substituents. The mechanism involves electrophilic attack by **1a** on the β carbon of the styrene system to give cationic intermediate **3**. This undergoes thermally and sterically dependent proton loss (*cf.* **3a-f**, **28a,b**) to give (*E*)-**4**, which provides aldehydes of this configuration upon hydrolysis, and (*Z*)-**4**, which provides the correct juxtaposition of functional groups for cyclization to aminoindenes. Formation of (*Z*)-**4** (R = H) is favored at elevated temperatures. Both α- and β-aryl substituents on the starting olefins (*cf.* **20**, **23**) provide steric as well as electronic constraints which are not completely understood; **20** affords aminoindene **21** but **23** affords only aldehyde **26**.

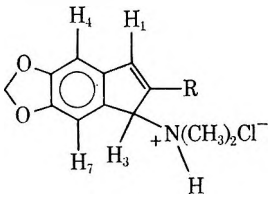
Table I
Conversion of Dimethylaminoindenes to Indanones



2-Substituted 5,6-methylenedioxy-indanone[b]	Yield, %	Mp, °C	Bp, °C (mm)	Chemical shift,[a] δ ppm 2H₃H₂	R	OCH₂O	H₄	H₇
2-Methyl (**8**) $C_{11}H_{10}O_3$	96–97	63.0–63.5	113–115 (0.025)	2.34–3.55	1.25 (d, J = 7 Hz)	6.04	6.79	7.09
2-*n*-Propyl (**18**) $C_{13}H_{14}O_3$	96–97	48–49	139.5–140.5 (0.1)	2.35–3.48	0.5–2.0	6.05	6.80	7.06
2-*n*-Butyl (**19**) $C_{14}H_{16}O_3$	96–97	46.5–47.5	134–136 (0.03)	2.42–3.50	0.7–2.2	6.05	6.81	7.09

[a] Chemical shifts relative to TMS in $CDCl_3$. [b] Satisfactory elemental analyses were reported for all compounds in the table.

Table II
Conversion of Methylenedioxy Olefins to Aminoindenes



2-Substituted dimethylamino-5,6-methylenedioxy-ind-1-ene[f]	Yield, %	Mp, °C (HCl salt or free amine)	Bp, °C (mm) of free amine	Chemical shift, δ ppm OCH₂O	H₁	H₃	H₄	H₇
2-Methyl (**7**) $C_{13}H_{16}NO_2Cl$	47	188–190 dec (salt)	112–116 (0.15)	5.86[a]	6.22	3.91	6.63	6.95
2-*n*-Propyl (**11**) $C_{15}H_{20}NO_2Cl$	71	177–178 (salt)	125–127.5 (0.25)	6.01[b]	6.61	4.82	6.77	7.50
2-*n*-Butyl (**14**) $C_{16}H_{22}NO_2Cl$	70	177–178.5 (salt)	133.5–136 (0.35)	6.00[b]	6.51	4.80	6.76	7.51
2-Phenyl (**21**) $C_{18}H_{17}NO_2$	16[c] 25[e]	134–135 (amine)	Not distilled	5.90[d]	6.86	4.62	6.77	7.06

[a] Chemical shifts relative to TMS of free base in $(CD_3)_2CO$. [b] Chemical shifts relative to TMS of HCl salts in $CDCl_3$. [c] A 16% yield is obtained if the reaction is carried out as described in the Experimental Section. [d] Chemical shifts relative to TMS of free base in $CDCl_3$. [e] A 25% yield is obtained if olefin **21** is added directly to the previously warmed (steam bath), stirred Vilsmeier–Haack reagent and the mixture subsequently is heated for 3 hr. [f] Satisfactory elemental analyses were reported for all compounds in the table.

Experimental Section

Proton magnetic resonance spectra were obtained with a Varian A-60A spectrometer. Mass spectra were recorded utilizing a Du Pont 21-491 mass spectrometer interphased with a Hewlett-Packard 2100A computer. All aminoindenes and indanones showed the expected molecular ion. Infrared spectra were obtained with a Perkin-Elmer 257 spectrometer. Purity of starting olefins was confirmed using a Hewlett-Packard Model 402 gas chromatograph equipped with a flame ionization detector and glass columns containing 10% Carbowax on Chromosorb W (80–100 mesh). Elemental analyses were performed by Clark Microanalytical Laboratories, Urbana, Ill.

Crystals of **5** and **26** suitable for diffraction study were grown by slow evaporation of hexane solutions at room temperature, mp 64–66 and 96–97°, respectively. Crystal densities of 1.313 and 1.316 g cm^{-3} (23°), respectively, were measured by flotation in KI–H_2O using a Westpfal balance. Integrated intensities (I) of reflections of the form hkl and hkl, for which $\sin\theta \leq 0.91$, were collected in the θ–2θ mode with a Nonius CAD-IV automated diffractometer using Cu Kα radiation (λ = 1.5418 Å). Integrated intensities less than $2\sigma(I)$ were considered unobservably weak and were arbitrarily assigned values of $\sigma(I)/2$. The atomic scattering factors were taken from the International Tables for X-ray crystallography.[27] Computer programs used in this study were written for the IBM 1130 and PDP 10 systems.[28] Both structures were solved with the aid of MULTAN.[28,29] The block-diagonal, least-squares procedure was used to refine atomic positional and thermal parameters. Hydrogen atoms were refined isotropically (b = 5.0 Å^2).

The final tables of structure factors, atomic positional and thermal parameters, bond lengths and angles, and other conformational detail will appear in the definitive report of the crystal structures of **5** and **26**.[30]

A. Source or Synthesis of Starting Olefins. **(*E*)-1-(3,4-Methylenedioxyphenyl)prop-1-ene (isosafraole, 2)** was purchased from Pfaltz and Bauer, Flushing, N. Y., and was used without further purification.

(*E*)-1-(3,4-Methylenedioxyphenyl)pent-1-ene (9). *n*-Butyllithium (0.43 mol) in hexane (120 ml, 21.4% *n*-BuLi) was added by syringe in 30-ml portions to a stirred solution of 30 g (0.20 mol) of piperonal (15) (Pfaltz and Bauer) in 300 ml of anhydrous Et_2O maintained at −78° under a N_2 atmosphere. The mixture was allowed to warm to room temperature while stirring overnight. The mixture was cooled to −10° and saturated NaCl solution (100 ml) was added to decompose the excess *n*-BuLi. The aqueous layer was extracted with Et_2O (175 ml) and the organic layer was washed with H_2O and saturated NaCl solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The resulting viscous brown oil was distilled, affording 27.6 g (66.3%) of a yellow oil **[1-(3,4-methylenedioxyphenyl)pentan-1-ol]** (**16**), bp 112–114° (0.1 mm). Redistillation through a 12-in. Vigreux col-

umn afforded alcohol, bp 113.5–115.5° (0.15 mm), which was 95% pure (glpc). A solution of this alcohol (12.0 g, 0.06 mol) and *p*-toluenesulfonic acid (0.75 g, 0.004 mol) in benzene (300 ml) was allowed to reflux until no H_2O was collected in a Dean-Stark trap (*ca.* 30 min). The reaction mixture was diluted with 250 ml of Et_2O, washed with H_2O, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Distillation of the yellow residue afforded 10.4 g (95.0%) of a colorless liquid (**9**): bp 90–92° (0.3 mm); nmr ($CDCl_3$) δ for the calculated ABX_2 spectrum shows eight lines for the AB part (AB, 2 H, vinyl protons), δ_A 6.24, δ_B 5.98, and (X, 2 H, $CH_2CH_2CH_3$) δ_X 2.12 with J_{AB} = 15.5, J_{AX} = 0, J_{BX} = 5.5–6.0 Hz; δ 0.95 (t, 3 H, CH_3, J_{CH2Me} = 6.5 Hz), 1.47 (sextet, 2 H, $CH_2CH_2CH_3$, $J_{CH_2CH_2}$ = 5.5–6 Hz), 6.6–6.9 (m, 3 H aromatic).

Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.8; H, 7.42. Found: C, 75.70; H, 7.45.

(*E*)-1-(3,4-Methylenedioxyphenyl)hex-1-ene (12). To a stirred mixture (maintained in a dry atmosphere) containing 100 ml of anhydrous Et_2O and 9.3 g (0.4 g-atom) of Mg (turnings) was added dropwise 60.4 g (0.4 mol) of 1-bromopentane. After the addition, the stirred mixture was refluxed for an additional 30 min to dissolve all remaining metal. The brown solution was cooled to 0° and piperonal (**15**, 60.0 g, 0.4 mol) dissolved in 200 ml of anhydrous Et_2O was added dropwise with stirring. After 1 hr the mixture was extracted with two 150-ml portions of saturated NH_4Cl solution. The aqueous layers were washed with 150 ml of Et_2O and the combined Et_2O solutions were washed with saturated NaCl solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was distilled, affording 60.9 g (68.4%) of a viscous oil (**17**).

1-(3,4-methylenedioxyphenyl)hexan-1-ol (17) had bp 135–138° (0.35 mm). Redistillation through a 12-in. Vigreux column afforded alcohol **17**, bp 113–115° (0.12 mm), which was 96% pure (glpc). Dehydration of this alcohol under conditions described for the preparation of **9** afforded **12**, bp 108–110° (0.3 mm), in 92% yield. The sample was 96% pure (glpc). Redistillation (spinning-band column) afforded **12**, bp 95–97° (0.15 mm), in analytically pure form: nmr ($DCCl_3$) δ for the calculated ABX_2 spectrum shows eight lines for AB part (AB, 2 H, vinyl protons), δ_A 6.21, δ_B 6.04, and (X, 2 H, CH_2CH_3) δ_X 2.14 with J_{AB} = 15.5, J_{AX} = 0, J_{BX} = 5.5 Hz; δ 0.7–1.65 (m, 9 H, $CH_2CH_2CH_2CH_3$), 6.6–6.9 (m, 3 H, aromatic).

Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.4; H, 7.90. Found: C, 76.15; H, 8.08.

(*E*)-1-(3,4-Methylenedioxyphenyl)-2-(phenyl)ethene (20) was prepared according to the method of Tiffeneau and Levy[21,22] affording pale yellow needles (50%), mp 91–92° (lit.[21] mp 94–95°, lit.[22] mp 93–94°).

Anal. Calcd for $C_{15}H_{12}O_2$: C, 80.3; H, 5.39. Found: C, 79.94; H, 5.72.

1-(3,4-Methylenedioxyphenyl)-1-(phenyl)ethene (23). To 3,4-methylenedioxyacetophenone[31] (**25**, 7.5 g, 0.046 mol), mp 84.5–85.5° (lit.[31] mp 85°, lit.[32] mp 83–84°), in benzene (100 ml) was added phenylmagnesium bromide (0.06 mol in 100 ml of Et_2O). After the usual work-up the resulting tertiary alcohol **24** was dehydrated under conditions described for the preparation of **9**. Distillation afforded 8.2 g (78.5%) of **23**: bp 124–126° (0.25 mm); nmr ($CDCl_3$) δ 5.32 (broad s, 2 H, vinyl H's), 5.74 (s, 2 H, OCH_2O), 6.5–6.9 (m, 3 H, Ar), 7.26 (broad s, 5 H, Ph).

Anal. Calcd for $C_{15}H_{12}O_2$: C, 80.3; H, 5.39. Found: C, 80.38; H, 5.28.

B. General Procedure for Vilsmeier–Haack Cyclization (Method II). To a cooled (ice bath), round-bottom flask containing dimethylformamide (DMF) (45 g, 0.61 mol) was added dropwise with stirring $POCl_3$ (18.4 g, 0.12 mol). The mixture was stirred in an ice bath for 15–20 min and the olefin (0.10 mol) was added dropwise. After the addition, the reaction mixture was immediately heated on a steam bath for 3 hr. The resulting black mixture was poured into 400 ml of ice-H_2O and unreacted olefin was removed by extraction with two 175-ml portions of Et_2O. The aqueous layer was made basic by the addition of 10% aqueous NaOH solution and any aminoindenes were extracted with three 150-ml portions of Et_2O. The combined Et_2O layers were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Distillation of volatile aminoindenes **7**, **11**, and **14** afforded yellow liquids which were air sensitive and decomposed upon standing at room temperature. The amines were converted to the stable HCl salts, which were recrystallized as white solids from EtOH-Et_2O. The free amine, **2-phenyl-3-dimethylamino-5,6-methylenedioxyind-1-ene (21)**, was not distilled. It was stable and could be crystallized from low-boiling petroleum ether containing a small amount of benzene (decolorized with charcoal). Physical constants and analytical data for the aminoindenes **7**, **11**, **14**, and **21** and the hydrochloride salts are listed in Table II.

C. Aldehyde Products Obtained during Vilsmeier–Haack Reactions. (*E*)-2-Methyl-3-(3,4-methylenedioxyphenyl)acrylaldehyde (5) was isolated in 48% yield when **2** served as starting olefin and the reaction was carried out according to Schmidle and Barnett[15] (method I). Recrystallization from benzene–hexane afforded crystals, mp 64–66.5° [lit.[15] bp 110–130° (0.1 mm)]. When the reaction was carried out under Vilsmeier–Haack cyclization conditions (method II, above) **5** was isolated in 23% yield by distillation of the residue resulting from ether extraction of the H_2O-diluted reaction mixture.

2-*n*-Propyl-3-(3,4-methylenedioxyphenyl)acrylaldehyde (10) was prepared from 3.85 g (0.03 mol) of $POCl_3$, 7.3 g (0.1 mol) of DMF, and 4.75 g (0.03 mol) of **9** according to the method of Schmidle and Barnett[15] (method I), affording 2.6 g (48%) of yellow oil, bp 115–117° (0.1 mm).

Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.55; H, 6.42. Found: C, 71.24; H, 6.35.

(*E*)-3-Phenyl-3-(3,4-methylenedioxyphenyl)acrylaldehyde (26). Treatment of olefin **23** (2.2 g, 0.01 mol), DMF (4.5 g, 0.061 mol), and $POCl_3$ (1.84 g, 0.012 mol) as described under method II affords, after addition of NaOH to the aqueous layer and extraction with ether, 1.75 g (69.5%) of **26** as pale yellow needles (hexane–benzene): mp 97–98° (2,4-DNPH mp 233–235° dec); nmr ($CDCl_3$) δ 5.97 (s, 2 H, OCH_2O), 6.34 (d, 1 H, vinyl, $J_{H\text{-}CHO}$ = 8 Hz), 9.43 (d, 1 H, CHO), 6.7–6.9 (m, 3 H, Ar), 7.1–7.6 (m, 5 H, Ph). No aminoindene was detected and 0.22 g of polymer formed during the reaction.

Anal. Calcd for $C_{16}H_{12}O_3$: C, 76.2; H, 4.79. Found: C, 76.34; H, 4.87.

Cinnamaldehyde (30). In methods I and II, styrene (**29**, 10.4 g, 0.10 mol), DMF (50 g, 0.68 mol), and $POCl_3$ (20 g, 0.13 mol) afforded 5.5 g (41.6%) of **30**, bp 84–87° (2.0 mm) [lit.[15] bp 84–87° (2.0 mm)]. Glpc analysis showed the remaining portion of the reaction mixtures to be styrene (**29**).

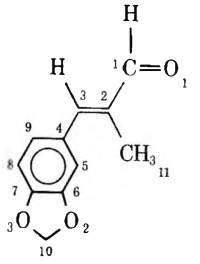
D. Conversion of 2-Substituted 3-Dimethylamino-5,6-methylenedioxyind-1-enes 7, 11, and 14 to 2-Substituted 5,6-Methylenedioxy-1-indanones 8, 18, and 19, Respectively. The HCl salts of aminoindenes **7**, **11**, and **14** (0.02 mol) were dissolved in a solution of NaOH (10.0 g, 0.25 mol) in 200 ml of H_2O–EtOH (1:1), stirred at room temperature overnight, diluted with 200 ml of H_2O, and extracted with three 75-ml portions of Et_2O. The combined Et_2O layers were washed with saturated NaCl solution (100 ml), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The yellow residue was distilled under reduced pressure, affording nearly colorless liquids which crystallized on cooling. The distillates were recrystallized from petroleum ether (bp 30–60°) or petroleum ether–benzene, affording white, crystalline samples of indanones **8**, **18**, and **19**, respectively. Physical constants and analytical data for the indanones are listed in Table I.

E. Conversion of 2-Phenyl-3-dimethylamino-5,6-methylenedioxyind-1-ene (21) to 2-Phenyl-2-hydroxy-5,6-methylenedioxy-1-indanone (22). A solution of NaOH (4.0 g, 0.1 mol) in 80 ml of H_2O–EtOH (1:1) was added to **21** (1.14 g, 0.004 mol). The mixture was stirred at room temperature overnight, diluted with H_2O, and extracted with three 100-ml portions of Et_2O. The combined Et_2O layers were washed with 100 ml of saturated NaCl solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The brown solid residue (0.6 g, 0.002 mol, 50%) was recrystallized from absolute EtOH, affording pale yellow needles (**22**): mp 169.5–170.5°; nmr (DMSO-d_6) δ 7.29 (s, 5 H, aromatic), 7.12 (s, 1 H, H_7 proton), 7.08 (s, 1 H, H_4 proton), 6.19 (s, 2 H, OCH_2O), 6.22 (s, 1 H, –OH exchangeable with D_2O), 3.46 and 3.42 (d, 2 H, geminal H_3 protons); mass spectrum (70 eV) *m/e* (rel intensity) 268 (35), 135 (11), 105 (base), 77 (30).

Anal. Calcd for $C_{16}H_{12}O_4$: C, 71.6; H, 4.47. Found: C, 71.58; H, 4.59.

F. X-Ray Diffraction Study of 5. The material crystallizes in monoclinic space group $P2_1/n$. The unit cell parameters are: a = 5.082 (2), b = 8.578 (3), c = 22.016 (7) Å, β = 96.38 (1)°. The theoretical density is 1.324 g cm^{-3}, corresponding to four molecules per unit cell. Other than systematic absences there are 592 out of 1621 measured independent reflections for which $(I) < 2\sigma(I)$. The structure was solved using 201 of the highest (>1.60) renormalized $|E|$ values. An E map afforded positions for all nonhydrogen atoms. Refinement of atomic positional and thermal parameters converged at R_{all}[33] = 0.128 and R_{obsd} = 0.095. Hydrogen atoms were located in a difference Fourier map. The final cycles of re-

finement converged at R_{all} = 0.075 and R_{obsd} = 0.039. The calculated C(1)-C(2)-C(3)-C(4) torsion angle of +177.3 (3)° clearly establishes the *E* geometry shown in **5**. The angle between the normals to the least-squares planes defined by the methylenedioxyphenyl and the O(1)-C(1)-C(2)-C(3)-C(11)-C(4) systems is 5.1°.



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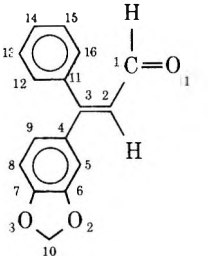
G. X-Ray Diffraction Study of 26. The material crystallizes in monoclinic space group $P2_1/n$. The unit cell parameters are: a = 6.310 (3), b = 8.939 (4), c = 22.572 (8) Å, β = 97.75 (1)°. The theoretical density is 1.328, corresponding to four molecules per unit cell. Other than systematic absences there are 462 out of 2185 measured independent reflections for which $(I) < 2\sigma(I)$. The structure was solved using 220 of the highest (>1.70) renormalized $|E|$ values. An *E* map afforded positions for all nonhydrogen atoms. Refinement of atomic positional and thermal parameters converged at R_{all} = 0.119 and R_{obsd} = 0.106. Hydrogen atoms were located in a difference Fourier map. The final cycles of refinement converged at R_{all} = 0.052, R_{obsd} = 0.039. The calculated C(1)-C(2)-C(3)-C(4) torsion angle of −173.4 (2)° clearly establishes the *E* geometry in **26**. The angles between the normals (N) to the least-squares planes defined by the methylenedioxyphenyl (N_1), O(1)-C(1)-C(2)-C(3)-C(4)-C(11) (N_2) and phenyl (N_3) systems are: N_1-N_2 = 24.7°, N_2-N_3 = 62.7°, and N_1-N_3 = 74.8°.



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Registry No.—(*E*)-**5**, 51003-21-5; **7**, 51003-77-1; **7** hydrochloride, 51003-78-2; **8**, 51003-79-3; (*E*)-**9**, 51003-18-0; (*E*)-**10**, 51021-63-7; **11**, 51003-80-6; **11** hydrochloride, 51003-81-7; (*E*)-**12**, 51003-17-9; **14**, 51003-82-8; **14** hydrochloride, 51003-83-9; **15**, 120-57-0; **16**, 5422-01-5; **17**, 6412-93-7; **18**, 51003-84-0; **19**, 51003-85-1; (*E*)-**20**, 51003-16-8; **21**, 51003-86-2; **22**, 51003-87-3; **23**, 51003-88-4; **25**, 3162-29-6; (*E*)-**26**, 51003-15-7.

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(33) $R_{all} = (\sum||F_{meas}| - |F_{calcd}||/\sum|F_{meas}|)$ and is a reliability index based on all data. R_{obsd} refers to the index for all but unobservably weak reflections.

Pteridines. III. Unexpected Facile Ring Closure of 2-Amino-6-phenethylpteridin-4(3*H*)-one in the Presence of Fluorosulfonic acid[1,2]

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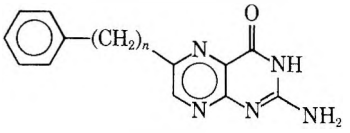
2-Amino-6-phenethylpteridin-4(3*H*)-one (**1**) underwent a novel ring closure to 10-amino-5,6-dihydronaphtho[2,1-*g*]pteridin-8(9*H*)-one (**3**) in 74% yield on mild treatment with a 1:4 mixture of fluorosulfonic acid and trifluoroacetic acid. The structure of **3** was deduced on the basis of uv and nmr spectral data and supported chemically by aromatization to 10-aminonaphtho[2,1-*g*]pteridin-8(9*H*)-one (**5**) with selenium dioxide. A mechanism is proposed involving an unusual pteridine carbonium ion with the positive charge at C-7 delocalized anchimerically by the 6-phenethyl substituent.

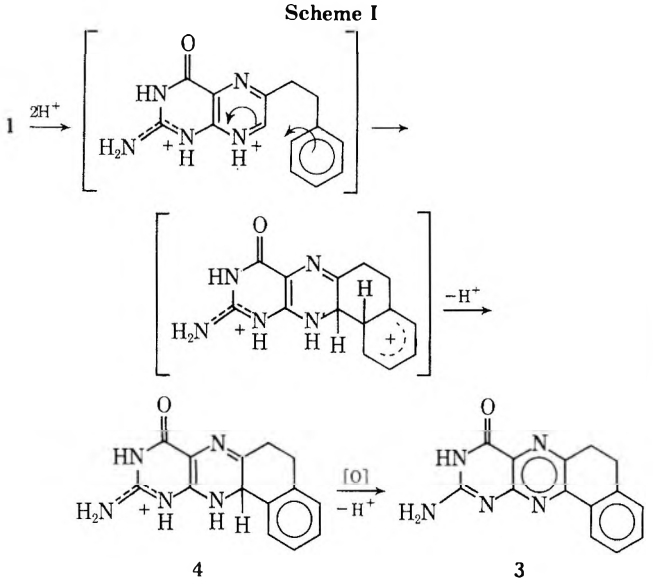
2-Amino-6-phenethylpteridin-4(3*H*)-one (**1**) and 2-amino-6-(3-phenylpropyl)pteridin-4(3*H*)-one (**2**) were prepared recently in this laboratory from 2,4,5-triamino-6-hydroxypyrimidine *via* a novel unidirectional pteridine synthesis involving the use of 1-methylsulfinyl-4-phenyl-2-butanone and 1-methylsulfinyl-5-phenyl-2-pentanone, respectively, as "latent" α-keto aldehydes.[3] This method of synthesis was superior to earlier procedures[4,5] in a number of respects. In the course of our characterization of **1** and **2** by nmr spectrometry an unusual event was observed which forms the subject of this report.



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

When the nmr spectrum of **1** was determined in trifluoroacetic acid solution, the CH_2CH_2 protons were observed as a multiplet at δ 3.2 and the C-7 proton on the pteridine ring was discerned as a sharp singlet at δ 8.53.[3] Upon addition of fluorosulfonic acid to a final concentration of 20%,[3,6] the solution became warm and the color changed from amber to deep red. At the same time a pronounced change occurred in the nmr spectrum, including most notably the replacement of the original CH_2CH_2 multiplet at δ 3.2 by a singlet at δ 3.43. In addition, broad absorption at δ 7.85–8.65 and a new singlet at δ 6.50 became evident. Contrastingly, nmr spectra of the 6-(3-phenylpropyl) homolog **2** showed persistence of the $CH_2CH_2CH_2$ signal as a multiplet even in the presence of fluorosulfonic acid. The change in nmr spectrum of **1** was suggestive of a specific chemical reaction in which the 6-phenethyl group was probably an important requisite. We considered the possibility of a cyclization process as depicted in Scheme I.

Scheme I



Addition of the foregoing 1:4 fluorosulfonic–trifluoroacetic acid solution of compound **1** to a large volume of 95% ethanol caused instantaneous discharge of the dark red color and evolution of an unpleasant odor suggestive of sulfinic acid. At the same time a pale yellow solid appeared, which on isolation proved to be distinctly different (ir, uv, nmr) from **1**. The yield was nearly quantitative and remained in excess of 75% even on a 2-g scale. The product was homogeneous by tlc analysis and could be recrystallized unchanged and in excellent recovery from 80% formic acid.

The uv spectrum of the product in 0.1 *N* sodium hydroxide showed maxima at 240, 273, and 387 nm, whereas the spectrum of compound **1** contained maximum absorption only at 254 and 363 nm.[3] The significant bathochromic shift manifested in the spectrum of this new compound indicated the likelihood that the action of fluorosulfonic acid had given rise to an extension of conjugation as a consequence of a rearrangement.

The nmr spectrum of the material recovered after dilution of the 1:4 fluorosulfonic–trifluoroacetic acid mixture with ethanol and recrystallization from 80% formic acid was different from the spectrum prior to quenching. When the product was redissolved in 1:4 fluorosulfonic–trifluoroacetic acid, the previously observed singlet at δ 3.43 (*vide supra*) now was replaced by a multiplet at δ 3.80 and the singlet at δ 6.50 was no longer discernible. In trifluoroacetic acid alone, the nmr spectrum revealed a complex pattern of aromatic proton absorption in the δ 7.2–8.6 region and a broad singlet with poorly resolved fine structure at δ 3.30. This spectrum contrasted sharply with that of **1** in trifluoroacetic acid alone,[3] which contained a prominent C-7 pteridine proton singlet at δ 8.53, a single strong peak at δ 7.13 corresponding to five aromatic protons in a freely rotating phenyl group, and a well-defined CH_2CH_2 multiplet centered at δ 3.20. Thus, nmr evidence indicated that, in the presence of a very strong acid such as fluorosulfonic acid, a transient intermediate **4** (Scheme I) was generated from **1** which underwent immediate conversion into a new species (**3**) upon quenching with ethanol. That the latter transformation probably entailed an

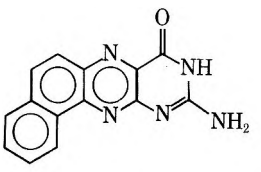
oxidative step was consistent with the very pronounced odor of sulfinic acid, which could be assumed to arise from fluorosulfonic acid or its ethanolysis product, ethyl sulfate, as part of a redox reaction.

Microchemical analysis established the empirical formula of the product to be $C_{14}H_{11}N_5O$, whereas the starting material **1** had the composition $C_{14}H_{13}N_5O$. Thus, fluorosulfonic acid treatment of **1** appeared to have effected an oxidative change involving the loss of two hydrogens. On the basis of the microanalytical results as well as uv and nmr spectral evidence cited above, the rearrangement product was assigned structure **3**. This is a new example of the heretofore only sparsely studied naphtho[2,1-*g*]pteridine ring system.[7] Structure **3** satisfactorily accommodated the extended conjugation shown by the uv spectrum and was consistent with the absence of a C-7 pteridine proton in the nmr spectrum. Moreover, a plausible mechanism could be deduced for the cyclization of **1** to **3** as shown in Scheme I.

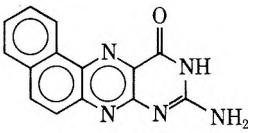
Protonation of N-8 in pteridines by very strong acids has been postulated previously[6] in order to explain the effectiveness of fluorosulfonic acid as an nmr solvent permitting a clear distinction between isomeric 6- and 7-substituted pteridines.[3,6] It was therefore reasoned that protonation at N-8 might also impart some positive character to the adjacent C-7 position, especially if additional charge delocalization could be provided *via* participation of a suitably placed phenyl group. A 6-phenethyl derivative would be especially appropriate in this regard, since formation of a resonance-stabilized species (see Scheme I) would occur *via* closure of a six-membered ring. Expulsion of a bridgehead proton (providing steric relief) would lead to an intermediate **4** having, in essence, a 7,8-dihydropteridine structure. Analogously to other known oxidations of condensed 7,8-dihydropteridines to pteridines,[8] further transformation of **4** into **3** would be expected to take place rapidly under oxidizing conditions.

Support for the mechanism outlined in Scheme I was derived from the nmr spectrum of the dark red 1:4 fluorosulfonic–trifluoroacetic acid mixture prior to quenching with ethanol. As stated above, a singlet was observed at δ 6.50 prior to quenching which was absent in the spectrum of the eventual product and was likewise not seen in the spectrum of homolog **2** under the same conditions. The origin of this signal, apparently unique in the spectrum of the 6-phenethyl derivative, is believed to be the newly formed benzylic bridgehead proton occupying what was once the C-7 position of the pteridine moiety. The disappearance of this signal on quenching is consistent with instantaneous oxidation of the 7,8-dihydropteridine intermediate **4** to the pteridine **3**.

Direct chemical evidence for the tetracyclic nature of compound **3** was also obtained *via* selenium dioxide dehydrogenation experiments,[9] which gave a 75% yield of a new bright-yellow substance having the composition $C_{14}H_9N_5O$. The uv spectrum of this dehydrogenation product in 0.1 *N* sodium hydroxide contained maxima at 232, 285, and 428 nm. Since these values were consistent with a fully aromatized chromophore, the dehydrogenation product was formulated as structure **5**. An isomeric tetracyclic 2-aminopteridin-4(3*H*)-one, compound **6**, was obtained in 1954 by Timmis and coworkers by acid hydrolysis of the 2,4-diaminopteridine derivative.[10] The latter was formed on thermal condensation of 2-naphthol and 2,4,6-triamino-5-nitrosopyrimidine at 150°.[11] A sample of compound **6** was synthesized *via* this route and found to absorb at 254, 291, and 420 nm in 0.1 *N* sodium hydroxide. Additionally, compounds **5** and **6** both showed a characteristic bright blue uv fluorescence on tlc, possessed similar ir spectra, and resembled each other closely in their ready recrystallizability from 80% formic acid.



5



6

It is interesting to consider possible reasons for the singular behavior of compound **1** in the presence of very strong acid. A likely explanation for the fact that ring closure of **1** is so facile is that formation of a resonance-stabilized positively charged intermediate (Scheme I) is energetically favorable in this particular instance because the five carbon atoms among which the positive charge is distributed can exist in a planar configuration. Such a configuration is readily achieved when the newly created ring is six membered and thus relatively strain-free. When cyclization involves formation of a seven-membered ring, as in the 6-(3-phenylpropyl)homolog **2**, unfavorable ring distortion forces and eclipsing phenomena conspire to block this pathway. In preference to cyclization, therefore, simple substitution at the para position takes place,[3] presumably as a consequence of electrophilic attack by fluorosulfonic acid itself or the known mixed anhydride $CF_3C(O)OSO_2F$. The existence of this alternative pathway is supported by nmr evidence indicating gradual change of the aromatic proton signal in the 6-(3-phenylpropyl) compound **2** from a singlet to a typical AB quartet.[3,12]

The present serendipitous discovery of a reaction wherein the C-7 position of a pteridine functions as an electrophile because of protonation at N-8 represents a novel observation in pteridine chemistry.[13]

Experimental Section

Ir spectra were taken with a Perkin-Elmer Model 137B double-beam recording spectrophotometer and quantitative uv spectra were measured on Cary Model 11 and 15 spectrophotometers. Nmr spectra were determined on a Varian A-60 instrument with Me_4Si as the reference. When FSO_3H was present in the solvent mixture a sealed capillary containing Me_4Si was placed in the nmr sample tube. Melting point determinations were performed in Pyrex capillary tubes in a Mel-Temp apparatus (Laboratory Devices, Inc., Cambridge, Mass.). Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

10-Amino-5,6-dihydronaphtho[2,1-*g*]pteridin-8(9*H*)-one (3). A stirred solution of compound **1** (3.5 g, 0.013 mol)[3] in trifluoroacetic acid (35 ml) was treated dropwise with flurorsulfonic acid (8.75 ml). After being allowed to stand at room temperature for 30 min the dark red mixture was poured into 95% ethanol (875 ml). The initial pink color was rapidly discharged from the malodorous mixture and a yellowish solid deposited in the flask. The solid was filtered, washed with 95% ethanol and ether, and recrystallized (charcoal) from 80% formic acid (180 ml) to yield **3** as a pale yellow powder weighing 1.8 g (74%): mp >360°; nmr (CF_3CO_2H) δ 7.2–8.6 (m, aromatic protons), 3.3 (broad singlet with fine structure, CH_2CH_2); nmr (1:4 FSO_3H–CF_3CO_2H) δ 7.6–8.2 (m, aromatic protons), 3.8 (m, CH_2CH_2); uv (0.1 *N* NaOH) 240 nm (ϵ 21,590), 273 (18,830), 387 (15,290).

Anal. Calcd for $C_{14}H_{11}N_5O \cdot 0.5H_2O$: C, 61.30; H, 4.41; N, 25.53. Found: C, 61.55; H, 4.14; N, 25.55.

10-Aminonaphtho[2,1-*g*]pteridin-8(9*H*)-one (5). A mixture of compound **3** (0.5 g, 0.0018 mol) and powdered selenium dioxide (0.2 g, 0.0018 mol) in glacial AcOH (40 ml) was stirred under reflux for 4 hr. The hot mixture was then suction filtered and the filtrate was evaporated to dryness under reduced pressure. The filtered solid and the residue from evaporation were combined and redissolved in hot 80% formic acid (30 ml). Treatment with decolorizing carbon, dilution with a small volume of water, and slow cooling gave several crops totaling 0.36 g (77% yield), mp >360°. A sample recrystallized for microanalysis was washed

thoroughly with water and then dried at 100° (0.1 mm) in a drying pistol containing powdered KOH in order to remove the last traces of formic acid, uv (0.1 *N* NaOH) 232 nm (ε 31,820), 285 (38,340), 428 (13,530).

Anal. Calcd for $C_{14}H_9N_5O \cdot 0.25H_2O$: C, 62.79; H, 3.57; N, 26.15. Found: C, 62.80; H, 3.37; N, 26.08.

Registry No.—**1**, 4215-03-6; **3**, 50803-83-3; **5**, 50803-84-4.

References and Notes

(1) This investigation was supported in part by Research Contract DADA-17-71-C-1001 from the U. S. Army Research and Development Command, Office of the Surgeon General, and by Research Grant C6516 from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service. This is publication no. 1198 from the U.S. Army Research Program on Malaria.
(2) Paper II: A. Rosowsky, M. Chaykovsky, M. Lin, and E. J. Modest, *J. Med. Chem.*, **16**, 869 (1973).
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(7) (a) W. C. J. Ross, *J. Chem. Soc.*, 219 (1948); (b) M. E. Fernholz and H. Fernholz, *Chem. Ber.*, **84**, 257 (1951); (c) G. Henseke and H. G. Patzwaldt, *ibid.*, **89**, 2904 (1956).
(8) *Cf.* E. C. Taylor and F. Yoneda, *J. Org. Chem.*, **37**, 4464 (1972), for a somewhat related *in situ* oxidation of a condensed 7,8-dihydropteridine to a pteridine.
(9) A. Rosowsky, K. K. N. Chen, M. E. Nadel, N. Papathanasopoulos, and E. J. Modest, *J. Heterocycl. Chem.*, **9**, 275 (1972).
(10) D. G. I. Felton, T. S. Osdene, and G. M. Timmis, *J. Chem. Soc.*, 2895 (1954).
(11) D. G. I. Felton and G. M. Timmis, *J. Chem. Soc.*, 2881 (1954).
(12) The similar gradual appearance of an AB pattern indicative of para substitution was noted previously[3] with 2-amino-7-phenethylpteridin-4(3*H*)-one and 2-amino-7-(3-phenylpropyl)pteridin-4(3*H*)-one, neither of which would be anticipated to undergo cyclization if the mechanism in Scheme I is valid.
(13) We are grateful tc one of the referees for pointing out that the creation of an electrophilic center at C-7 on protonation is akin to the effect of an *N*-oxide. A convenient method has been reported recently for the direct synthesis of pteridine 8-oxides: H. Yamamoto, W. Hutzenlaub, and W. Pfleiderer, *Chem. Ber.*, **106**, 3175 (1973).

Nucleotides. II. Syntheses and Deblocking of 1-Oxido-2-pyridylmethyl Protected Nucleosides and Nucleotides[1,2]

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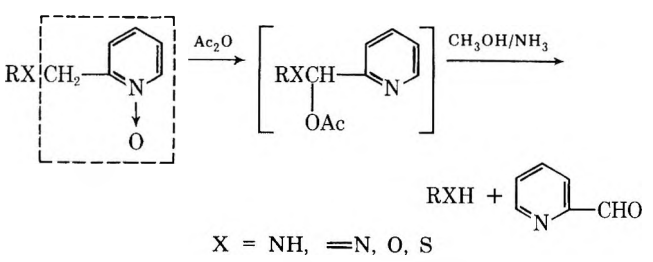
1-Oxido-2-pyridylmethyl group (op group) was found to be useful for protection of amino or hydroxyl groups of adenine, nucleosides (cytidine and adenosine), or phosphate functions of nucleotides (uridine 5′-phosphate and adenosine 5′-phosphate). N^6-(1-Oxido-2-pyridylmethyl)adenine (**1**) was prepared by the reaction of 1-oxido-2-pyridylmethylamine (**9**) and 6-methylsulfonylpurine (**11**). N^4-(1-Oxido-2-pyridylmethyl)cytidine (**2**) and N^6-(1-oxido-2-pyridylmethyl)adenosine (**3**) were also prepared by the reactions of **9** and appropriate sulfonate or sulfone derivatives of nucleosides **8** and **13**. 1-Oxido-2-pyridylmethyl nucleoside 5′-phosphates (**4**, **5**, and **6**) were prepared in excellent yields by the reactions of the nucleotides with 1-oxido-2-pyridyldiazomethane (**15**), a water-soluble alkylating agent newly developed for the present investigation. By the use of **15** op protection could be introduced into phosphate functions of nucleotides in aqueous solution in excellent yields. Deblocking of these op-protected nucleoside (**2**) and nucleotides (**4** and **6**) could be achieved in satisfactory yields (86–96%) by treatment with acetic anhydride, followed by methanolic ammonia.

In the past few years, the development of procedures for the chemical synthesis of oligonucleotides has depended to a significant extent on the design of a new protecting group with specific properties.[3]

In the preceding paper it was shown that 1-oxido-2-pyridylmethyl group (op group)[4] was useful as an easily removable blocking group for amino, imino, and hydroxyl functions[5] (Chart I).

Chart I



The present paper deals firstly with the preparation of 1-oxido-2-pyridylmethyl protected nucleosides **2** and **3** (Chart II) as well as 1-oxido-2-pyridylmethyl protected adenine (**1**), secondly with the preparation of the nucleotide derivatives **4**, **5**, and **6** by the use of 1-oxido-2-pyridyl diazomethane (**15**), and finally with the deblocking of these compounds (**2**, **5**, and **6**) with acetic anhydride treatment and subsequent hydrolysis.

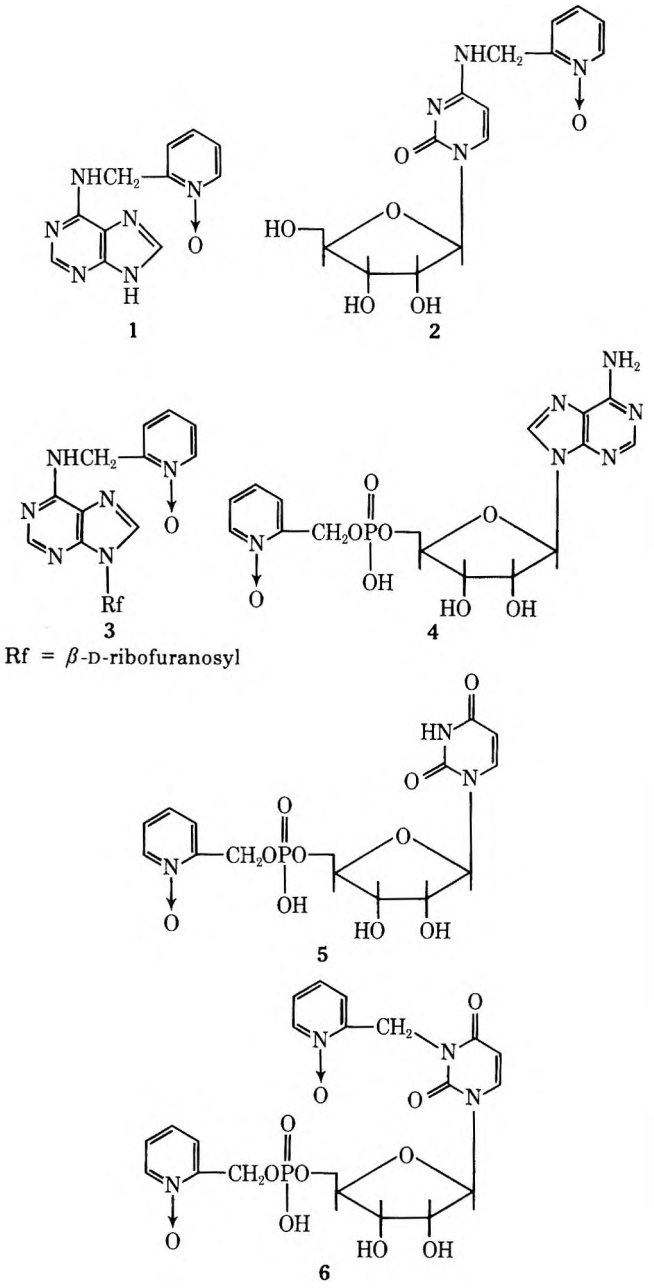
Although two op-protected nucleosides (**2** and **3**) might be prepared by Dimroth rearrangement[6] of the respective 1- or 3-op-substituted nucleosides, we have adopted alternative routes (see Chart III).

Oxidation of 4-thiouridine (**7**)[7] with potassium permanganate (at 0° for 15 min) afforded the corresponding 4-sulfonate (**8**).[8] Without isolation, the reaction mixture was treated with 1-oxido-2-pyridylmethylamine (**9**) at room temperature for 25 hr to give the expected N^4-(1-oxido-2-pyridylmethyl)cytidine (**2**) (crude yield was almost quantitative) which was purified by charcoal treatment. The product was homogeneous on tlc and paper chromatography.

The structural confirmation of **2** rests upon the elemental analysis and spectral data (uv, ir, and nmr). Although the isolated yield was rather poor (34.7%), the possibility of optimizing isolation (charcoal treatment) conditions could improve the yield.

N^6-(1-Oxido-2-pyridylmethyl)adenine (**1**) was prepared according to a route shown in Chart IV. The synthetic sequence starts with 6-methylthiopurine (**10**),[9] which on oxidation with aqueous bromine solution afforded the corresponding 6-methylsulfonylpurine (**11**), contaminated with a small amount of 6-methylsulfinylpurine. Without purification, the mixture was treated with 1 equiv of 1-oxido-2-pyridylmethylamine (**9**) to yield **1** in 20% yield. The structure was confirmed by elemental analyses as well as spectral data.

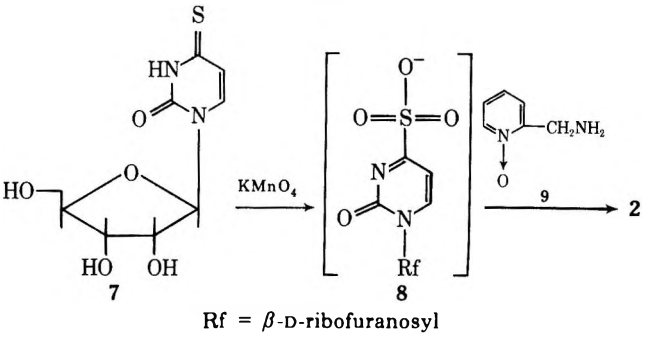
Chart II



Rf = β-D-ribofuranosyl

Treatment of 6-ethylthiopurine-9-(β-D-ribofuranosyl)purine (12) with aqueous bromine solution afforded 6-sulfonylpurine ribonucleoside (13), which was then treated with 1 equiv of 9 to give N^6-(1-oxido-2-pyridylmethyl)adenosine (3). The product 3 was purified by silica gel chromatography. Structural confirmation comes from spectral (uv and ir) data and the fact that acid hydrolysis of 3 afforded the N^6-op-adenine 1.

Chart III



Rf = β-D-ribofuranosyl

For the preparation of 4–6, a new water-soluble alkylating agent, 1-oxido-2-pyridyldiazomethane (15), was introduced.

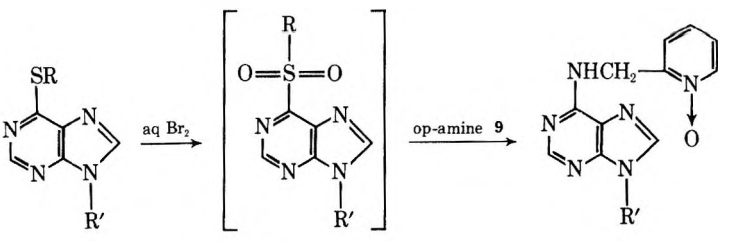
It is well established that diazomethane, the parent of the diazoalkanes, is one of the most versatile and useful reagents in organic chemistry. As a methylating agent of reasonably acidic substances, diazomethane has ideal properties. Methyl group is, however, of no use as a protecting group, because of difficulties encountered in its removal.

The synthetic sequence of 15 starts with 2-formylpyridine 1-oxide,[10] which was converted into the corresponding *p*-tosylhydrazone (14) (Chart V) in 79% yield, which in turn was treated with 1 equiv of sodium ethoxide in ethanol at 50°. After work-up, compound 15 was obtained in a yield of 47% as a chloroform solution which contained a small amount of 2-ethoxymethylpyridine 1-oxide (*ca.* 10%) as a by-product. The chloroform solution was colored; ir absorption maxima appeared at 2080 (N≡N⁺) and 1235 cm^{-1} (N→O). This solution was employed for the subsequent experiment.

The reaction of the chloroform solution of 15 with acetic or benzoic acid took place rapidly at room temperature with evolution of nitrogen to give 1-oxido-2-pyridylmethyl acetate, mp 67–68°, or benzoate, mp 125–126°, respectively. Yields of the acetate or the benzoate were almost quantitative.

Treatment of an aqueous solution of adenosine 5′-phosphate (16) with the chloroform solution of 15 at room temperature afforded the corresponding 1-oxido-2-pyridylmethyladenosine 5′-phosphate (4) (Chart VI). The product was purified by DEAE-cellulose column chromatography. Hydrolysis of 4 with snake venom phosphodiesterase afforded adenosine 5′-phosphate (16) and 1-oxido-2-pyridylcarbinol (17) in a molar ratio of 1:1. The yield of 4 was 90%.

Chart IV



Base series			
R = CH_3	10	11	1
R′ = H			
Nucleoside			
R = C_2H_5	12	13	3
R′ = β-D-ribofuranosyl			

Chart V

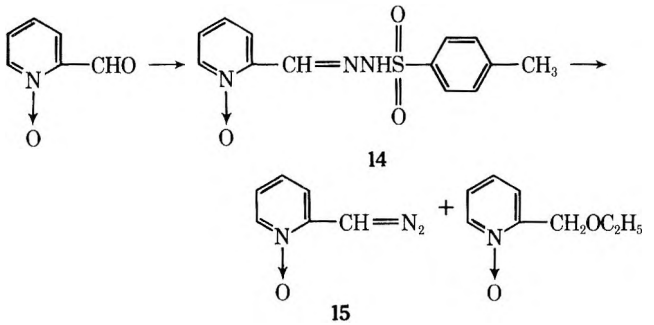
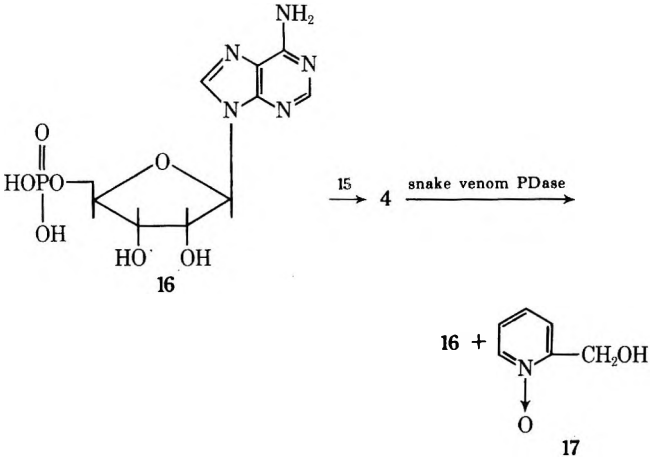
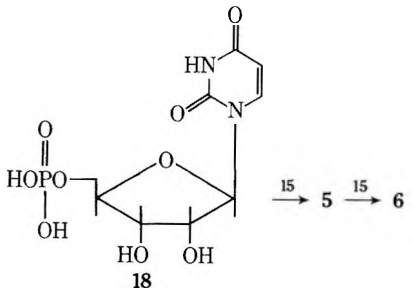


Chart VI



On treatment of uridine 5′-phosphate (18) with the reagent 15 at 20° for 30 min, 1-oxido-2-pyridylmethyluridine 5′-phosphate (5) was obtained in 89% yield (Chart VII). The structure of 5 was confirmed by the enzymatic hydrolysis (snake venom phosphodiesterase) to 1-oxido-2-pyridylcarbinol (17) and 18 (Chart VIII) and by the comparison of its spectral properties and electrophoretic mobilities with those of an authentic sample which had been prepared by a general procedure including deacetylation from 2′,3′-di-*O*-acetyluridine 5′-phosphate (19)[13] and 17 by the use of 2,4,6-triisopropylbenzene sulfonyl chloride (TPS) as a condensing agent.

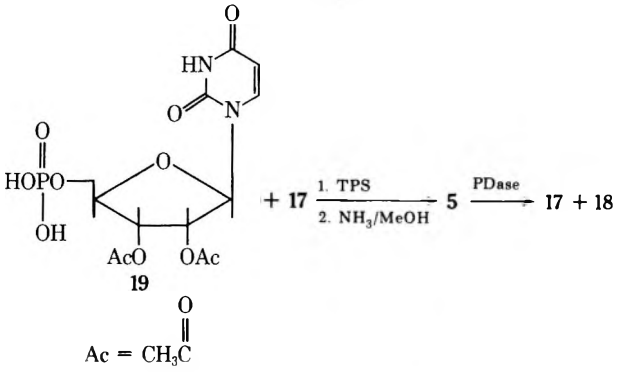
Chart VII



Prolonged treatment (20 hr) of 18 with the reagent 15 afforded a mixture of 5 and 1-oxido-2-pyridylmethyl-3-(1-oxido-2-pyridylmethyl)uridine 5′-phosphate (6) in 85% total yields. Separation of 6 and 5 could be achieved by a DEAE-cellulose column chromatography.

The structure confirmation of 6 was carried out as follows. Hydrolysis of 6 either with a mixture of snake venom phosphodiesterase and alkaline phosphomonoesterase or initially with the phosphodiesterase and subsequently with the phosphomonesterase afforded 3-(1-oxido-2-pyridylmethyl)uridine (20) (Chart IX) which was found to be identical with a sample which had been prepared

Chart VIII



according to a route in Chart X: 2′,3′-*O*-isopropylideneuridine (21) was treated with 1-oxido-2-pyridylmethyl chloride (22)[12] in the presence of potassium carbonate in DMF for 3 hr to give 2′,3′-*O*-isopropylidene-3-(1-oxido-2-pyridylmethyl)uridine (23). Deacetonization with refluxing 20% aqueous acetic acid afforded an authentic sample of 20.

Chart IX

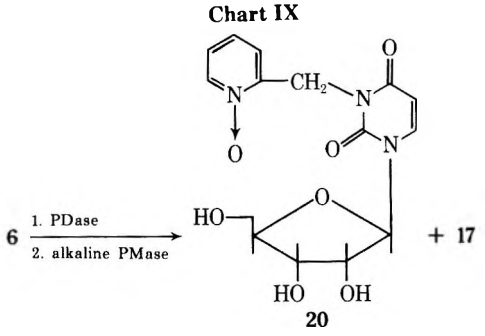
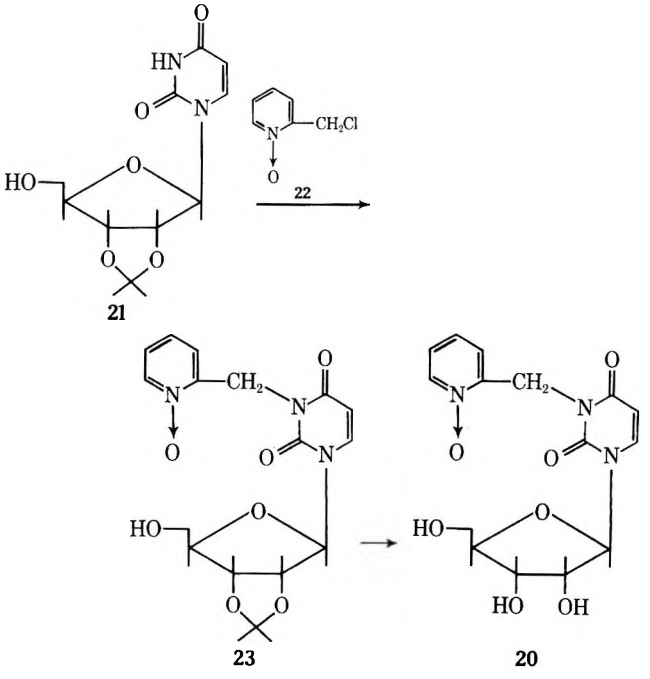


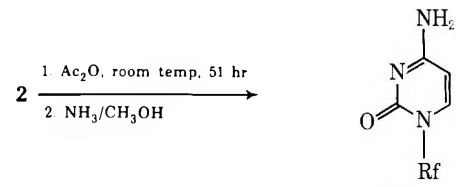
Chart X



Deblocking of the 1-oxido-2-pyridylmethyl group of 2 was achieved by treatment with acetic anhydride at room temperature for 51 hr, followed by methanolic ammonia treatment (Chart XI). Recovery of cytidine was 86.7%.

Deblocking of nucleotides 4 and 6 could be achieved in 96 and 86% yields, respectively, by treatment of the nucleotides with acetic anhydride at 60° for 35 hr (in the

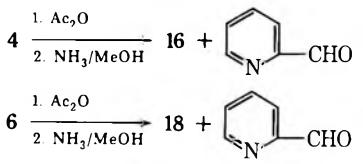
Chart XI



Rf = β-D-ribofuranosyl

case of **4**) and at 37° for 72 hr (in the case of **6**) and by subsequent methanolic ammonia treatment (Chart XII).

Chart XII



Thus it was found that the 1-oxido-2-pyridylmethyl group was quite useful for the protection of nucleosides and nucleotides. It is worthy of note that our new reagent (**15**) was found to be capable of introduction of op protection into hydroxyl functions of the phosphate of the nucleotides even in aqueous solution.

As a logical extention of the present investigation, we are trying to apply this protection for the synthesis of the oligoribonucleotides.

Experimental Section

General. The ultraviolet spectra were determined using a Hitachi recording spectrophotometer (Model 3T) and gas chromatography was carried out by a Shimazdu gas chromatograph (Model GC-4-APF). Infrared spectra were taken on an infrared spectrophotometer (DS-701G) in KBr tablets. Nuclear magnetic resonance (nmr) spectra were determined with a Hitachi high-resolution nmr spectrometer (Model R24) in deuteriochloroform. The chemical shifts were reported in parts per million downfield from tetramethylsilane as internal standard. Snake venom 5′-nucleotidase (*Clotalus adamanteus*) was obtained from Sigma Chemical Co. Digestion with this enzyme was carried out as reported.[16] Snake venom phosphodiesterase was obtained from Worthington Biochemicals Co. and was dissolved 1 mg in 1 ml. This solution was used for the enzymatic digestion.

Paper electrophoresis (PEP) was performed on Toyo-Roshi paper No. 51A (45 × 10 cm) impregnated with 0.05 *M* triethylammonium bicarbonate (TEAB, pH 8.0) using 700 V or with 0.05 *M* acetate buffer (pH 3.7) using 1000 V conducted on flat-bed apparatus. Paper chromatography was carried out by the ascending technique on Toyo-Roshi paper No. 51A using the following systems: solvent A, *n*-BuOH–AcOH–H_2O (5:2:3); solvent B, *i*-PrOH–NH_4OH–H_2O (7:1:2). DEAE cellulose refers to the product of Jujo Seishi Co. and a gift therefrom which was used in the bicarbonate form. Silica gel for the column chromatography refers to Kieselgel 60 (Merck). Silica gel for the thin layer chromatography (tlc) refers to Kieselgel HF 254 (Merck). Two-dimensional tlc on Avicel SF plate (10 × 10 cm) was performed with solvent A and then with solvent B. In each case, about 1–2 $A_{260\,nm}$ units of nucleotides were used. Extraction and estimation of each spot were carried out as reported.[17] The following molar extinction coefficients were used: 1-oxido-2-pyridylmethyladenosine 5′-phosphate (**4**), 25,000; 1-oxido-2-pyridylmethyluridine 5′-phosphate (**5**), 18,500; and 1-oxido-2-pyridylmethyl-3-(1-oxido-2-pyridylmethyl)-uridine 5′-phosphate (**6**), 27,000.

Unless otherwise specified, the solvent was removed under reduced pressure (with a water aspirator) with a rotating evaporator.

The melting points are uncorrected. Elemental analyses were performed by a staff of the analytical laboratory in the Faculty of Pharmaceutical Sciences, Hokkaido University.

1-Oxido-2-pyridylmethyl Chloride HCl (22). Improved Method. In a three-necked flask, 1-oxido-2-pyridylcarbinol (**17**, 10.0 g) was dissolved in 100 ml of chloroform. There was added dropwise 12.6 g (7.7 ml, 1.1 equiv) of freshly distilled thionyl chloride at 0° in 2 hr. After the addition was complete, the mixture was heated at 50–60° (bath temperature) for 2 hr. The reaction mixture was allowed to come to room temperature. Ethanol (0.5 ml) was added to decompose excess thionyl chloride. The reaction mixture was then concentrated to dryness. The residue was crystallized from acetone, mp 105–109°, yield 12.39 g (86.6%).

1-Oxido-2-pyridylmethylamine Hydrochloride (9). Crude product (without crystallization) prepared from 7.3 g of **17** was dissolved in 300 ml of saturated ammonium hydroxide (0°). The solution was kept at room temperature overnight and then concentrated to dryness. The residue was crystallized from 120 ml of absolute ethanol. The first crop weighed 5.03 g. After concentration, the mother liquor gave 1.0 g of **9**, total yield 6.03 g (58%), mp 114–115°.

Anal. Calcd for $C_6H_9N_2OCl$: C, 44.87; H, 5.79; N, 16.92; Cl, 22.08. Found: C, 44.69; H, 5.70; N, 17.10; Cl, 22.07.

1-Oxido-2-pyridylmethylamine. 1-Oxido-2-pyridylmethylamine hydrochloride (**9**, 1.8 g) was neutralized with a resin (Dowex 1, OH^- form). After filtration, the filtrate was concentrated to dryness. Crystallization from ethyl acetate–acetonitrile–ethyl ether (1:1:1) gave the analytical sample, yield, 1.0 g, mp 82–83°.

Anal. Calcd for $C_6H_8N_2O$: C, 58.06; H, 6.45; N, 22.58. Found: C, 57.94; H, 6.42; N, 22.35.

N^6-(1-Oxido-2-pyridylmethyl)adenine (1). 6-Methylthiopurine (3.2 g) was oxidized with saturated aqueous bromine solution (150 ml) for 30 min.[9] The solution was neutralized with a resin (Dowex 1 OH^- form, 53 ml). The resin was filtered off. The filtrate was concentrated to dryness. The residue (1.4 g) was dissolved in aqueous methanol (1:1) and then treated with 1-oxido-2-pyridylmethylamine prepared from 0.79 g of the chloride **22**. The solution was heated for 1 hr and then concentrated to dryness. The residue was twice recrystallized from water: mp 235–237° dec; yield 0.93 g (20%); uv λ_{max} (H_2O) 260 nm (ε 25,000), λ_{max} (pH 1) 260, 275 nm (sh), λ_{max} (pH 11) 270 nm.

Anal. Calcd for $C_{11}H_{10}N_6O$: C, 54.54; H, 4.16; N, 34.69. Found: C, 54.30; H, 4.15; N, 34.49.

Oxidation of 4-Thiouridine (7) and Syntheses of N^4-(1-Oxido-2-pyridylmethyl)cytidine (2). To a solution of 4-thiouridine[8] (**7**, 1.0 g, 380 mmol) in 80 ml of phosphate buffer (pH 7.0) was added at 0° 1 equiv of 0.1 *M* potassium permanganate solution. The mixture was kept at the same temperature for 15 min.[7] Manganese dioxide formed was removed by centrifugation. One equivalent of **9** was added to the filtrate. The solution was adjusted to pH 8.5 with 0.5 *M* potassium hydroxide and stored for 25 hr at room temperature. After checking that the reaction was complete by uv, the mixture (which contained 99% crude yield of **2**) was treated with activated charcoal (Shirasagi brand, 2.5 g). The charcoal was collected by filtration, washed with water, extracted with 50% aqueous ethanol containing 2% ammonia, and filtered. The filtrate was concentrated to dryness and recrystallized from water, mp 202–205°, yield 0.326 g (34.7%).

Anal. Calcd for $C_{15}H_{18}N_4O_6$: C, 51.42; H, 5.18; N, 15.99. Found: C, 51.04; H, 5.21; N, 16.05.

N^6-(1-Oxido-2-pyridylmethyl)adenosine (3). To a solution of 9-(β-D-ribofuranosyl)-6-ethylthiopurine (**12**, 1.21 g, 3.87 mmol) in 260 ml of phosphate buffer (pH 7.0) was added 1 equiv of saturated aqueous bromine solution. After checking that bromine had been completely consumed with an iodine–iodide–starch paper, another 1 equiv of bromine solution was added. The solution was kept at room temperature overnight. There was then added 0.58 g (1 equiv) of **9**. The solution was adjusted to pH 8.5 with 2 *N* sodium hydroxide and kept at ambient temperature for 24 hr. The solution was concentrated to dryness. The residue was dissolved in methanol and filtered. The filtrate was concentrated to dryness. The residue was again dissolved in 3 ml of methanol and applied to a silica gel column (weight of silica gel, 80 g). The column was washed with 2 l. of $CHCl_3$–MeOH (7:1). Fractions containing **3** were collected and concentrated to dryness (850 mg). The residue was rechromatographed in a similar way, except that 30 g of silica gel was used and the column was washed with $CHCl_3$–MeOH (5:1). Fractions containing **3** were collected and concentrated to dryness. The residue was crystallized from water: mp 182–185° dec; yield 286 mg (20%); uv λ_{max} (H_2O) 260 nm, λ_{max} (pH 1) 260 nm (275 nm, sh), λ_{max} (pH 11) 260 nm (270 nm, sh).

Acid Hydrolysis of N^6-(1-Oxido-2-pyridylmethyl)adenosine (3). Compound **3** (10 mg) was dissolved in 0.1 *N* HCl (2 ml). The solution was heated under reflux for 1 hr. R_f values of the hydrolysate (paper chromatography, solvent A and B) were 0.63 and 0.75, respectively, which were found to be identical with the re-

spective R_f value of **1**. Uv of the extracts of each spot was similar to that of **1**.

***p*-Tosylhydrazone of 2-Formylpyridine 1-Oxide.** 2-Formylpyridine 1-oxide[10] prepared by selenium dioxide oxidation of 250 g of α-picoline was dissolved in 1 l. of methanol. This solution was treated with 500 g of *p*-tosylhydrazine dissolved in 1 l. of methanol to give 470 g of product (79.4%), mp 135–137°.

Anal. Calcd for $C_{13}H_{13}N_3O_3S$: C, 53.61; H, 4.46; N, 14.43; S, 11.00. Found: C, 53.49; H, 4.50; N, 14.29; S, 10.98.

1-Oxido-2-pyridyldiazomethane (15, Chloroform Solution). The *p*-tosylhydrazone of 2-formylpyridine 1-oxide (10 mmol) was dissolved in 40 ml of ethanolic sodium ethoxide prepared from the equivalent of sodium. The solution was heated at 50° for 20 min and then concentrated to dryness. The residue was dissolved in 50 ml of chloroform. Insoluble material (sodium *p*-toluenesulfinate) was filtered off. The filtrate was employed for alkylation. Glc (column: silicone ov-1 on Chromosorb, column temperature 150°, detector temperature 215°) showed that the above solution contained 2-ethoxymethylpyridine 1-oxide (*ca.* 10%) in addition to **15**. The ether was isolated by preparative tlc: mp of the picrate 125° (crystallized from methanol–ethyl ester); yield 280 mg (10%); ir (neat) 2080 (N≡N⁺), 1235 cm^{-1} (⁺N–O⁻).

Anal. Calcd for $C_{14}H_{14}N_4O_9$: C, 44.00; H, 3.69; N, 14.65. Found: C, 44.02; H, 3.70; N, 3.66.

Determination of Concentration of 15 in Chloroform Solution. Metallic sodium (870 mg) was dissolved in 50 ml of dry ethanol. To the solution was added 11 g of the *p*-tosylhydrazone of 2-formylpyridine 1-oxide in portions. The solution was refluxed for 1 hr and then concentrated to dryness. The residue was dissolved in 50 ml of chloroform. Insoluble material was filtered off. There was then added 4.7 g of benzoic acid to the filtrate. The solution was kept at room temperature for 3 hr and then concentrated to dryness. The residue was triturated with 50 ml of 10% $NaHCO_3$. Product was collected by filtration, yield 4.1 g (47%, based on the *p*-tosylhydrazone), mp 125–126°.[5] Based on the assumption that the alkylation was quantitative, the yield of **15** could be estimated to be 47%. The above chloroform solution had contained *ca.* 5.13 g of **15**.

General Procedure for Alkylation with 15 (Alkylation of Benzoic Acid as a Representative). To a chloroform solution (30 ml) of 1-oxido-2-pyridyldiazomethane (**15**) prepared from 2.99 g of the *p*-tosylhydrazone and 0.23 g of sodium was added a DMF solution (30 ml) of benzoic acid (1.0 g). The solution was kept at room temperature for 3 hr and then concentrated to half of its volume, and water was added. Crystals deposited were collected and recrystallized from ethanol, yield 1.02 g (quantitative).[5a]

1-Oxido-2-pyridylmethyladenosine 5′-Phosphate (4). To a suspension of adenosine 5′-phosphoric acid (**16**, 46.2 mg) in 10 ml of water was added sodium hydrogen carbonate solution until solution resulted. There was then added a chloroform solution (20 ml) of **15** prepared from 1.98 g of the *p*-tosylhydrazone. The solution was kept at room temperature overnight. After making sure that the reaction was complete (by paper electrophoresis), the aqueous layer was extracted with three 10-ml portions of chloroform and separated. The aqueous layer was applied to a DEAE-cellulose column (1.6 × 40 cm). The column was initially washed with 500 ml of water and then with a linear gradient of 500 ml of water and 500 ml of 0.2 *M* TEAB solution. The effluent was monitored at 260 nm. Ten grams of effluent was collected as one fraction. Fractions 14–27 were pooled and rechromatographed under similar conditions: fractions 15–23 (fraction 1a) were colored and discarded; fractions 24–29 containing **4** (1b) were pooled and concentrated. PEP examination of fraction 1b showed the presence of a single spot corresponding to **4**, which showed a positive reaction against a metaperiodate–benzidine spray reagent:[15] uv λ_{max} (pH 2) 257 nm, λ_{max} (H_2O) 258 nm [ε (p) 25,000];[14] yield 90%.

Structural Confirmation of the Product 4. Fraction 1b (50 μl, 15 $A_{260\,nm}$ units) and 30 μl of 0.1 *M* TEAB solution were mixed and adjusted to 100 μl with distilled water. The solution was incubated with 20 μl of snake venom phosphodiesterase solution at 37° overnight. Electrophoretic examination (pH 8.0) of the reaction mixture showed the presence of adenosine 5′-phosphate (**16**) and 1-oxido-2-pyridylcarbinol (**17**) in a molar ratio of 1:1.

1-Oxido-2-pyridylmethyluridine 5′-Phosphate (5). Uridine 5′-phosphate (**18**, disodium salt, $2.5H_2O$, 300 mg, 0.606 mmol) was converted to the free acid with Dowex 50Wx8 (H^+ form). The solution (10 ml) of the free acid was mixed with a chloroform solution (20 ml) of **15** which had been prepared by the above general procedure. The mixture was kept stirring for 20 min at room temperature. The solvent was removed. The residue was dissolved in a small amount of water. The solution was applied to a DEAE-cellulose column (3.5 – 30 cm). The column was initially washed with 100 ml of water and then with 0.06 *M* TEAB solution. Fractions containing **5** were collected and adjusted to pH 4 with a resin (Dowex 50Wx8, H^+ form). The solution was concentrated to dryness at 30°, yield 9800 $A_{260\,nm}$ units (0.534 mmol), 89%.

Structural Confirmation of the Product (5). An incubation mixture contained 30 $A_{260\,nm}$ units of **5**, 20 μl of snake venom phosphodiesterase, and 100 μl of 0.3 *M* triethylammonium bicarbonate solution. The mixture was incubated at 37° for 15 hr. Nucleotide **5** was completely hydrolyzed and the reaction mixture contained uridine 5′-phosphate (**18**) and 1-oxido-2-pyridylcarbinol (**17**) in a molar ratio of 1:1. Uv spectral properties and electrophoretic mobilities (at pH 3.7 as well as at pH 8.0) of **5** were identical with those of an authentic sample of 1-oxido-2-pyridylmethyluridine 5′-phosphate (**5**), prepared as described below.

Alternative Synthesis of 1-Oxido-2-pyridylmethyluridine 5′-Phosphate (5). Synthesis of 2′,3′-Di-*O*-acetyluridine 5′-Phosphate (19). To a solution of uridine 5′-phosphate (disodium salt H_2O, 3.7 g, 7.62 mmol, determined spectrophotometrically) in 50 ml of pyridine was added acetic anhydride (20 ml). The mixture was kept in the dark at room temperature for 6 days. A clear solution resulted. There was then added methanol (25 ml) at 5° and then the mixture was allowed to come to 30°. The solution was concentrated to dryness. The residue was dissolved in 40% aqueous pyridine (50 ml). The solution was allowed to stand at room temperature for 12 hr. The solvent was removed. The residue was triturated with ethanol (100 ml) to yield a white powder, which was dried over phosphorus pentoxide at 60°. Tlc examination showed the presence of a new spot (which gave a negative reaction against a metaperiodate–benzidine spray reagent).[15] Uv spectra were quite similar to those of **18**, yield 3.2 g (84.5%, calculated as disodium salt $2.5H_2O$).

Synthesis of 5. 1-Oxido-2-pyridylcarbinol (**17**, 125 mg, 1 mmol) and nucleotide **19**[13] (412 mg, 1 mmol) were dissolved in DMF (5 ml). The solvent was removed *in vacuo* (1 mm). The completely dried residue was dissolved in DMF (4 ml). There was then added TPS (604 mg, 2 mmol). The solution was kept at room temperature for 24 hr. Cold water (3 ml) was added to the reaction mixture at 5°. The solution was allowed to come to room temperature and was kept at the same temperature for 1 hr. Tri-*n*-butylamine (1.5 ml) was added. The mixture was kept at room temperature for 30 min and filtered. The filtrate was treated with three 30-ml portions of ether. The aqueous layer was concentrated to dryness. Paper electrophoresis showed the presence of a single spot whose mobility was different from that of **17** and **18**. The reaction mixture was then applied to a DEAE-cellulose column (1.2 × 40 cm, fraction volumn 11 ml). The column was washed with a linear gradient of 500 ml of water and 500 ml of 0.3 *M* TEAB. Fractions 11–19 were pooled (4.400 $A_{260\,nm}$ units). A portion (35 $A_{260\,nm}$ units) was concentrated to dryness. The residue was dissolved in methanolic ammonia (1 ml). The solution was kept at room temperature for 20 hr. The mixture was concentrated to dryness, electrophoretic mobility $R_{5'UMP}$ (pH 3.7) 1.01. Enzymatic hydrolysis of this sample with snake venom phosphodiesterase showed that this nucleotide was completely hydrolyzed to uridine 5′-phosphate (**18**) and **17**. The rest of the mixture was similarly treated; 1-oxido-2-pyridylmethyluridine 5′-phosphate (**5**) was obtained in a yield of 70%. This sample was used as an authentic sample of **5** for the above-mentioned comparison.

1-Oxido-2-pyridylmethyl-3-(1-oxido-2-pyridylmethyl)uridine 5′-Phosphate (6). To a chloroform solution (30 ml) of **15** prepared from 2.83 g of the *p*-tosylhydrazone of 2-formylpyridine 1-oxide was added an aqueous solution (10 ml) of uridine 5′-phosphate (**18**, disodium salt, 133.6 mg, 1000 $A_{260\,nm}$ units). The solution was kept at room temperature overnight. Paper electrophoretic examination (at pH 8.0) of the reaction mixture showed the absence of the starting material **18**. The aqueous layer was separated and washed with three 10-ml portions of chloroform and was then applied to DEAE-cellulose column chromatography (1.6 × 40 cm, fraction size 10 ml). The column was washed with a linear gradient of 500 ml of water and 500 ml of 0.2 *M* TEAB solution. Fractions 32–48 (which are referred to as fraction 1) and fractions 49–59 (fraction 2) were separately pooled. Fraction 1 contained products (**5** and **6**), whereas fraction 2 contained a small amount of the starting material (**18**). Fraction 1 was rechromatographed under similar conditions. On chromatogram, two peaks (1a and 1b) appeared: 1a, fractions 22–29; 1b, fractions 35–40. Total optical density (TOD) in fraction 1a was 1000 $A_{260\,nm}$ units; TOD in fraction 1b was 500 $A_{260\,nm}$ units. Electrophoretic mobilities of nucleotides in fraction 1a and 1b were $R_{5'UMP}$ 0.52 and 0.67 (at pH 8.0), respectively. On the basis of

these relative electrophoretic mobilities and the spectral data it was tentatively concluded that fraction 1a and 1b contained bis-op-protected uridine 5′-phosphate (6) and op-protected uridine 5′-phosphate (5), respectively.

Confirmation of the Structure of Nucleotides in Fraction 1a and 1b. Enzymatic Hydrolysis of Nucleotides 6 in Fraction 1a. An incubation mixture contained 30 $A_{260\,nm}$ units of fraction 1a (50 μl), 40 μl of 0.14 *M* TEAB solution, 40 μl of snake venom phosphodiesterase, and 40 μl of alkaline phosphomonoesterase. The mixture was incubated at 37° for 20 hr.

PEP (pH 8.0) and paper chromatographic (solvent A) examination showed that 6 in fraction 1a was completely hydrolyzed with these enzymes to 1-oxido-2-pyridylcarbinol (17), inorganic phosphate, and 3-(1-oxido-2-pyridylmethyl)uridine (20). The structure of 20 was unequivocally established by comparison with a sample which was prepared by an unambiguous synthesis.

The structure of 5 in fraction 1b was determined as described before.

3-(1-Oxido-2-pyridylmethyl)-2′,3′-*O*-isopropylideneuridine (23). 2′,3′-*O*-Isopropylideneuridine (21, 2.85 g, 10 mmol) was treated with 1-oxido-2-pyridylmethyl chloride HCl (22, 1.8 g, 12.4 mmol) in the presence of dried, powdered K_2CO_3 (4.0 g) in DMF (25 ml) at room temperature for 36 hr. The reaction mixture was then filtered. The filtrate was concentrated to dryness. The residue was triturated with ether and filtered. Recrystallization from aqueous acetone (30 ml, 5:1) afforded the analytical sample: yield 3.20 g (80%); mp 204–205°; uv λ_{max} (0.1 *N* HCl) 256.5 nm, λ_{max} (H_2O) 256.0 nm, λ_{max} (0.1 *N* NaOH) 255 nm. The elemental analysis and nmr were expected for 23: nmr (TMS external standard, DMSO-d_6) 1.30 (s, 3, CH_3 of isopropylidene), 1.5 (s, 3, CH_3 of isopropylidene), 3.3 (s, 2, 5′-CH_2), 4.2 (m, 1, 5′-OH), 5.9 (d, 1, anomeric proton), multiplet centered around 7.3 (m, 3, pyridine), 8.0 ppm (d, 1, 6-H), absence of signals downfield from 9.0 ppm.

Anal. Calcd for $C_{18}H_{21}N_3O_7$: C, 55.24; H, 5.41; N, 10.74. Found: C, 55.52; H, 5.42; N, 10.49.

3-(1-Oxido-2-pyridylmethyl)uridine (20). A solution of 23 (780 mg, 2.0 mmol) in 20% aqueous acetic acid was refluxed for 2 hr. The solution was concentrated to dryness. The residue was recrystallized from ethanol: mp 186–187°; yield 630 mg (90%); R_f (solvent B) 0.69; nmr (TMS external standard, DMSO-d_6) 3.65 (s, 2, 5′-CH_2), 5.04 (s, 2, methylene of α-picolyl), 5.80 (d, 1, anomeric proton), 5.88 (d, 2, 5-H), 7.30 (m, 3, pyridine), 8.20 (d, 1, 6-H); uv λ_{max} (0.1 *N* HCl) 256 nm (ε 18,500), λ_{max} (H_2O) 256.5 nm (ε 18,500), λ_{max} (0.1 *N* NaOH) 256 nm (ε 18,500).

Anal. Calcd for $C_{15}H_{17}N_3O_7$: C, 51.27; H, 4.88; N, 11.96. Found: C, 51.14; H, 4.81; N, 11.74.

Deblocking. Conversion of N^4-(1-Oxido-2-pyridylmethyl)cytidine to Cytidine. N^4-(1-Oxido-2-pyridylmethyl)cytidine (2, 100 mg, 0.286 mmol) was dissolved in acetic anhydride (10 ml). The solution was allowed to stand with stirring at 30° for 51 hr. The solution was concentrated to dryness. The residue was dissolved in methanolic ammonia in a stoppered vessel. The solution was kept at room temperature overnight. The mixture was concentrated to dryness. The residue was dissolved in a small amount of water. The aqueous solution was applied to a Dowex 1x8 column (1.2 × 32 cm formate form, fraction size 15 ml). The column was initially washed with water (750 ml) and then with 0.2 *M* formic acid (500 ml). The effluent was monitored at 260 nm. Fractions containing cytidine were pooled and concentrated to dryness. Recovery of cytidine was 0.248 mmol (86.7%). This sample was found to be identical with cytidine on the criteria of uv spectra and R_f value in solvent systems A and B.

Conversion of 1-Oxido-2-pyridylmethyl-3-(1-oxido-2-pyridylmethyl)uridine (6) to Uridine 5′-Phosphate (18). To a solution of 6 (triethylammonium salt, 991 $A_{260\,nm}$ units) in DMF (20 ml) was added acetic anhydride (50 ml). The mixture was kept at 37° for 72 hr. The solution was concentrated to dryness below 40°. The residue was dissolved in methanol (60 ml) saturated with ammonia. The mixture was kept at room temperature overnight. The solvent was removed. The residue was dissolved in a small amount of water. The aqueous solution was applied to a DEAE-cellulose column (0.7 × 40 cm). The column was initially washed with 200 ml of water (the effluent was discarded) and then with 0.2 *M* TEAB solution (200 ml). Fractions containing 18 were collected, concentrated to dryness, and lyophilized, PEP $R_{5'\,UMP}$ 1.08 (pH 8.0). Uv spectra were identical with those of authentic 5′-UMP, yield 229 $A_{260\,nm}$ units (86%).

Conversion of 1-Oxido-2-pyridylmethyladenosine 5′-Phosphate (4) to Adenosine 5′-Phosphate (16). Nucleotide 4 (triethylammonium salt, 6200 A_{260nm} units) was dissolved in 5 ml of acetic anhydride. The solution was heated at 60° for 35 hr. The solution was then concentrated to dryness below 40°. The residue was dissolved in 10 ml of methanol saturated with ammonia at 0°. The solution was kept at room temperature overnight. The solvent was removed. The residue was applied to a DEAE-cellulose column (3 × 40 cm). The column was washed with 500 ml of water and then with a linear gradient of 0.2 *M* tetraethylammonium bicarbonate solution (1.5 l.) and water (1.5 l.), fraction size 18 g. Fractions containing 16 (fractions 59–85) were concentrated to dryness and lyophilized, PEP $R_{5'\,AMP}$ 1.00 (pH 8.0), R_f (EtOH–1 *M* $AcONH_4$, 1:1) 0.41. Uv spectra were identical with those of an authentic sample of 5′-AMP, yield 3560 $A_{260\,nm}$ units (96%).

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Registry No.—**1**, 50921-44-3; **2**, 51022-68-5; **3**, 50921-80-7; **4**, 50908-30-0; **5**, 50921-81-8; **6**, 50908-28-6; **7**, 13957-31-8; **9**, 50921-45-4; **9** hydrochloride, 50921-46-5; **12**, 13286-04-9; **15**, 50908-23-1; **16**, 61-19-8; **17**, 10242-36-1; **18**, 58-97-9; **19**, 48215-95-8; **20**, 50908-29-7; **21**, 362-43-6; **22** hydrochloride, 20979-34-4; **23**, 50921-79-4; 6-methylthiopurine, 50-66-8; 2-formylpyridine 1-oxide, 7216-40-2; 2-formylpyridine 1-oxide *p*-tosylhydrazone, 50908-22-0; 2-ethoxymethylpyridine 1-oxide picrate, 21901-67-7.

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s-Triazolo[1,5-a]pyrimidine Nucleosides. Site of N-Glycosylation Studies and the Synthesis of an N-Bridgehead Guanosine Analog[1]

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Direct glycosylation of *O*-trimethylsilyl-5-chloro-*s*-triazolo[1,5-*a*]pyrimidin-7-one (1) with 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide in acetonitrile at room temperature gave 5-chloro-3-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-*s*-triazolo[1,5-*a*]pyrimidin-7-one (3) in good yield, which on aminolysis with methanolic ammonia furnished 5-chloro-3-β-D-ribofuranosyl-*s*-triazolo[1,5-*a*]pyrimidin-7-one (5). Treatment of 5 with nucleophilic reagents gave 5-substituted 3-β-D-ribofuranosyl-*s*-triazolo[1,5-*a*]pyrimidin-7-ones, including 5-mercapto- (8e), 5-methylamino- (8c), 5-dimethylamino- (8d), and 5-amino-3-β-D-ribofuranosyl-*s*-triazolo[1,5-*a*]pyrimidin-7-one (8b), an analog of guanosine possessing a bridgehead nitrogen atom. Treatment of 5 with hydrazine gave a rearrangement product (7) identified as 3-[pyrazolin-5(1*H*,2*H*)-on-3-ylamino]-4-β-D-ribofuranosyl-*s*-triazole. Treatment of 5 with liquid ammonia gave a ring-opened product which was tentatively identified as 6-amino-2-[*N*-(β-D-ribofuranosyl)cyanamido]pyrimidin-4-one (9). A similar product tentatively identified as 4-amino-6-chloro-2-[*N*-(β-D-ribofuranosyl)cyanamido]pyrimidine (17) was formed under the glycosylation conditions with *N*-trimethylsilyl-7-amino-5-chloro-*s*-triazolo[1,5-*a*]pyrimidine (14). Glycosylation of *O*-trimethylsilyl-5-methyl-*s*-triazolo[1,5-*a*]pyrimidin-7-one (2) and *N*,*O*-bis(trimethylsilyl)-7-amino-*s*-triazolo[1,5-*a*]pyrimidin-5-one (16) gave the 3-β-D-ribofuranosyl derivatives (4 and 18, respectively), whereas glycosylation of *N*-trimethylsilyl-7-amino-*s*-triazolo[1,5-*a*]pyrimidine (15) gave *only* the 4-β-D-ribofuranosyl derivative (19). The sites of glycosylation have been determined unequivocally by chemical conversion to compounds of known structure and by pmr spectral comparisons of the H-2 chemical shifts. The anomeric configuration of 5 has been determined unequivocally as β by cyclonucleoside formation.

In recent years many unnatural nucleosides have been described which resemble at first glance the natural purine nucleosides, adenosine and guanosine, but which actually differ in some minor aspect. The number of these "counterfeits" which could be prepared and identified employing alternative heterocyclic systems has been limited by the capability of the organic chemist to unequivocally assign the site of glycosylation and anomeric configuration. In many cases the efficiency of a particular nucleoside preparation has been decreased by the lack of specificity of the glycosylation reaction and the formation of two or more isomeric glycosyl derivatives,[2,3] requiring tedious separation and characterization.

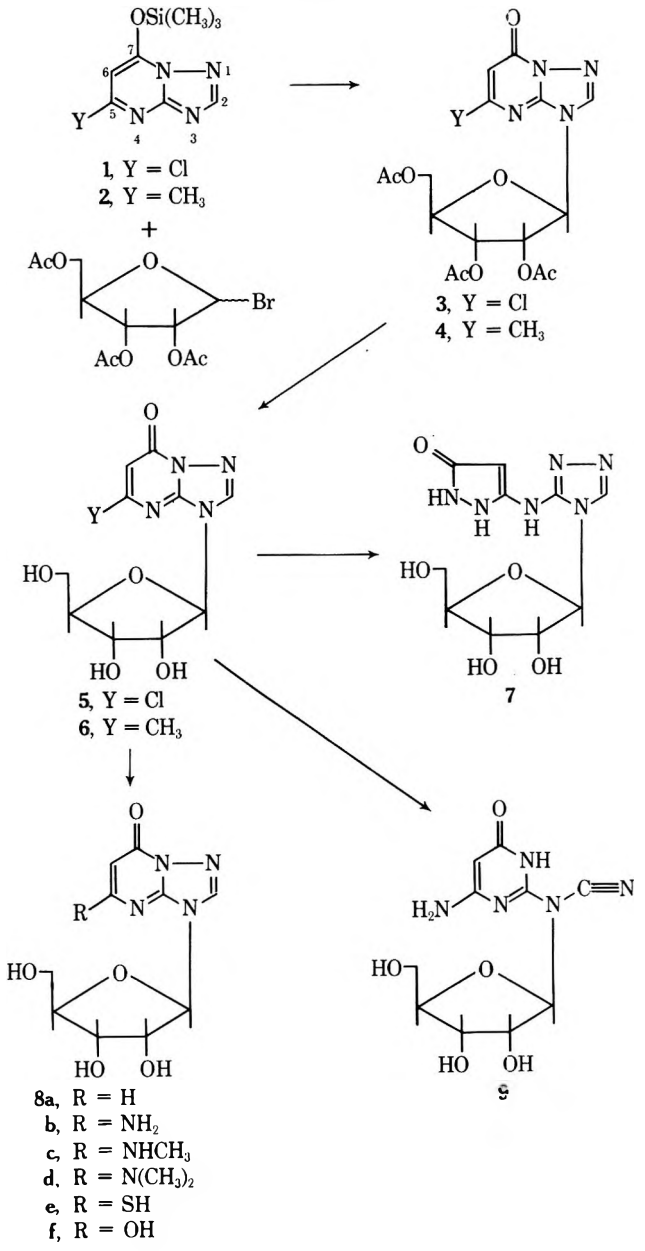
It was the initial objective of our investigation to prepare the guanosine analog in the *s*-triazolo[1,5-*a*]pyrimidine system, a bridgehead nitrogen system easily pictured as purine with N-1 and C-5 interchanged. This heterocyclic system is of particular interest since the corresponding nucleosides lack an N(H) function at position 1 of purine; hydrogen bonding of the Watson–Crick type, therefore, would not be possible.

Winkley, *et al.*,[3] have described the glycosylation of *s*-triazolo[1,5-*a*]pyrimidin-7-one, but the procedure gave a mixture of the 3- and 4-ribofuranosyl isomers and no evidence was presented for the assignment of the β configuration at the anomeric center. Recently, Tindall, *et al.*,[4] and Schmidt and Townsend[5] have demonstrated the directive effect of certain 8-halogen derivatives upon the site of purine glycosylation. For this reason 5-chloro-*s*-triazolo[1,5-*a*]pyrimidin-7-one[6] was chosen as the starting material for the nucleoside synthesis. The halogen at the position adjacent to N-4 could be predicted to deactivate that nitrogen in the glycosylation reaction. Treatment of 5-chloro-*s*-triazolo[1,5-*a*]pyrimidin-7-one with hexamethyldisilazane according to the general procedure described by Wittenberg[7] gave the trimethylsilyl derivative (1, Scheme I) which was treated with 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide in acetonitrile at room temperature to furnish a good yield of a single crystalline triacetylated nucleoside (3). Nucleoside 3 was the only nucleoside which could be detected by tlc or column chromatography procedures (some heterocyclic starting material could be isolated from the reaction product). Similarly, in other glycosylation reactions reported in this study, no other nucleosides were detected by tlc other than those isolated and characterized in the Experimental Section. Treatment of 3 with methanolic ammonia at ambient temperature gave the deacetylated nucleoside 5, which was shown by elemental analysis to have retained the 5-chloro group. Dehalogenation of 5 with 10% palladium on carbon in a hydrogen atmosphere gave 3-β-D-ribofuranosyl-*s*-triazolo[1,5-*a*]pyrimidin-7-one (8a) identical with an authentic sample,[3,8] confirming the directive affect of the 5-chloro group to give exclusively the N-3 glycosyl derivative.

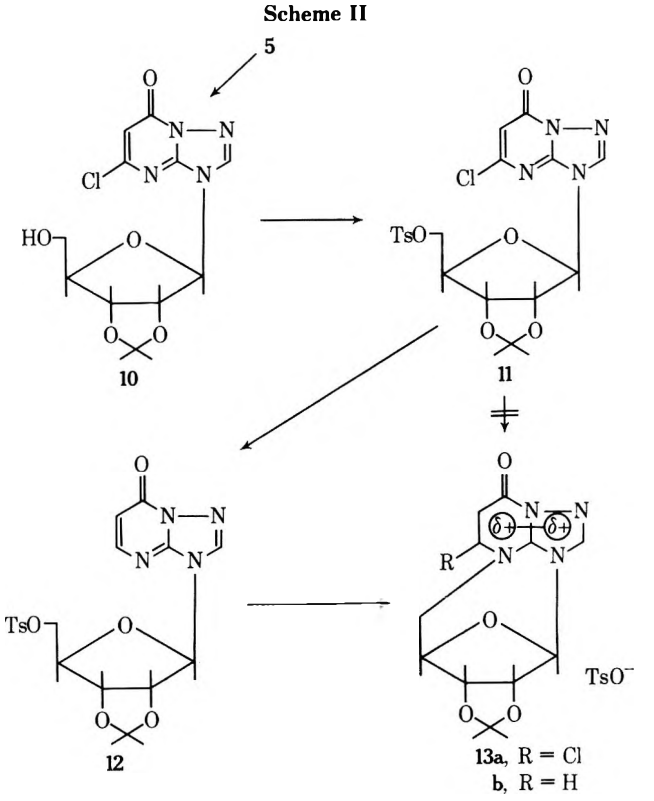
Our first attempt to prepare the guanosine analog 8b from 5 by treatment with liquid ammonia in a sealed vessel gave a product (9) in excellent yield, which lacked the strong ultraviolet absorption (near 270 nm) characteristic of other *s*-triazolo[1,5-*a*]pyrimidin-7-ones. In the case of 9 a strong absorption in the infrared spectrum at 2230 cm^{-1} was also observed. Since 9[9] possessed a pyrimidine-like ultraviolet spectrum and cleavage of the triazole between the adjacent nitrogens would give an *N*-cyanopyrimidine derivative, the structure of 9 was tentatively assigned as 6-amino-2-[*N*-(β-D-ribofuranosyl)cyanamido]pyrimidin-4-one. The tentative structure assignment was supported by elemental analysis and by pmr spectral analysis, which showed only one aromatic proton, corresponding to H-5 of pyrimidine (or H-6 of *s*-triazolo[1,5-*a*]pyrimidine). A similar product showing an absorption in the infrared spectrum at 2235 cm^{-1} was isolated[10] in 1963 from a Hilbert–Johnson type alkylation reaction, but a structure was not proposed.

Treatment of 5 with *methanolic* ammonia at room temperature for several days gave 5-amino-3-β-D-ribofuranosyl-*s*-triazolo[1,5-*a*]pyrimidin-7-one (8b),[11] the guanosine analog. The 5-chloro moiety was further demonstrated to be reactive toward other nucleophilic agents under mild conditions by treatment with methylamine and dimethylamine to furnish the corresponding 5-methylamino (8c) and 5-dimethylamino (8d) derivatives. Treatment of 5 with thiourea in ethanol gave, instead of the expected 5-mercapto nucleoside (8e), the glycosyl-cleavage product,

Scheme I



Scheme II



5-chloro-s-triazolo[1,5-a]pyrimidin-7-one. When **5** was stirred at ambient temperature for 2 hr with methanolic hydrogen sulfide–ammonium carbonate, however, the 5-mercapto nucleoside (**8e**) could be isolated in good yield. 5-Hydroxy-3-β-D-ribofuranosyl-s-triazolo[1,5-a]pyrimidin-7-one (**8f**, the xanthosine analog) was prepared from **5** by the method of Goodman, *et al.*,[12] using alkaline 2-mercaptoethanol.

Treatment of **5** with methanolic hydrazine gave a derivative (**7**) which was presumed on the basis of elemental analysis to be the 5-hydrazino derivative. However, there was a conspicuous absence of an absorption in the 270-nm region of the ultraviolet spectrum characteristic of s-triazolo[1,5-a]pyrimidine derivatives. Theorizing that ring opening and reclosure had occurred as well as the nucleophilic displacement of chloride, the structure **7** (see Scheme I) was tentatively assigned to the compound. Ultraviolet spectral comparisons of the hydrazine-treated product (**7**) with 3-aminopyrazolin-5(1*H*,2*H*)-one showed them to be very similar and therefore supported the structure of **7** as 3-[pyrazolin-5(1*H*,2*H*)-on-3-ylamino]-4-β-D-ribofuranosyl-s-triazole, since 3-amino-s-triazole and the carbohydrate moiety have no significant absorption in the ultraviolet spectral region.

Although the anomeric configuration of **5** could tentatively be assigned β on the basis of several empirical rules (see ref 1 for a brief discussion of those rules), a more rigorous proof was in order for this unusual heterocyclic nucleoside series. Isopropylidenation of the 5-chloro nucleoside (**5**) gave **10** (Scheme II), which was treated with *p*-toluenesulfonyl chloride in pyridine to furnish the 5′-*O*-*p*-toluenesulfonyl-2′,3′-*O*-isopropylidene derivative (**11**). Treatment of **11** with DMSO or acetonylacetone at 100–110° for 2–4 hr did *not* produce the cyclonucleoside (**13a**). This result would indicate either that **5** has the α configuration[13] or that N-4 (because of the adjacent electron-withdrawing chloro group) is not nucleophilic enough to displace the 5′-tosylate. Treatment of the 5-chloro-2′,3′-*O*-isopropylidene-5′-*O*-*p*-toluenesulfonyl nucleoside (**11**) with 10% palladium on carbon in a hydrogen atmosphere gave the corresponding dehalogenated derivative (**12**). A solution of **12** in DMSO was heated at 100° for 4 hr to effect cyclonucleoside formation (**13b**), allowing the anomeric configuration of **5** (and hence **8a–f**) to be unequivocally assigned β. The identity of **13b** as the cyclonucleoside was confirmed by the presence of an ionic sulfonate absorption in the infrared spectrum at 1200 cm^{-1} and the drastic decrease in chromatographic mobility in nonpolar solvents of **13b** compared to **12**. Instead of the 10-nm bathochromic shift observed with cyclonucleoside formation in the purine series,[14] a small (3 nm) hypsochromic shift was observed with the formation of **13b**.

Since the ability of aromatic halogens to influence the site of glycosylation has now been firmly established, several other heterocyclic derivatives were utilized in the glycosylation reaction in order to assess the directive effects of other substituents at C-5.

Glycosylation of *O*-trimethylsilyl-5-methyl-s-triazolo[1,5-a]pyrimidin-7-one (**2**) under the same alkylation conditions used for **1** gave a single nucleoside product (**4**) which was deacetylated with methanolic ammonia. The site of glycosylation of the deacetylated nucleoside product (**6**) was not easily assigned since **6** could not be converted to a nucleoside of known structure. The ultraviolet maxima of

Table I
H-2 Chemical Shifts in the Pmr Spectra of Some 3- and 4-Substituted *s*-Triazolo[1,5-*a*]pyrimidine Derivatives

Substituted *s*-triazolo-[1,5-*a*]pyrimidine	3 or 4 substituent	H-2 chemical shift,[a] ppm	
7-One	3-Methyl[3]	8.91	
7-One	4-Methyl[3]		8.31
7-One	3-β-D-Ribofuranosyl (**8a**)[3]	9.19	
7-One	4-β-D-Ribofuranosyl (**20**)[3]		8.33
5-Chloro-7-one	3-β-D-Ribofuranosyl (**5**)	9.22	
5-Methyl-7-one	3-β-D-Ribofuranosyl (**6**)	9.10	
5-Amino-7-one	3-β-D-Ribofuranosyl (**8b**)	9.20	
5-Methylamino-7-one	3-β-D-Ribofuranosyl (**8c**)	8.88	
5-Dimethylamino-7-one	3-β-D-Ribofuranosyl (**8d**)	8.85	
5-Mercapto-7-one	3-β-D-Ribofuranosyl (**8e**)	8.80	
5-Hydroxy-7-one	3-β-D-Ribofuranosyl (**8f**)	9.09	
7-Amino-5-one	3-β-D-Ribofuranosyl (**18**)	8.98	
7-Amino	4-β-D-Ribofuranosyl (**19**)		8.18

[a] Pmr spectra were determined on a Hitachi R20A instrument using DMSO-d_6 as a solvent and DSS as an internal reference.

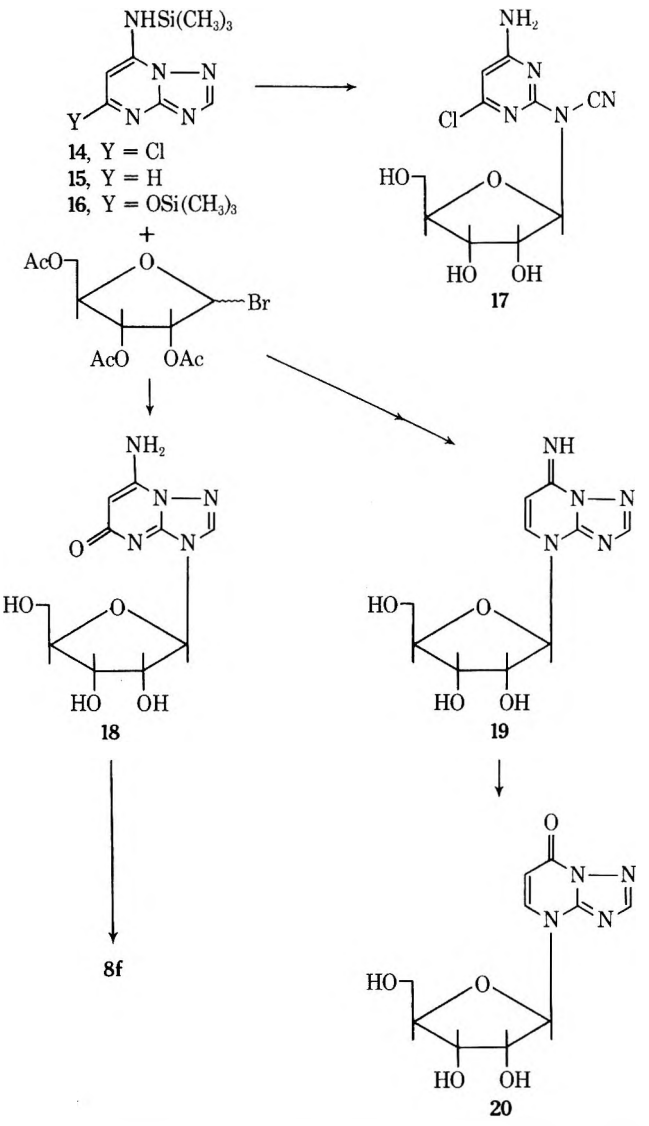
the 3- and 4-methyl-*s*-triazolo[1,5-*a*]pyrimidine derivatives were not sufficiently different to permit assignment of the site of glycosylation of **6**. Pmr spectral comparison of the H-2 chemical shift of **6** with the corresponding shifts in DMSO-d_6 (see Table I) of the 3- and 4-methyl derivatives as well as the H-2 chemical shifts of the 3-β-D-ribofuranosyl (**8a**) and 4-β-D-ribofuranosyl (**20**) derivatives indicated **6** to be a 3-D-ribofuranosyl derivative. A summary of the pmr chemical shifts in Table I shows that glycosylation or alkylation on N-3 causes the H-2 chemical shift to be in the region 8.9–9.2 ppm, while the H-2 chemical shift of the corresponding N-4 isomers appears in the region 8.1–8.3 ppm.

The structure establishment of **6** as 5-methyl-3-β-D-ribofuranosyl-*s*-triazolo[1,5-*a*]pyrimidin-7-one made it evident that the 5-methyl group adjacent to N-4 prevented glycosylation at N-4.

Glycosylation of *N*-trimethylsilyl-7-amino-5-chloro-*s*-triazolo[1,5-*a*]pyrimidine (**14**, Scheme III) would be predicted to yield the N-3 glycosyl product on the basis of previous studies. In fact, only one nucleoside product could be isolated from the reaction and this material possessed an infrared absorption at 2230 cm^{-1} and a pyrimidine-like ultraviolet spectrum similar to that of **9**. Deacetylation in the usual manner gave a nucleoside (**17**)[9] whose tentative structure was assigned as 4-amino-6-chloro-2-[*N*-(β-D-ribofuranosyl)cyanamido]pyrimidine and was supported by the elemental analysis.

Glycosylation of the *N*-trimethylsilyl derivative of 7-amino-*s*-triazolo[1,5-*a*]pyrimidine (**15**) with 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide in a fusion reaction using aluminum chloride as a catalyst gave a single nucleoside product, which after treatment with methanolic ammonia in the usual manner gave an amino nucleoside (**19**). The structure of **19** was assigned as 7-imino-4-β-D-ribofuranosyl-*s*-triazolo[1,5-*a*]pyrimidine on the basis of pmr data (see Table I). The site of glycosylation was established as N-4 by acidic hydrolysis of the imino function in **19** to the corresponding 7-oxo derivative (**20**) which was identical with an authentic sample[3] by ultraviolet and infrared spectral comparisons as well as chromatographic mobility comparisons. The formation of a single nucleoside product is surprising, since in the glycosylation of the corresponding 7-oxo analog,[3] *both* N-3 and N-4 isomers were isolated in near-equal amounts. It may be therefore inferred that the remote 7-amino (imino) group may also have some directive effect upon the determination of the site of glycosylation.

Scheme III



Glycosylation of the same system plus a bulky but electron-donating trimethylsilyloxy group at C-5 (**16**) gave again only one nucleoside product, which was deacetylated in the same manner to give 7-amino-3-β-D-ribofuranosyl-*s*-triazolo[1,5-*a*]pyrimidin-5-one (**18**) in good yield. The site of glycosylation as N-3 was determined on the basis of spectroscopic data (see Table I) and the deamination of **18** to **8f** (whose structure has been unequivocally determined).

Thus it appears that the determination of the site of glycosylation is influenced not only by the presence of electron-withdrawing groups but also the presence of bulky substituents adjacent to potential glycosylation sites.

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 obtained on a Varian A-60 spectrophotometer and a Hitachi R-20A spectrophotometer in DMSO-d_6 using DSS as an internal reference. Ultraviolet spectra were recorded on a Cary Model 15 spectrometer and infrared spectra on a Perkin-Elmer 257 spectrophotometer (KBr pellets). Elemental analyses were performed by M-H-W Laboratories, Garden City, Mich. Evaporations were carried out under reduced pressure with bath temperature below 30°. Detection of components on silica gel

F-254 (EM Reagents) was by ultraviolet light and with 10% sulfuric acid in methanol spray followed by heating. Chromatography solvent mixtures were by volume and the silica gel for column chromatography was purchased from E. Merck (7734).

Trimethylsilyl derivatives of various s-triazolo[1,5-a]pyrimidines were prepared by heating the heterocyclic derivatives under reflux in an excess of freshly distilled hexamethyldisilazane with a catalytic amount of ammonium sulfate under anhydrous conditions until complete solution was achieved and evolution of ammonia ceased (20–25 hr). The excess hexamethyldisilazane was removed by distillation under reduced pressure and the residue (oil or crystalline solid) was used directly without further purification. Glycosylation reaction mixtures were analyzed by tlc; all spots possessing ultraviolet absorption and a carbohydrate moiety (detected by spraying with 10% H_2SO_4 in MeOH and heating) were isolated and characterized.

5-Chloro-3(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-s-triazolo[1,5-a]pyrimidin-7-one (3). To tetra-*O*-acetyl-β-D-ribofuranose (10.5 g, 0.033 mol) in dry dichloromethane (50 ml) at −20° was added a solution of dry dichloromethane (originally 50 ml) which had been saturated at −20° with dry hydrogen bromide gas. The mixture was protected from moisture with a drying tube and allowed to warm to 0°. The solvent was evaporated and the resulting syrup was coevaporated twice with dry toluene (50 ml). The residual syrup was dissolved in "Nanograde" acetonitrile (100 ml) and was added to the trimethylsilyl derivative [1, prepared from 5.2 g (0.030 mol) of 5-chloro-s-triazolo[1,5-a]pyrimidin-7-one[6] in dry acetonitrile (50 ml). The reaction vessel was sealed and the mixture was stirred at room temperature. After 48 hr the reaction mixture was filtered to remove some solid material (heterocyclic starting material, 0.6 g) and the dark filtrate was evaporated to a syrup. Sodium bicarbonate (5.0 g), water (20 ml), and ethanol (50 ml) were added. The mixture was evaporated to dryness. Coevaporation with absolute ethanol several times afforded a dry residue which was extracted with chloroform (3 × 100 ml). The combined extracts were washed with cold saturated aqueous sodium bicarbonate solution (2 × 100 ml) followed by water (3 × 100 ml). The chloroform phase was dried over anhydrous sodium sulfate and then evaporated to dryness to a foam which was triturated with absolute ethanol (75 ml) at 0°. The solid that separated was collected, washed with ethanol, and crystallized from aqueous ethanol with charcoal treatment to yield 7.5 g of product (58%), mp 202°. A small sample was recrystallized from aqueous ethanol to obtain analytically pure sample: mp 203°; $[\alpha]^{25}D$ −10.3° (c 1.0, DMSO); uv λ_{max} (pH 1) 284 nm (ε 11,200), λ_{max} (pH 7) 284 nm (ε 12,900), and λ_{max} (pH 11) 284 nm (ε 11,600).

Anal. Calcd for $C_{16}H_{17}N_4O_8Cl$: C, 44.81; H, 3.97; N, 13.07. Found: C, 44.80; H, 4.03; N, 12.90.

5-Methyl-3-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-s-triazolo[1,5-a]pyrimidin-7-one (4). A solution of 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide from 5.5 g (0.017 mol) of tetra-*O*-acetyl-β-D-ribofuranose in dry acetonitrile (80 ml) was added to the trimethylsilyl derivative [2, prepared from 2.30 g (0.0153 mol) of 5-methyl-7-hydroxy-s-triazolo[1,5-a]pyrimidine[15] and the resulting solution was stirred at room temperature for 45 hr in a sealed reaction vessel. After 5 hr some solid had begun to form, and, upon termination of the reaction, the mixture was nearly solid. The solid was collected and washed with acetonitrile. The combined filtrate and washings were evaporated to dryness. The resulting foam was triturated with cold ethanol (25 ml) and the solid that separated was collected. The combined solids were crystallized from aqueous ethanol to provide pure material to yield 4.0 g (64%): mp 224°; $[\alpha]^{25}D$ −25.4° (c 1.0, DMSO); uv λ_{max} (pH 1) 240 nm (sh, ε 5700), 280 (14,300), λ_{max} (pH 7) 240 nm (ε 5700), 280 (13,900), and λ_{max} (pH 11) 240 nm (sh, ε 5700), 280 (14,100).

Anal. Calcd for $C_{17}H_{20}N_4O_8$: C, 50.00; H, 4.94; N, 13.72. Found: C, 50.09; H, 4.92; N, 13.80.

5-Chloro-3-β-D-ribofuranosyl-s-triazolo[1,5-a]pyrimidin-7-one (5). 5-Chloro-3-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-s-triazolo[1,5-a]pyrimidin-7-one (3, 5.0 g, 0.0116 mol) was dissolved in methanolic ammonia (100 ml, saturated at 0°). The container was sealed and left at room temperature overnight. The solution was then filtered and the filtrate was evaporated to dryness. The residue was triturated with anhydrous ether (4 × 75 ml) and the ether-insoluble gum was dissolved in a minimum volume of ethanol. It was applied to a silica gel column (3.5 × 50 cm) prepacked in ethyl acetate–water–isopropyl alcohol (4:2:1, upper phase). The column was eluted with the same solvent system and 15-ml fractions were collected. The fractionation was monitored by tlc on silica gel using the eluting solvent as the developer. The fractions 60–100 were pooled and the solvent was evaporated; the residual syrup was triturated with ethanol (20 ml) whereupon the compound crystallized out as white needles to yield 3.0 g (85%), mp 168–169°. Recrystallization from aqueous ethanol gave analytically pure crystals: mp 169–170°; $[\alpha]^{25}D$ −14.1° (c 1.0, DMSO); uv λ_{max} (pH 1) 283 nm (ε 13,600), λ_{max} (pH 7) 283 nm (ε 10,800), and λ_{max} (pH 11) 242 nm (sh, ε 5500), 283 (13,600).

Anal. Calcd for $C_{10}H_{11}N_4O_5Cl$: C, 39.68; H, 3.64; N, 18.51. Found: C, 39.67; H, 3.83; N, 18.53.

5-Methyl-3-β-D-ribofuranosyl-s-triazolo[1,5-a]pyrimidin-7-one (6). 5-Methyl-3-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-s-triazolo[1,5-a]pyrimidin-7-one (4, 3.0 g, 0.0073 mol) was dissolved in methanolic ammonia (60 ml, saturated at 0°). The container was sealed and left at room temperature overnight. The solution was filtered and the filtrate was evaporated to dryness. The residue was collected, washed thoroughly with cold ethanol, and recrystallized from ethanol containing a few drops of water to yield 1.9 g (92%): mp 240° dec; $[\alpha]^{25}D$ −37.2° (c 1.0, DMSO); uv λ_{max} (pH 1) 242 nm (sh, ε 6200), 280 (13,800); λ_{max} (pH 7) 242 nm (sh, ε 6000), 280 (13,800); and λ_{max} (pH 11) 242 nm (sh, ε 6200), 280 (13,800).

Anal. Calcd for $C_{11}H_{14}N_4O_5$: C, 46.81; H, 5.00; N, 19.85. Found: C, 46.88; H, 4.85; N, 19.88.

3-[Pyrazolin-5(1*H*,2*H*)-on-3-ylamino]-4-β-D-ribofuranosyl-s-triazole (7). 5-Chloro-3-β-D-ribofuranosyl-s-triazolo[1,5-a]pyrimidin-7-one (5, 1.0 g, 0.0033 mol) was suspended in anhydrous methanol (30 ml), and hydrazine (10 ml, 95%) was added with stirring at room temperature. Immediately a clear solution was obtained which began to turn brown. The mixture was refrigerated overnight and the solvent was evaporated. The residual syrup was coevaporated several times with methanol and finally triturated with ethanol (25 ml). The solid that separated was collected, washed with cold ethanol (2 × 5 ml), and crystallized from aqueous ethanol to yield 0.65 g (66%) of 7: mp 225° dec; $[\alpha]^{25}D$ −45.4° (c 1.0, DMSO); uv λ_{max} (pH 1) 240 nm (ε 8700); λ_{max} (pH 7) 240 nm (ε 7500); and λ_{max} (pH 11) 233 nm (ε 10,200).

Anal. Calcd for $C_{10}H_{14}N_6O_5$: C, 40.27; H, 4.73; N, 28.18. Found: C, 40.43; H, 4.84; N, 28.45.

3-β-D-Ribofuranosyl-s-triazolo[1,5-a]pyrimidin-7-one (8a). 5-Chloro-3-β-D-ribofuranosyl-s-triazolo[1,5-a]pyrimidin-7-one (5, 0.5 g, 0.00165 mol) was dissolved in 50% aqueous ethanol (25 ml) containing a few drops of concentrated ammonium hydroxide. To this solution was added 150 mg of palladium on carbon (10%) and the mixture was hydrogenated at 40 psi at room temperature for 3 hr, after which the catalyst was removed by filtration on a Celite pad and washed with hot ethanol (2 × 10 ml). The combined filtrates and washings were evaporated to dryness. Coevaporation with absolute ethanol several times afforded white solid which was recrystallized from aqueous ethanol as colorless needles to yield 0.25 g (57%): mp 245–246° dec; mmp with authentic sample[3] 245–247° dec; $[\alpha]^{26}D$ −39.5° (c 1.0, H_2O) [lit.[3] mp 243–248° dec; $[\alpha]^{30}D$ −39.3° (c 1.0, H_2O)]; uv λ_{max} (pH 1, 7, 11) 242 nm (ε 5900) and 285 (12,600).

Anal. Calcd for $C_{10}H_{12}N_4O_5$: C, 44.78; H, 4.51; N, 20.89. Found: C, 44.70; H, 4.52; N, 20.90.

5-Amino-3-β-D-ribofuranosyl-s-triazolo[1,5-a]pyrimidin-7-one (8b). 5-Chloro-3-β-D-ribofuranosyl-s-triazolo[1,5-a]pyrimidin-7-one (5, 0.50 g, 0.00165 mol) was dissolved in methanolic ammonia (25 ml, saturated at room temperature) and the solution was allowed to stand at room temperature in a stoppered pressure bottle for several days. The solution was evaporated to dryness and the residue was coevaporated several times with methanol to a foam. The dry foam was dissolved in anhydrous methanol (10 ml), filtered, and cooled and an excess of anhydrous ether was added. The copious precipitate that separated was collected, washed with ether, and dried to yield 250 mg, no definite melting point: $[\alpha]^{25}D$ −14.8° (c 1.0, H_2O); uv λ_{max} (pH 1) 238 nm (sh, ε 6300), 280 (9030); λ_{max} (pH 7) 245 nm (sh, ε 5700), 281 (9780); and λ_{max} (pH 11) 245 nm (sh, ε 4700), 281 (9780).

Anal. Calcd for $C_{10}H_{13}N_5O_5 \cdot H_2O$: C, 39.87; H, 5.02; N, 23.25. Found: C, 39.96; H, 4.90; N, 23.40.

5-Methylamino-3-β-D-ribofuranosyl-s-triazolo[1,5-a]pyrimidin-7-one (8c). 5-Chloro-3-β-D-ribofuranosyl-s-triazolo[1,5-a]pyrimidin-7-one (5, 1.0 g, 0.0033 mol) was dissolved in methanolic monomethylamine (50 ml, saturated with anhydrous monomethylamine at 0°) and the solution was allowed to stand at room temperature in a stoppered pressure bottle. After 24 hr, the solution was filtered and the filtrate was evaporated to dryness. The syrup was coevaporated several times with absolute ethanol to remove last traces of monomethylamine. The residual foam was triturat-

ed with cold methanol and the solid that separated was collected and washed with methanol (2 × 5 ml). It was crystallized from aqueous methanol as needles to yield 0.30 g (31%): mp 192° dec; $[\alpha]^{25}D$ −5.7° (*c* 1.0, DMSO); uv λ_{max} (pH 1) 225 nm (ε 29,700), 268 (12,800); λ_{max} (pH 7) 226 nm (ε 29,700), 268 (12,800); and λ_{max} (pH 11) 227 nm (ε 29,700), 267 (13,100).

Anal. Calcd for $C_{11}H_{15}N_5O_5$: C, 44.44; H, 5.09; N, 23.56. Found: C, 44.33; H, 5.00; N, 23.46.

5-Dimethylamino-3-β-D-ribofuranosyl-*s*-triazolo[1,5-*a*]pyrimidin-7-one (8d). 5-Chloro-3-β-D-ribofuranosyl-*s*-triazolo[1,5-*a*]pyrimidin-7-one (**5**, 1.0 g, 0.0033 mol) was dissolved in methanolic dimethylamine (50 ml, saturated with anhydrous dimethylamine at 0°) and the solution was allowed to stand at room temperature in a stoppered pressure bottle. After 65 hr the crystalline needles that separated were collected and washed with methanol. The combined filtrate and washings were evaporated to dryness. The syrup was coevaporated several times with absolute ethanol to remove last traces of dimethylamine. The crystalline residue was collected and washed with ethanol. The combined solids were recrystallized from aqueous methanol to yield 0.90 g (88%): mp 220–221° dec; $[\alpha]^{25}D$ −2.4° (*c* 1.0 g, DMSO); uv λ_{max} (pH 1) 228 nm (ε 31,100), 274 (14,000); λ_{max} (pH 7) 230 nm (ε 31,100), 273 (14,300); and λ_{max} (pH 11) 232 nm (ε 31,100), 273 (14,300).

Anal. Calcd for $C_{12}H_{17}N_5O_5$: C, 46.30; H, 5.50; N, 22.50. Found: C, 46.22; H, 5.31; N, 22.27.

5-Mercapto-3-β-D-ribofuranosyl-*s*-triazolo[1,5-*a*]pyrimidin-7-one (8e). Dry ammonium carbonate (1.2 g, 0.0105 mol) in absolute methanol (10 ml) was saturated with anhydrous hydrogen sulfide gas at −5°. 5-Chloro-3-β-D-ribofuranosyl-*s*-triazolo[1,5-*a*]pyrimidin-7-one (**5**, 0.5 g, 0.00165 mol) was added and the mixture was stirred at room temperature for 2 hr. The exothermic reaction was accompanied by gas evolution. Water (10 ml) containing concentrated ammonium hydroxide (1.0 ml) was added. The reaction mixture was heated at 60° for 30 min, cooled, and filtered and the filtrate was carefully neutralized with glacial acetic acid. The mixture was again filtered and the filtrate was evaporated to dryness. The residue was collected, washed with ethanol (3 × 5 ml), and crystallized from water–ethanol with charcoal treatment to yield 0.15 g (31%): mp 218° dec; $[\alpha]^{25}D$ +8.3° (c 1.0, DMSO); uv λ_{max} (pH 1) 236 nm (ε 18,900), 287 (12,000); λ_{max} (pH 7) 236 nm (ε 18,900), 287 (12,000); and λ_{max} (pH 11) 237 nm (ε 15,300), 276 (sh, 11,600), 298 (12,300).

Anal. Calcd for $C_{10}H_{12}N_4O_5S$: C, 40.00; H, 4.03; N, 18.66. Found: C, 39.86; H, 3.77; N, 18.84.

5-Hydroxy-3-β-D-ribofuranosyl-*s*-triazolo[1,5-*a*]pyrimidin-7-one (8f). Method 1. A solution of 5-chloro-3-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-*s*-triazolo[1,5-*a*]pyrimidin-7-one (**3**, 1.1 g, 0.00256 mol) and mercaptoethanol (0.65 ml, 0.009 mol) in methanol (20 ml) was treated with 1 *N* sodium methoxide (8.8 ml) and water (0.08 ml) and heated at reflux temperature for 4 hr. The reaction mixture was cooled and filtered and the filtrate was evaporated to dryness. The residue was dissolved in methanol (10 ml) containing glacial acetic acid (0.8 ml) and concentrated to about 5 ml. The solution was then applied to a silica gel column [2.5 × 45 cm, prepacked in ethyl acetate–water–isopropyl alcohol (4:2:1, upper phase)]. The column was eluted with the same solvent system and 10-ml fractions were collected. The fractionation was monitored by tlc, the appropriate fractions were pooled, and the solvent was evaporated. The residual syrup was dissolved in ethanol (4–5 ml) and excess anhydrous ether was added. The copious white precipitate that separated was collected, washed with ether, and dried to obtain amorphous powder, yield 0.20 g (28%): $[\alpha]^{25}D$ +12.5° (c 1.0, H_2O); uv λ_{max} (pH 1) 230 nm (sh, ε 7100), 315 (3300); λ_{max} (pH 7) 230 nm (sh, ε 6800), 315 (3300); λ_{max} (pH 11) 232 nm (sh, ε 5000), 287 (5900).

Anal. Calcd for $C_{10}H_{12}N_4O_6 \cdot \frac{1}{2}H_2O$: C, 40.96; H, 4.44. Found: C, 41.00; H, 4.50.

Method 2. Deamination of Isoguanosine Analog (18). To an ice-cold solution of 7-amino-3-β-D-ribofuranosyl-*s*-triazolo[1,5-*a*]pyrimidin-5-one (**18**, 0.9 g, 0.00317 mol) in water (10 ml) and glacial acetic acid (1.5 ml) was added sodium nitrite (1.5 g, 0.0217 mol). The flask was loosely stoppered and stirred overnight at 0–5°. The solution was evaporated to dryness, and the residue was dissolved in water (20 ml) and neutralized with sodium bicarbonate. The neutral solution was taken to dryness, dissolved in ethyl acetate containing a few drops of methanol, and applied to a silica gel column (2.5 × 40 cm) prepacked in ethyl acetate–water–isopropyl alcohol (4:2:1, upper phase). The column was eluted with the above solvent system and 15-ml fractions were collected. The fractionation was monitored by tlc on silica gel and the fractions containing the major product were pooled. The solvent was evaporated and the residue was dissolved in ethanol (2–3 ml). Excess anhydrous ether (50 ml) was added. The white precipitate was collected and dried over methanol under vacuum to furnish a white, hygroscopic solid. Uv, ir, and chromatographic behavior were identical with those of the compound prepared by method 1.

6-Amino-2-[*N*-(β-D-ribofuranosyl)cyanamido]pyrimidin-4-one (9). 5-Chloro-3-β-D-ribofuranosyl-*s*-triazolo[1,5-*a*]pyrimidin-7-one (**5**, 1.0 g, 0.0033 mol) was dissolved in liquid ammonia (20 ml) and the solution was allowed to stand at room temperature in a sealed steel reaction vessel for 24 hr. After cooling the vessel was opened and the solution was evaporated to dryness. The residue was coevaporated several times with methanol to a foam. The foam was triturated with anhydrous ether (150 ml), and the white solid that separated was collected, washed thoroughly with anhydrous ether, and dissolved in water (50 ml). The aqueous solution was freeze dried to obtain white powder, yield 0.60 g: $[\alpha]^{25}D$ −5.1° (*c* 1.0, DMSO); uv λ_{max} (pH 1) 231 nm (ε 10,900), 265 nm (sh, 6600); λ_{max} (pH 7) 236 nm (ε 7700), 273 (6000); and λ_{max} (pH 11) 236 nm (ε 8000); ir 2230 cm^{-1}; pmr (DMSO-d_6) δ 5.89 (1 H, doublet, $J_{1',2'}$ = 5.5 Hz, H-1'), 5.69 (1 H, singlet, H-6).

Anal. Calcd for $C_{10}H_{13}N_5O_5$: C, 42.40; H, 4.63; N, 24.73. Found: C, 42.39; H, 4.53; N, 24.69.

5-Chloro-3-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-*s*-triazolo[1,5-*a*]pyrimidin-7-one (10). 2,2-Dimethoxypropane (1.0 ml) and 70% perchloric acid (1.0 ml) were added to dry acetone (250 ml);[16] the mixture was protected from moisture and stirred at room temperature for 5 min before 5-chloro-3-β-D-ribofuranosyl-*s*-triazolo[1,5-*a*]pyrimidin-7-one (**5**, 0.80 g, 0.00265 mol) was added in one portion. The mixture was stirred for 45 min and pyridine (1.0 ml) was added. The volume was reduced to 25 ml, 10% aqueous sodium bicarbonate (30 ml) was added, and the remaining acetone was removed. Cold water (20 ml) was added to the aqueous solution, which was then left at 5° overnight. The white, crystalline material that separated was collected, washed with cold water (2 × 5 ml), and recrystallized from ethanol–water as needles to yield 0.60 g (67%): mp 190°; pmr (DMSO-d_6) δ 1.38, 1.57 (6 H, two singlets, 2',3'-isopropylidene).

Anal. Calcd for $C_{13}H_{15}N_4O_5Cl$: C, 45.55; H, 4.38; N, 16.35. Found: C, 45.48; H, 4.40; N, 16.40.

5-Chloro-3-(2,3-*O*-isopropylidene-5-*O*-*p*-toluenesulfonyl-β-D-ribofuranosyl)-*s*-triazolo[1,5-*a*]pyrimidin-7-one (11). Compound **10** (0.50 g, 0.00146 mol) was dissolved in dry pyridine (5 ml), and *p*-toluenesulfonyl chloride (0.30 g, 0.00157 mol) was added. The solution was left in the dark at 5° for 36 hr with occasional shaking. The solution was poured into ice–water (200 ml) and the mixture was extracted with chloroform (3 × 50 ml). The combined organic layers were washed with cold 1 *M* sulfuric acid (2 × 50 ml) followed by cold water until the washings were neutral. The chloroform solution was dried over anhydrous sodium sulfate and evaporated to 10 ml, and methanol (25 ml) was added before the remaining chloroform was removed. Dry ether was added, and the white solid that separated was collected and crystallized from methanol to yield 0.48 g (67%): mp 176°; pmr (DMSO-d_6) δ 7.47 (4 H, quartet, benzenoid H of tosyl), 1.34, 1.54 (6 H, two singlets, 2',3'-isopropylidene).

Anal. Calcd for $C_{20}H_{21}N_4O_7SCl$: C, 48.33; H, 4.23; N, 11.28. Found: C, 48.21; H, 4.37; N, 11.15.

3-(2,3-*O*-Isopropylidene-5-*O*-*p*-toluenesulfonyl-β-D-ribofuranosyl)-*s*-triazolo[1,5-*a*]pyrimidin-7-one (12). 5-Chloro-3-(2,3-*O*-isopropylidene-5-*O*-*p*-toluenesulfonyl-β-D-ribofuranosyl)-*s*-triazolo[1,5-*a*]pyrimidin-7-one (**11**, 0.5 g, 0.001 mol) was dissolved in 50% aqueous ethanol (25 ml) containing a few drops of concentrated ammonium hydroxide. To this solution was added 120 mg of palladium on carbon (10%) and the mixture was hydrogenated at 40 psi at room temperature for 3 hr, after which the catalyst was removed by filtration on a Celite pad. The catalyst was washed with hot ethanol (2 × 10 ml). The combined filtrate and washings were evaporated. The residual white solid was crystallized from aqueous ethanol as needles to yield 0.30 g (65%): mp 190° dec; uv λ_{max} (pH 1) 270 nm (ε 10,500); λ_{max} (pH 7) 270 nm (ε 11,000); λ_{max} (pH 11) 275 nm (ε 11,900); pmr (DMSO-d_6) δ 8.96 (1 H, singlet, H-2), 7.92 (1 H, doublet, H-5), 7.46 (4 H, quartet, benzenoid H of tosyl), 6.17 (1 H, doublet, H-6), 1.34, 1.54 (6 H, two singlets, 2',3'-isopropylidene).

Anal. Calcd for $C_{20}H_{22}N_4O_7S$: C, 51.95; H, 4.79; N, 12.12. Found: C, 51.96; H, 4.57; N, 12.10.

3-(2,3-*O*-Isopropylidene-β-D-ribofuranosyl)-*s*-triazolo[1,5-*a*]pyrimidin-7-one 5',4-Cyclonucleoside *p*-Toluenesulfonate (13b). 3-(2,3-*O*-Isopropylidene-5-*O*-*p*-toluenesulfonyl-β-D-ribofuranosyl)-*s*-triazolo[1,5-*a*]pyrimidin-7-one (**12**, 0.10 g) was added to dry dimethyl sulfoxide (5 ml) and the mixture was heated, with

stirring, at 100–110° for 4 hr. After chilling overnight the solution was filtered and the filtrate was evaporated to dryness. The residue was taken in ethanol, decolorized by charcoal treatment, and triturated with anhydrous ether (25 ml). The white solid that separated was collected, washed with ether (2 × 10 ml), and crystallized from aqueous ethanol to yield 50 mg: mp >240° dec; uv λ_{max} (pH 1) 267 nm (ϵ 8600); λ_{max} (pH 7) 267 nm (ϵ 8600); and λ_{max} (pH 11) 273 nm (ϵ 10,600); ir 1200 cm^{-1}.

4-Amino-6-chloro-2-[*N*-(β-D-ribofuranosyl)cyanamido]pyrimidine (17). To the trimethylsilyl derivative (**14**) from 3.4 g (0.020 mol) of 5-chloro-7-amino-*s*-triazolo[1,5-*a*]pyrimidine[6] was added 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide [from 7.0 g (0.022 mol) of tetra-*O*-acetyl-β-D-ribofuranose] in anhydrous acetonitrile (100 ml). The reaction vessel was sealed and stirred at room temperature for 27 hr. The reaction mixture was filtered and the filtrate was evaporated to a syrup. Sodium bicarbonate (3.0 g), water (10 ml), and ethanol (25 ml) were added. The mixture ws evaporated to dryness. Coevaporation with absolute ethanol several times afforded dry residue which was extracted with chloroform (3 × 100 ml). The combined extracts were washed with cold saturated aqueous sodium bicarbonate solution (2 × 100 ml) followed by water (3 × 100 ml) and dried over anhydrous sodium sulfate. The chloroform was evaporated to dryness to a foam which was dissolved in a minimum volume of chloroform and applied to a silica gel column (4.5 × 35 cm) prepacked in chloroform. The column was eluted with chloroform–acetone (8:2) and each 25-ml fraction was collected. The fractionation was monitored by tlc and appropriate fractions were pooled and solvent evaporated to yield cream-colored foam, 1.5 g: uv λ_{max} (pH 1) 235, 275 nm; λ_{max} (pH 7) 235, 275 nm; and λ_{max} (pH 11) 235, 275 nm; ir 2230 cm^{-1}.

The above blocked nucleoside (1.4 g) was dissolved in methanolic ammonia (50 ml, methanol presaturated with ammonia at 0°) and the solution was allowed to stand at room temperature overnight. The solution was filtered and the filtrate was evaporated to dryness. The residue was triturated with anhydrous ether (5 (5 × 25 ml) and filtered. The semisolid was dissolved in a minimum volume of water and chromatographed on a silica gel column (2.5 × 35 cm) eluting with isopropyl alcohol–water–ethyl acetate (1:2:4, upper phase). The appropriate fractions were pooled and solvent was evaporated. The residual solid was crystallized from aqueous ethanol to yield 0.5 g: mp 128–130°; uv λ_{max} (pH 1) 235 nm (ϵ 9050), 275 (6050); λ_{max} (pH 7) 235 nm (ϵ 9050), 275 (6050); and λ_{max} (pH 11) 235 nm (ϵ 9050), 275 (6050); ir 2230 cm^{-1}; pmr (DMSO-d_6) δ 5.95 (1 H, doublet, $J_{1',2'}$ = 6.0 Hz, H-1'), 6.31 (1 H, singlet, H-6).

Anal. Calcd for $C_{10}H_{12}N_5O_4Cl$: C, 39.81; H, 4.00; N, 23.21. Found: C, 39.57; H, 4.15; N, 23.11.

7-Amino-3-β-D-ribofuranosyl-*s*-triazolo[1,5-*a*]pyrimidin-5-one (18, Isoguanosine Analog). To the bis(trimethylsilyl) derivative (**16**), prepared from 4.53 g (0.033 mol) of 7-amino-*s*-triazolo-[1,5-*a*]pyrimidin-7-one,[6] was added 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide [prepared from 10.5 g (0.033 mol) of tetra-*O*-acetyl-β-D-ribofuranose] in dry acetonitrile (100 ml). The reaction vessel was sealed and stirred at room temperature for 75 hr. The clear brown solution was evaporated to a syrup. Sodium bicarbonate (5.0 g), water (20 ml), and ethanol (50 ml) were added. The mixture was evaporated to dryness. Coevaporation with absolute ethanol several times afforded a dry residue which was extracted with chloroform (3 × 100 ml) and dried over anhydrous sodium sulfate. The chloroform solution was decolorized with charcoal and evaporated to yield a foam which was highly soluble in water. The foam was dissolved in a minimum volume of water and applied to a silica gel column (5 × 75 cm) prepacked in ethyl acetate–water–isopropyl alcohol (4:2:1, upper phase). The column was eluted with the same solvent system and 30-ml fractions were collected. The fractionation was monitored by tlc on silica gel with the eluting solvent as the developer. Fractions 120–160 were pooled and the solvent was evaporated to yield a cream-colored foam, 9.5 g (78%): $[\alpha]^{25}D$ +41.6° (c 0.5, H_2O); uv λ_{max} (pH 1) 267 nm (ϵ 15,600); λ_{max} (pH 7) 265 nm (ϵ 10,700); and λ_{max} (pH 11) 265 nm (ϵ 10,700).

The above acetylated nucleoside (8.0 g) was dissolved in methanolic ammonia (200 ml, saturated at 0°) and was allowed to stand at room temperature overnight. The solution was filtered, the solvent was evaporated, and the residue was triturated with absolute ethanol. The solid material was filtered, dissolved in a minimum volume of water, and chromatographed on a silica gel column (3.5 × 50 cm) eluting with isopropyl alcohol–ammonium hydroxide–water (7:1:2). The fractions containing the major uv-absorbing component were pooled and the solvent was evaporated. The resulting foam was dissolved in water and freeze dried (3.50 g, 64%) to yield a hygroscopic solid: $[\alpha]^{25}D$ −3.2° (c 1.0, H_2O); uv λ_{max} (pH 1) 266 nm (ϵ 13,300); λ_{max} (pH 7) 264 nm (ϵ 9100); and λ_{max} (pH 11) 264 nm (ϵ 9100).

Anal. Calcd for $C_{10}H_{13}N_5O_5$: C, 42.40; H, 4.63; N, 24.73. Found: C, 42.22; H, 4.41; N, 24.92.

7-Imino-4-β-D-ribofuranosyl-*s*-triazolo[1,5-*a*]pyrimidine (19). To the syrupy trimethylsilyl derivative (**15**) from 5.4 g (0.040 mol) of 7-amino-*s*-triazolo[1,5-*a*]pyrimidine[17] was added 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide [prepared from 14.0 g (0.044 mol) of tetraacetyl ribofuranose] and a catalytic amount of $AlCl_3$ (about 50 mg). The mixture was thoroughly mixed and heated at 100° (oil-bath temperature) for 10 min with oil pump vacuum applied and good stirring. Within 2–3 min the mixture began to solidify, accompanied by frothing. The reaction mixture was cooled, $AlCl_3$ was decomposed by the addition of cold water, and the reaction mixture was extracted with chloroform (250 ml). The chloroform solution was washed with aqueous sodium bicarbonate solution (2 × 100 ml) followed by water (3 × 75 ml) and then dried over anhydrous sodium sulfate. After removal of the drying agent, the chloroform was evaporated and the residual foam (12.0 g) was dissolved in enough benzene–ethyl acetate (1:1) to facilitate pouring and applied to a silica gel column (4.5 × 50 cm, 70–230 mesh) prepacked in benzene–ethyl acetate (1:1). The column was eluted with benzene–ethyl acetate–ethanol (5:5:1) and 20-ml fractions were collected. The fractionation was monitored by tlc on silica gel with the eluting solvent as the developer. The fractions containing the major uv-absorbing component were pooled and the solvent was evaporated to afford 4.0 g of cream-colored amorphous 7-amino-4-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-*s*-triazolo[1,5-*a*]pyrimidine.

The blocked nucleoside (4.0 g) was dissolved in methanolic ammonia (100 ml, saturated at 0°) and was allowed to stand at room temperature overnight. The solution was filtered and the solvent was evaporated. The solid that separated was collected, washed with cold methanol (2 × 10 ml), and recrystallized from ethanol as needles to yield 2.0 g (19%): mp 177° dec; $[\alpha]^{25}D$ −55.4° (c 1.0, H_2O); uv λ_{max} (pH 1) 291 nm (ϵ 17,800); λ_{max} (pH 7) 289 nm (ϵ 15,100); and λ_{max} (pH 11) 274 nm (ϵ 15,100).

Anal. Calcd for $C_{10}H_{13}N_5O_4$: C, 44.94; H, 4.90; N, 26.21. Found: C, 44.78; H, 5.00; N, 26.33.

4-β-D-Ribofuranosyl-*s*-triazolo[1,5-*a*]pyrimidin-7-one (20). To an ice-cold solution of 7-imino-4-β-D-ribofuranosyl-*s*-triazolo[1,5-*a*]pyrimidine (**19**, 0.10 g) in water (1 ml) and glacial acetic acid (0.15 ml) was added sodium nitrite (0.15 g). The flask was loosely stoppered and stirred overnight at 0–5°. The clear solution was evaporated *in vacuo* to dryness. The residue was dissolved in water (5 ml) and carefully neutralized with solid sodium bicarbonate. The neutral solution was taken to dryness, dissolved in a minimum volume of ethyl acetate containing a few drops of methanol, and applied to a silica gel column (1.5 × 30 cm) prepacked in ethyl acetate–water–isopropyl alcohol (4:2:1, upper phase). The column was eluted with the same solvent system and 10-ml fractions were collected. The fractionation was monitored by tlc on silica gel and the appropriate fractions were pooled. The solvent was evaporated and the residue was triturated with ethanol (5 ml). The solid was collected and crystallized from water–ethanol to yield 30 mg, mp 220–222°, mmp with authentic sample 218–221°; uv, ir, and chromatographic behavior were identical with those reported for an authentic sample.[3]

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Registry No.—**1**, 50805-14-6; **2**, 50805-15-7; **3**, 50805-19-1; **4**, 50805-20-4; **5**, 50805-21-5; **6**, 50805-22-6; **7**, 50805-23-7; **8a**, 32817-07-5; **8b**, 50805-24-8; **8c**, 50805-25-9; **8d**, 50805-26-0; **8e**, 50805-27-1; **8f**, 50805-28-2; **9**, 50805-29-3; **10**, 50805-30-6; **11**, 50805-31-7; **12**, 50805-32-8; **13b**, 50805-34-0; **14**, 50805-16-8; **15**, 50805-17-9; **16**, 50805-18-0; **17**, 50805-35-1; **18**, 50805-36-2; **19**, 50805-37-3; **20**, 33037-54-6; tetra-*O*-acetyl-β-D-ribofuranose, 13035-61-5; 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide, 39110-68-4.

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Micellar Effects upon the Reaction of the Tri-*p*-anisylmethyl Cation with Aliphatic Amines[1]

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Anionic micelles of sodium lauryl sulfate, NaLS, catalyze the reaction of the tri-*p*-anisylmethyl cation, R^+, with butyl- and hexylamines and with 2-methylpyrrolidine. The catalysis increases with increasing length of the alkyl group of the amine, but is decreased by its branching. Cationic micelles of cetyltrimethylammonium bromide, CTABr, have little effect on the reaction rate, but nonionic micelles of Igepal are feebly catalytic.

Micellar effects upon the reaction of nucleophilic anions with stable triphenylmethyl dye cations have been extensively studied.[3,4] For example, cationic micelles catalyzed, and anionic micelles inhibited, attack of hydroxide ion. Micellar effects upon the attack of water on the more reactive tri-*p*-anisylmethyl cation (R^+) have also been examined. Anionic micelles increase, but cationic and nonionic micelles decrease, k_b, but these micelles have no effect on k_f.[9] The reactions with hydroxide and azide ions were strongly inhibited by anionic micelles.

$$R^+ + H_2O \underset{k_b}{\overset{k_f}{\rightleftharpoons}} ROH + H^+$$

The present work covers micellar effects on the reaction of R^+ with aliphatic amines,[10] using cetyltrimethylammonium bromide (CTABr), sodium lauryl sulfate (NaLS), and Igepal (nonylphenyl polyethylene oxide, mol wt 1403).

Experimental Section

Materials and Rate Measurements. The purification of the surfactants has been described.[9] The tri-*p*-anisylmethyl cation was introduced as its chloride in dilute HCl. All solutions were made up using redistilled, deionized water, and were degassed.

The reactions were followed at 25.0° using a Durrum-Gibson stopped-flow spectrophotometer.[9] A solution of R^+ in dilute HCl, usually 0.1 *M*, was in one drive syringe, and the amine in NaOH was in the other (NaOH was in slight excess over HCl). The surfactant was in both syringes.

The first-order rate constants, k_ψ, in reciprocal seconds, were calculated using a Hewlett-Packard desk computer.

Results and Discussion

Effect of Micellar Charge. The effects of cationic and nonionic micelles upon the reaction of amines with R^+ are summarized in Table I, in which the values of k_ψ in the absence of surfactant are compared with those in the presence of CTABr and Igepal (Ig). Cationic micelles of CTABr have almost no effect on the rate of reaction, probably because R^+ is not taken up by the cationic micelles,[9] but these micelles markedly affect the equilibrium between R^+ and ROH in dilute acid.[11,12]

Nonionic micelles of Igepal catalyze the reaction of R^+ with *n*-hexylamine, which is the most hydrophobic amine used (Table I), suggesting that the rate enhancement is at least in part a proximity effect due to incorporation of the reagents in the micelle. This incorporation is almost certainly incomplete, and there is no rate maximum or plateau as is often observed in micellar catalysis.[4-8]

Anionic micelles of NaLS catalyze the reaction (Figures 1-3). At a constant amine concentration, the variation of rate constant with surfactant concentration is typical of micellar catalysis. There is little or no effect at very low concentrations of surfactant, but once micelles begin to form, the rate increases as reagents are incorporated into the micelle. The simple kinetic treatment predicts that the rate will not increase until the critical micelle concentration (cmc) of the surfactant is reached,[5-8,13] but the rate increase at NaLS concentrations well below the cmc[14] (Figures 1 and 2) is very common, especially with hydrophobic solutes, and arises because the reagents promote micellization, or there is some catalysis by submicellar aggregates.[5-8] The former explanation seems the more probable because the lowest surfactant concentrations necessary for catalysis are observed with the most hydrophobic amine.

The rate enhancements in the plateau region are given in Table II. They increase with increasing length of the amine chain, and decrease with chain branching.

One unusual feature of the micellar catalysis is that, with increasing surfactant concentration, the rates increase to plateau values, rather than to the maxima which are exhibited by most micellar-catalyzed bimolecular reactions.[16,17] These rate maxima have been ascribed to a dilution of the reagents in the micellar pseudophase once there are sufficient micelles to remove the reagents from the aqueous to the micellar phase;[16] *cf.* ref 7 for an alternative explanation.

The absence of rate maxima (Figures 1 and 2) may be due to the low surfactant concentrations required for catalysis, but formation of a reactive complex between R^+ and the amine should also give plateaux rather than rate maxima.

The rate of the water reaction of R^+ was unaffected by micelles, irrespective of their charge, and reactions of R^+

Table I
Effect of CTABr and Igepal on Reactions with Amines[a]

10^3 [amine], *M*	*n*-Butylamine			*n*-Hexylamine			Cyclohexylamine			2-Methylpyrrolidine		
	None[c]	CTABr[c]	Ig[c]	None[c]	CTABr[c]	Ig[c]	None	CTABr	Ig	None	CTABr	Ig
1.0										162	146	206
1.5										190		243
1.85	75	48	59									
2.0										234	233	300
2.5				97	92	144						
3.0										319	308	402
3.75	143	104	135				55	41				
4.0				164	179	361[b]				387	378	473
5.0				196	199	291	65	53				
						412[b]						
6.25				258	257							
7.5	299	289	277									
8.0				340	340	785[b]						
10.0				423	455	561						
						1035[b]						
12.5				657	635		128	109	134			
15.0							145		158			
17.5							170		184			
20.0							205		236			
25.0							245	207	286			

[a] Values of k_ψ, in reciprocal seconds at 25.0°, with 0.05 *M* NaCl. CTABr was 5×10^{-4} *M* and Igepal (Ig) was 2×10^{-4} *M* unless specified. [b] 4×10^{-4} *M* Igepal. [c] Surfactant.

Table II
Rate Enhancements in the Plateau Region[a]

Registry no.	Amine	k_{rel}[b]
109-73-9	*n*-Butylamine	2.5 (48×10^3)
13952-84-6	*sec*-Butylamine	2.4 (3.8×10^3)
111-26-2	*n*-Hexylamine	13 (50×10^3)
108-91-8	Cyclohexylamine	4.8 (9×10^3)
765-38-8	2-Methylpyrrolidine	4.3 (74×10^3)

[a] At 25.0° with [NaLS] $>1.5 \times 10^{-3}$ *M*. [b] Relative to the calculated second-order rate constant in the absence of surfactant. The values in parentheses are the second-order rate constants in the absence of micelles.[10]

with anionic nucleophiles were sharply inhibited by NaLS.[9] The micellar-catalyzed amine reaction thus differs from the other nucleophilic attacks upon R^+, but the catalysis is consistent with the generalization that attack of an electrophilic cation upon a neutral molecule is catalyzed by anionic micelles.[5-8]

Plots of k_ψ against amine concentration at a given concentration of NaLS curve upward (Figure 3), although

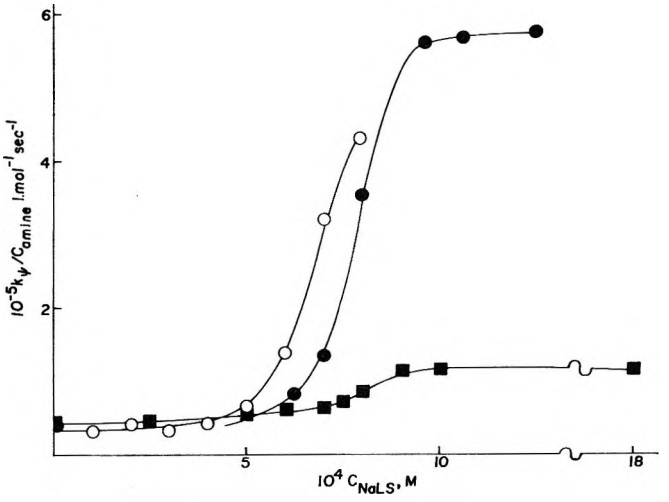

Figure 1. Rate enhancements by NaLS of the reactions of R^+ with primary amines: ■, *n*-$C_4H_9NH_2$, 7.5×10^{-3} *M*; ●, *n*-$C_6H_{13}NH_2$, 2×10^{-3} *M*; ○, *n*-$C_6H_{13}NH_2$, 3.75×10^{-3} *M*.

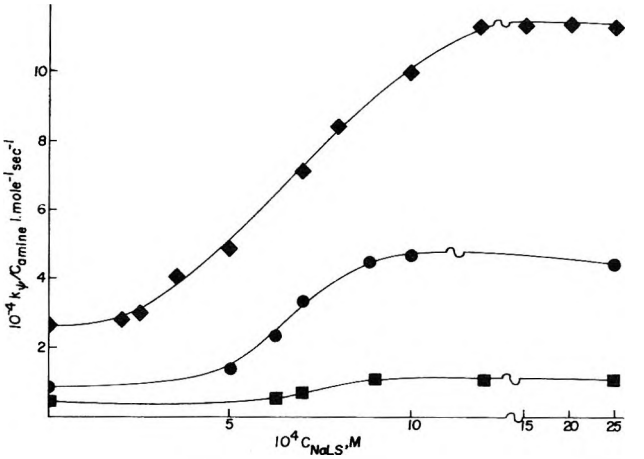

Figure 2. Rate enhancements by NaLS of the reactions of R^+ with secondary amines: ■, *sec*-$BuNH_2$, 5×10^{-2} *M*; ●, c-$C_6H_{11}NH_2$, 2×10^{-2} *M*; ♦, 2-methylpyrrolidine, 4×10^{-3} *M*.

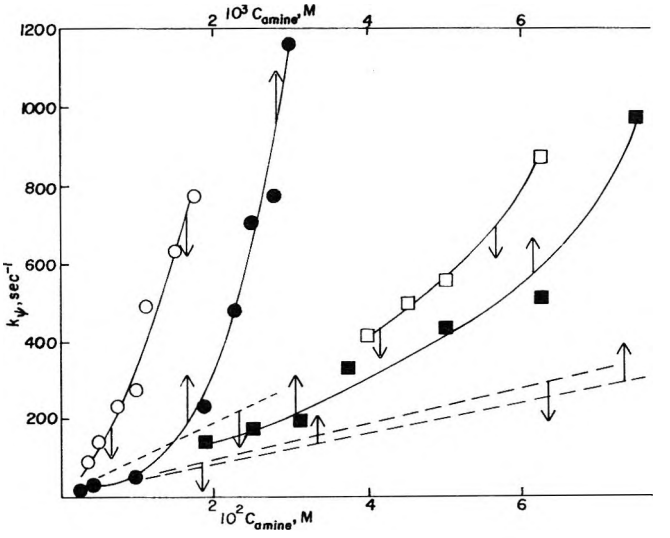

Figure 3. Relation between rate constant and amine concentration for reaction in 2.5×10^{-3} *M* NaLS: 1, ■, *n*-$BuNH_2$; 2, ●, *n*-$C_6H_{13}NH_2$; 3, □, *sec*-$BuNH_2$; 4, ○, c-$C_6H_{11}NH_2$. The broken lines are for reactions in the absence of surfactant.

Table III
Effect of Hydroxide Ion on the Reaction with Amines in NaLS[a]

10^2 [NaOH], M	*sec*-Butylamine[b]	2-Methylpyrrolidine[c]
0.5	119	
1.25	128	230 (12)
2.5	140	268
3.0		(14)
3.75	141	277
5.0	143	285
6.25	150	296
7.5	148	303 (26)

[a] Values of k_ψ, in reciprocal seconds, at 25.0° with 2.5×10^{-3} M NaLS, 10^{-3} M amine, 0.05 M NaCl; values in parentheses are in the absence of amine. [b] 1.25×10^{-2} M. [c] 10^{-3} M.

such plots usually have the opposite curvature. Amines probably modify the structure of the micelle so as to increase its catalytic efficiency, possibly by stabilizing the ammonium ion-like transition state by hydrogen bonding either to the amine or to the anionic head group of the surfactant.

Nature of the Reaction. For reaction of amines in water, it was necessary to allow for the contribution of the hydroxide ion which was generated in the equilibrium[10]

$$R_2'NH + H_2O \rightleftharpoons R_2'\overset{+}{N}H_2 + OH^-$$

but this problem is less serious for reaction in the presence of anionic micelles of NaLS, which stop the reaction of R^+ with hydroxide ion. In presenting the data, we do not correct for any reaction of R^+ with either water or hydroxide ion, because these should be very slow relative to the amine reaction.

For reactions in water, the slow step of the reaction of R^+ with ammonium or most amines is formation of the ammonium ion (I), which rapidly loses a proton,[10,19] and we assume that this is also true for reaction in an anionic micelle. However, proton loss is not rapid for reaction of

$$R^+ + R_2'NH \longrightarrow \underset{\text{I}}{R-\overset{+}{N}HR_2'} \xrightarrow{\text{fast}} RNR_2'$$

R^+ in water with pyrrolidine or 2-methylpyrrolidine,[10] and this may also be so for the micellar-catalyzed reaction of 2-methylpyrrolidine (Figure 2). (The reactions of pyrrolidine in micellized NaLS are too fast for convenient measurement.)

Added hydroxide ion has little effect upon the reaction of R^+ with primary amines in water, but it slightly increases the rate in the presence of micelles (Table III). This rate enhancement is probably not caused by a base-catalyzed decomposition of the ammonium ion (I) in the micelle, simply because hydroxide ion should be excluded from the Stern layer of an anionic micelle, and it is probably due to a suppression of the equilibrium formation of the ammonium and hydroxide ions, which should be increased by the anionic micelle. Because of the problem of allowing for this equilibrium in the presence of micelles, there is some uncertainty in the extent of catalysis by micelles of NaLS, especially for the most basic amine, 2-methylpyrrolidine, where $pK_a = 10.4$.[20]

Effect of Amine Structure. The rate enhancements in the plateau region (Table II) depend upon amine structure. For example, the rate enhancement with *n*-hexylamine is greater than with *n*-butylamine or cyclohexylamine. This effect of chain length of the reagent is often observed in micellar catalysis, even when the reagent is incorporated wholly into the micelle,[7] and it has been suggested that the larger *n*-alkyl groups bring the reaction center (the amine group) deeper into the Stern layer of the micelle because of favorable interactions between the *n*-alkyl groups of the reagent and the surfactant.[21] The decrease of reactivity with branching of the alkyl group of the reagent can be explained in the same way because a branched or cyclic alkyl group may not fit easily between the *n*-alkyl groups of the micellized surfactant. These observations suggest that hydrophobicity is not the controlling factor in micelle–substrate interactions.

The transition state for reaction of R^+ with an amine should have a structure similar to that of the ammonium ion (I), and hydrogen bonding to the ammonium protons should stabilize the transition state. Although there are water molecules in the Stern layer of the micelle,[5-8] the beneficial rate effects of bringing R^+ and the amine together on the micelle should be partially offset by a destabilization of the transition state relative to the initial state in the micellar phase. This counterbalancing effect is very common in micellar catalysis, and rate enhancements are generally small for reactions which have hydrophilic transition states. In this context, indicator measurements in aqueous NaLS show that anionic micelles stabilize the tri-*p*-anisylmethyl carbocation, R^+, much more than the *p*-nitroanilinium ion.[11]

Registry No.—CTABr, 56-09-0; Igepal, 9016-45-9; NaLS, 151-21-3; tri-p-anisylmethyl cation, 14039-13-5.

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Cyclobutylcarbinyl p-Bromobenzenesulfonate Solvolysis. 1-Aryl Substituent Effect

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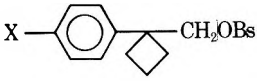
The solvolysis rates of a series of para-substituted 1-phenylcyclobutylcarbinyl brosylates has been determined in acetic acid and 2,2,2-trifluoroethanol. The data support an exclusively anchimerically assisted ionization, but the magnitude of ρ in a ρ-σ^+ plot and the value of k^{OMe}/k^{NO_2} indicate that the ability of the cyclobutane ring to compete with aryl-assisted ionization is significant.

The effect of one-ring substituents upon the rates and solvolysis products of cyclopropylcarbinyl derivatives has been the subject of considerable research.[1] In contrast, the study of one-ring substituent effects upon the rates and solvolysis products of the closely related cyclobutylcarbinyl derivatives has been the subject of only a preliminary investigation.[2] Wilt and Roberts found in their study of ring-size effects upon the acetolysis of neophyl-like substrates that 1-phenylcyclobutylcarbinyl brosylate (4-H) undergoes acetolysis (1) with only slightly faster rates than those of either cyclobutylcarbinyl or neophyl brosylate and (2) accompanied by 1,2-phenyl rearrangement rather than ring expansion.

The latter finding strongly indicates that phenyl neighboring-group participation dominates over that by the cyclobutyl group in the product-controlling step but the similar acetolysis rates for cyclobutylcarbinyl brosylate, 4-H, and neophyl brosylate (11.1×10^{-5}, 21.0×10^{-5}, and 6.84×10^{-5} sec^{-1}, respectively, at 75°[3,4]) leaves open the question as to whether anchimeric assistance to ionization by the two neighboring groups, cyclobutyl and phenyl, is similar or not provided relief of steric strain is equivalent for both substrates.[5]

In neighboring-group participation by phenyl and cycloalkyl groups under competitive circumstances, a convenient and well-established diagnostic test is the measurement of the para-substituent effect on the rate of reaction, especially in reference to some model substrate. Thus, we report in this paper the synthesis and solvolytic investigation of a series of 1-*p*-X-phenylcyclobutylcarbinyl derivatives.



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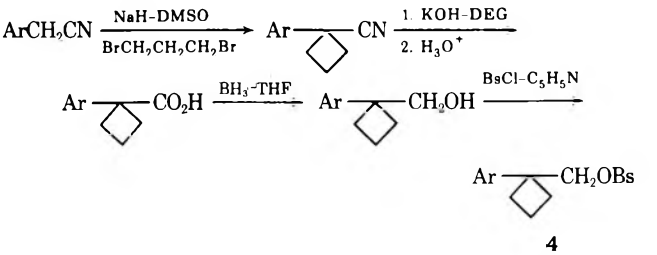
X = CH_3O, CH_3, H, Cl, NO_2

The data indicate that all substrates investigated undergo solvolysis *via* the k_Δ pathway and that the ability of the cyclobutane ring to compete with the aryl group in anchimeric assistance to the ionization of 4 is significant.

The synthesis of the 1-*p*-X-phenylcyclobutylcarbinyl brosylates was accomplished as shown in Scheme I. The key step in this synthesis scheme is the cyclization of the various para-substituted phenylacetonitriles in reasonable yield. The older, sodium amide–ether, high-dilution procedure[7] gives very low[8] yields of cyclic product, which has discouraged synthetic activity in this area. In sharp contrast, the NaH–DMSO procedure[9] affords higher yields of cyclization product than polymer.

Preparation of 1-*p*-nitrophenylcyclobutylcarbinyl brosylate was attended with special problems owing to the sensitivity of the nitro group to strongly basic conditions. Modification of a procedure[1f] used in the synthesis of 1-*p*-nitrophenylcyclopropylcarbinyl tosylate gave 1-*p*-nitrophenylcyclobutylcarbinyl brosylate as outlined in Scheme II.

Scheme I



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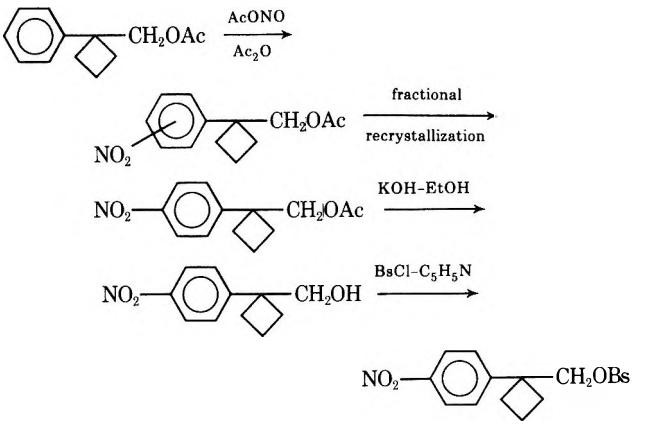
Scheme II



Results and Discussion

The kinetic data are summarized in Table I. Each of these esters was allowed to solvolyze in the indicated solvent and the course of the reaction was followed by titrating the liberated *p*-bromobenzenesulfonic acid. All reactions were strictly first order in *p*-bromobenzenesulfonic acid up to at least 80% conversion and furnished, within experimental error, 100% of the theoretical amount of acid present.

The observation[2] that 1-phenylcyclobutylcarbinyl brosylate yields exclusively rearranged products supports[10,11,12] a k_Δ pathway and is corroborated by the linear correlation (correlation coefficient 0.99) of log k_t for the 1-*p*-X-phenylcyclobutylcarbinyl brosylates with log k_t for the corresponding para-substituted neophyl brosylates (Figure 1). Both Coke[13] and Winstein[14] have demonstrated a good linear correlation between log k_t for the acetolysis of para-substituted neophyl tosylates at 75° and log k_Δ for the acetolysis of corresponding para-substituted β-arylethyl tosylates at the same temperature.

The range of ΔS^* for the acetolysis reactions recorded in Table I are also in agreement with those characteristic[15] of anchimerically assisted ionization (k_Δ). The ΔS^*

Table I
Summary of Solvolysis Rates for Para-Substituted 1-Phenylcyclobutylcarbinyl Brosylates

Registry no.	Para substituent[a]	Solvent[b]	Temp, °C	k_t, 10^5 sec^{-1}	ΔH^*, kcal/mol	ΔS^*, eu
50978-03-5	CH_3O	AcOH	45	8.8	22.0	−7
	CH_3O	AcOH	55	24.0		
	CH_3O	AcOH	65	74.4		
	CH_3O	AcOH	75	180		
	CH_3O	CF_3CH_2OH	25	25	16.7	−19
	CH_3O	CF_3CH_2OH	35	74		
	CH_3O	CF_3CH_2OH	45	183		
	CH_3O	CF_3CH_2OH	55	400		
50978-04-6	CH_3	AcOH	45	1.23	24.7	−1
	CH_3	AcOH	55	4.9		
	CH_3	AcOH	65	15.5		
	CH_3	AcOH	75	49		
	CH_3	CF_3CH_2OH	45	49	18.9	−19
	CH_3	CF_3CH_2OH	55	126		
	CH_3	CF_3CH_2OH	60	200		
	CH_3	CF_3CH_2OH	65	330		
50978-05-7	H	AcOH	45	0.62[c]	25.9	−1
	H	AcOH	55	1.97		
	H	CF_3CH_2OH	35	5.0	19.8	−19
	H	CF_3CH_2OH	45	15.5		
	H	CF_3CH_2OH	55	45.8		
	H	CF_3CH_2OH	65	107		
50978-06-8	Cl	AcOH	45	0.26	25.8	−3
	Cl	AcOH	55	0.92		
	Cl	AcOH	65	2.9		
	Cl	AcOH	75	9.5		
	Cl	CF_3CH_2OH	45	5.6	16.4	−26
	Cl	CF_3CH_2OH	55	13.7		
	Cl	CF_3CH_2OH	60	21		
	Cl	CF_3CH_2OH	65	30		
50978-07-9	NO_2	AcOH	55	0.186	27.5	0
	NO_2	AcOH	65	0.66		
	NO_2	AcOH	75	2.4		
	NO_2	CF_3CH_2OH	45	0.45	22.8	−11
	NO_2	CH_3CH_2OH	75	12.2		

[a] Initial concentration 0.015–0.030 *M*. [b] All runs in 2,2,2-trifluoroethanol buffered with urea at a concentration 10% in excess of theoretical amount of liberated *p*-bromobenzenesulfonic acid. [c] Compares with literature[2] value of 0.622×10^{-6} sec^{-1}.

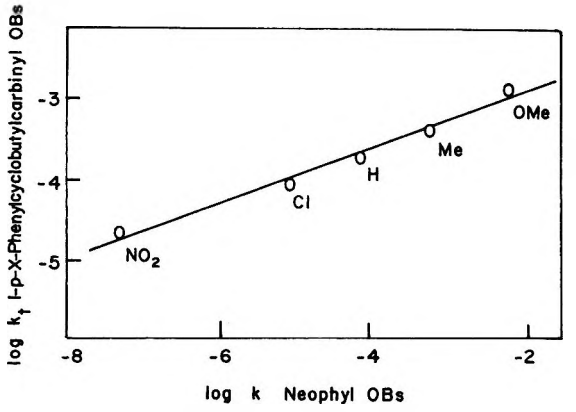


Figure 1. The linear dependence of log k_t for 1-*p*-X-phenylcyclobutylcarbinyl brosylates on log k for correspondingly para-substituted neophyl brosylates in AcOH at 75°.

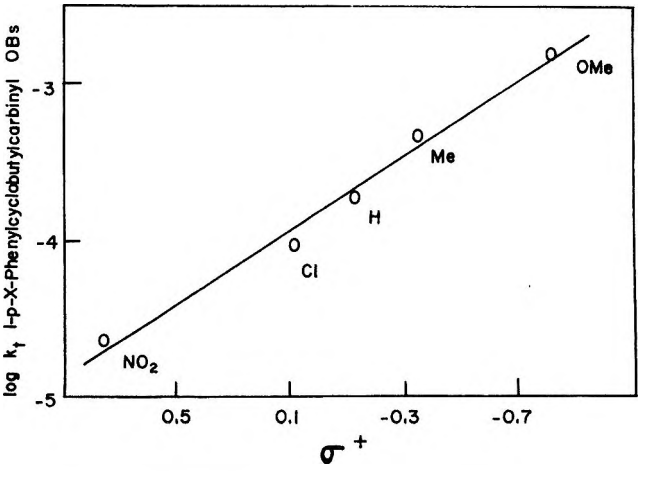


Figure 2. The linear dependence of log k_t for 1-*p*-X-phenylcyclobutylcarbinyl brosylates in AcOH at 75° on σ^+.

values for the trifluoroethanolysis reactions, on the other hand, contrast with those for acetolysis and are reminiscent of the contrasting ΔS^* values reported[1f] for 1-phenylcyclopropylcarbinyl tosylate in acetic acid and sulfolane.

A plot of log k_t for the 1-*p*-X-phenylcyclobutylcarbinyl brosylates against the Hammett σ constants[16] is nonlinear owing to greater than expected solvolysis rates for the *p*-methyl and *p*-methoxy compounds. The kinetic data are correlated (Figure 2) by use of σ^+ values,[17] the reaction constant, ρ, having a value of −1.0 (correlation coefficient 0.98). The sign of this ρ value suggests direct interaction between the para substituents and the developing cationic center in the acetolysis transition state; however, the magnitude of ρ for 4 is significantly lower than the −2.96 value of ρ reported[18] for the acetolysis of corresponding para-substituted neophyl brosylates, but quite similar in magnitude to the −0.9 value of ρ calculated[1f] for the acetolysis of corresponding para-substituted 1-phenylcyclopropylcarbinyl tosylates.

This difference in sensitivity to para substituents is conveniently analyzed by the use of the k^{OMe}/k^{NO_2} ratio data collected in Table II. As one can readily see, the ratio varies over three powers of ten, having a value of

Table II
Sensitivity of Selected Substrates to Para Substituents in Acetolysis Reactions, 75°

Compd	$k^{p\text{-OMe}}/k^{p\text{-NO}_2}$	Ref
Neophyl brosylate	80,000	18, 19
1-Phenylcyclobutylcarbinyl brosylate	75	
1-Phenylcyclopropylcarbinyl tosylate	39[a]	1f

[a] At 30°.

80,000 for the para-substituted 1-phenylcyclopropylcarbinyl tosylate series.

Since it is generally agreed[14,20] that neophyl arenesulfonates ionize exclusively with aryl assistance, and it has been clearly demonstrated[1] that the 1-phenylcyclopropylcarbinyl tosylate undergoes solvolysis without aryl assistance, the $k^{p\text{-OMe}}/k^{p\text{-NO}_2}$ ratio provides a useful scale for measuring the extent of charge dispersal into the benzene ring.

Accordingly, the low $k^{p\text{-OMe}}/k^{p\text{-NO}_2}$ ratio for the 1-phenylcyclobutylcarbinyl brosylate series indicates only a limited charge dispersal into the aryl substituent and strongly suggests that the rate acceleration[21] is due to cyclobutyl participation in the transition state leading to the first-formed cationic intermediate. This situation is very reminiscent of the solvolytic behavior of 1-phenylcyclopropylcarbinyl tosylate,[1] a first-formed intimate ion pair stabilized by cyclopropane ring σ interaction which undergoes significant orbital and structural reorganization before eventual capture by solvent.

Mechanistically these data can be discussed in terms of two reaction schemes (Scheme III and IV). Scheme III, involving an aryl-bridged species as the first-formed, rate-controlling intermediate, is considered unlikely owing to the very weak response to para substituents. Some variation of Scheme IV involving either a bisected cyclobutylcarbinyl cation, 4′, or cyclobutyl edge participation, 4″, is consistent with the experimental data. In this regard the relative rate data summarized in Table III are instructive, for they reveal that the anchimeric assistance[22] provided by the cyclobutane ring is significant—at least one-third that of the cyclopropane ring and greater than two-thirds that of the benzene ring.

While the activation entropies for the acetolysis reactions listed in Table I correlate nicely with the observation[15] that primary β-arylalkyl arenesulfonates which solvolyze *via* k_Δ typically have ΔS^* values of 0 to −10 eu, the inclusion of the activation parameters for the trifluoroethanolysis reactions (see Table I) reveals that the activation entropy correlation becomes much more complex. The dramatic and intriguing decrease in activation entropy when the ionizing medium is changed from acetic acid to trifluoroethanol can be attributed to enhanced solvation of the transition-state complex in the more strongly ionizing trifluoroethanol[25,26] rather than enhanced molecular reorganization. Although k_Δ/k_s increases with increasing solvent ionizing strength,[12,29,30] k_Δ/k_c decreases with increasing solvent ionizing strength.[31,32,33] This latter ratio, k_Δ/k_c, is a more accurate measurement of the degree of charge dispersal and accompanying molecular reorganization.

Scheme III

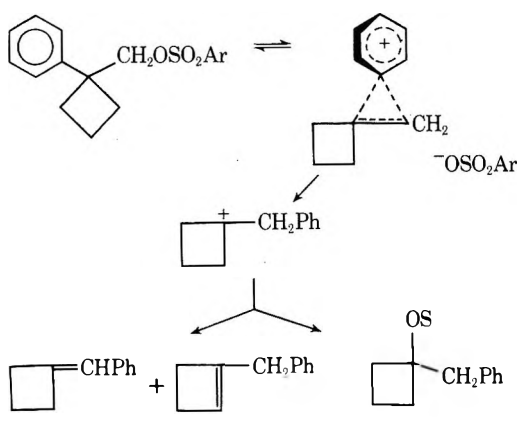
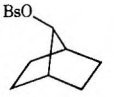
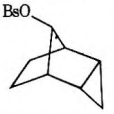
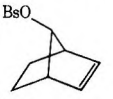
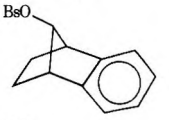
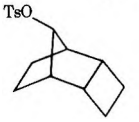
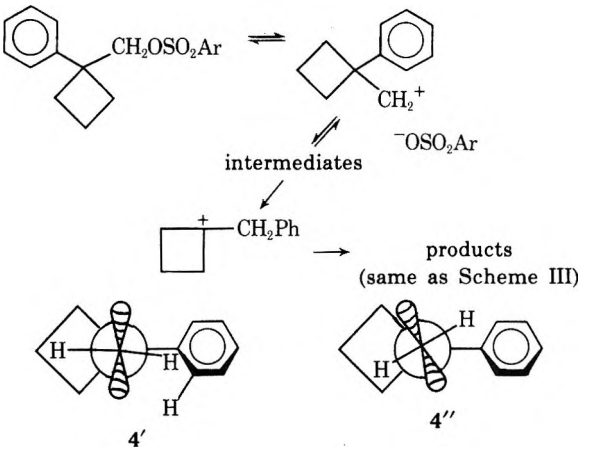


Table III
Relative Acetolysis Rates of Substituted 7-Norbornyl Derivatives

Compd	Temp, °C	Rel rate
		1
	100	10^{12}[e]
	25	10^{9}[b]
	25	$10^{5.7}$[c]
	25	$10^{4.3}$[d,e]

[a] J. S. Haywood-Farmer and R. E. Pincock, *J. Amer. Chem. Soc.*, **91,** 3020 (1969). [b] S. Winstein, M. Shatavsky, C. J. Norton, and R. B. Woodward, *ibid.*, **77,** 4183 (1955). [c] P. D. Bartlett and W. P. Giddings, *ibid.*, **82,** 1240 (1960). [d] M. Sakai, A. Diaz, and S. Winstein, *ibid.*, **92,** 4452 (1970). [e] Compared with 7-norbornyl tosylate.

Scheme IV



Experimental Section

Melting points were not corrected for stem exposure and were taken on a Mel-Temp apparatus. Infrared spectra were recorded on a Bausch and Lomb IR-270 spectrophotometer, and the ultraviolet spectra were obtained on a Beckman DK-2A spectrophotometer. A Beckman GC-4 chromatographic instrument equipped with a thermal conductivity detector and a 24 ft × 0.25 in. column of 20% Carbowax 20M on Chromosorb W, AW-DMCS (45–60 mesh) was used. All microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

Table IV
1-*p*-X-Phenylcyclobutanecarboxylic Acids (2)

Registry no.	X	Mp, °C	Yield, %	Calcd, % C	Calcd, % H	Found, % C	Found, % H	Formula
	H	107–108[a]	85					
50921-37-4	MeO	106–107	65	70.25	6.35	70.41	6.54	$C_{12}H_{14}O_3$
50921-38-5	Me	115–116	86	76.20	6.88	76.01	7.01	$C_{12}H_{14}O_2$
50921-39-6	Cl	89–90	74	62.80	5.26	63.01	5.30[b]	$C_{11}H_{11}ClO_2$

[a] Lit.[35] mp 107.5–108.5°. [b] Also found: Cl, 16.69; calcd Cl, 16.80.

Table V
1-*p*-X-Phenylcyclobutylcarbinols (3)

Registry no.	X	Mp, °C	Yield, %	Calcd, % C	Calcd, % H	Found, % C	Found, % H	Formula
	H	60[a]	83					
	MeO	Oil[b]	66					
50921-40-9	Me	29–30	90	81.75	9.16	81.75	9.02	$C_{12}H_{16}O$
50921-41-0	Cl	55–56	85	67.10	6.60	67.10	6.61[c]	$C_{11}H_{13}ClO$

[a] Lit.[2] mp 60–60.5°. [b] Identified as brosylate; assigned structure consistent with ir spectrum. [c] Also found: Cl, 17.79; calcd Cl, 18.00.

Table VI
1-*p*-X-Phenylcyclobutylcarbinyl Brosylates (4)

X	Mp, °C	Calcd, % C	Calcd, % H	Calcd, % Y	Found, % C	Found, % H	Found, % Y	Formula
MeO	75 dec	52.70	4.65	19.49[a]	52.85	4.70	19.37[a]	$C_{18}H_{19}BrO_4S$
Me	107 dec	54.70	4.84	20.22[a]	54.72	4.90	20.33[a]	$C_{18}H_{19}BrO_3S$
H	107 dec[b]							
Cl	118–119 dec	49.20	3.85	8.54[c]	49.32	3.78	8.43[c]	$C_{17}H_{16}BrClO_3S$
NO_2	123 dec	47.90	3.77	18.75[a]	48.05	3.77	18.58[a]	$C_{17}H_{16}BrNO_5S$

[a] Bromine. [b] Lit.[2] mp 108° dec. [c] Chlorine.

1-Phenylcyclobutanecarbonitrile (1-H) was prepared several times according to the method of Butler and Pollatz.[34] In a typical run, a 2-l., three-necked flask equipped with a mechanical stirrer, reflux condenser, thermometer, and pressure-equalized dropping funnel was charged under N_2 with 600 ml of dimethyl sulfoxide (purified by distillation over CaH) and 63.4 g (1.32 mol) of NaH (50% dispersion in mineral oil). After the vigorous reaction had subsided and cooling to 30° by means of an ice-water bath, a solution of benzyl cyanide (70.2 g, 0.60 mol) and 1,3-dibromopropane (133.2 g, 0.66 mol) in 400 ml of dry ether was added at a sufficient rate to maintain a 25–35° reaction temperature. The resultant thick slurry was stirred overnight and cooled in ice-water and 30 ml of 2-propanol was added dropwise followed by the addition of 500 ml of water. The mixture was then filtered through Filter-aid, the layers were separated, and the aqueous layer was extracted four times with 300-ml portions of ether. The combined ether layer and extracts were dried over $MgSO_4$, concentrated *via* rotovaporization, and distilled through a 30 × 1 cm glass helix packed column to yield 40.0 g (42%) of the nitrile 1-H, bp 80° (0.1 mm). Analysis by glpc revealed greater than 99% purity. Identity was established by conversion to the known carboxylic acid according to a published procedure.[35]

1-*p*-Chlorophenylcyclobutanecarbonitrile (1-Cl) was prepared from *p*-chlorobenzyl cyanide as described above, bp 169–170° (20 mm) [lit.[34] bp 168–169° (20 mm)]. Analysis by glpc revealed greater than 99% purity.

1-*p*-Methoxyphenylcyclobutanecarbonitrile (1-MeO) was prepared from *p*-methoxybenzyl cyanide (Research Organic/Inorganic Chemical Corp.) as described for 1-H in 42% yield, bp 117° (0.3 mm). Analysis by glpc revealed greater than 99% purity.

Anal. Calcd for $C_{12}H_{13}NO$: C, 77.00; H, 6.95; N, 7.48. Found: C, 77.30; H, 6.99; N, 7.33.

1-*p*-Methylphenylcyclobutanecarbonitrile (1-Me) was prepared from *p*-methylbenzyl cyanide (Research Organic/Inorganic Chemical Corp.) as described for 1-H in 42% yield, bp 93° (0.3 mm). Analysis by glpc revealed greater than 99% purity.

Anal. Calcd for $C_{12}H_{13}N$: C, 84.25; H, 7.64; N, 8.18. Found: C, 84.53; H, 7.54; N, 7.98.

1-*p*-X-Phenylcyclobutanecarboxylic acids (2) were prepared according to the method of Lyle[35] and the data for these acids are reported in Table IV.

1-*p*-X-Phenylcyclobutylcarbinols (3) were prepared by reduction of the acid 2 with borane in tetrahydrofuran[1b] and the data for these carbinols are given in Table V.

1-*p*-Nitrophenylcyclobutylcarbinol (3-NO_2). To a magnetically stirred solution of 1-phenylcyclobutylcarbinyl acetate (20.5 g, 0.1 mol, prepared by acetylation of 3-H) in 45 ml of acetic anhydride, a solution of fuming nitric acid (10.7 g) in 35 ml of acetic anhydride (prepared by slow addition of acid to anhydride to maintain temperature at 25°) was added at 0–3°. After stirring for 4 hr at 0° and standing overnight at room temperature, the mixture was poured onto 500 g crushed ice, and the resultant mixture was extracted three times with 80-ml portions of methylene chloride. The combined extracts were washed with cold, saturated aqueous sodium carbonate and dried over $MgSO_4$ and the solvent was removed by rotovaporization to yield 20.1 g (80%) of crude product. Analysis by glpc (220°, 75 cc/min flow rate He) revealed the absence of starting material and the presence of three peaks, A (11%), B (7%), and C (82%), with retention times of 6, 7, and 10.5 min, respectively. Recrystallization twice from 9:1 petroleum ether (bp 30–60°) yielded 14 g of pure C, mp 62°. Analysis by ir (fingerprint region) revealed the presence of a para-disubstituted benzene ring which was confirmed by uv, λ_{max} (EtOH) 280 mμ (ϵ 4820).[36] Hydrolysis of the 1-*p*-nitrophenylcyclobutylcarbinyl acetate (14 g) was accomplished by gentle reflux for 2 hr with 10.7 g of NaOH dissolved in 250 ml of 40% aqueous alcohol. After the usual work-up 9 g (80%) of 3-NO_2 was obtained, mp 70–71°. The infrared spectrum was consistent with the assigned structure.

Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.85; H, 6.31; N, 6.75.

1-*p*-X-Phenylcyclobutylcarbinyl brosylates (4) were prepared according to established procedure,[2] and the data for these esters are summarized in Table VI.

Solvents. Acetic acid solvent was prepared from 994.9 ml of glacial acetic acid (Matheson Scientific, 99.8%) and 5.1 ml of acetic anhydride. 2,2,2-Trifluoroethanol (Aldrich Chemical Co.) was redistilled just prior to use.

Rate measurements were accomplished by the usual ampoule technique.[1] Aliquots (5 ml) were sealed in each ampoule under nitrogen. The fast reactions (less than 1 hr half-life) were carried out in 25-ml volumetric flasks from which 2-ml aliquots were removed periodically. The titrating solutions were, for acetolysis,

0.050 *N* sodium acetate in acetic acid and, for 2,2,2-trifluoroethanolysis, 0..020 *N* sodium methoxide in anhydrous methanol.[37] The indicators used were Bromphenol Blue (in acetic acid) and Bromphenol Blue (in 20% aqueous alcohol), respectively.

Treatment of Kinetic Data. The thermodynamic activation parameters were obtained by IBM 1620 computer regression analysis. The correlation coefficients, *R*, and also the Hammett ρ value were obtained by IBM 1620 computer regression analysis.

Acknowledgment. Appreciation is expressed to Mr. Richard Chang for experimental assistance.

Registry No.—1-Phenylcyclobutanecarbonitrile, 14377-68-5; benzyl cyanide, 140-29-4; 1,3-dibromopropane, 109-64-8; 1-*p*-methoxyphenylcyclobutanecarbonitrile, 29786-45-6; *p*-methoxybenzyl cyanide, 104-47-2; 1-*p*-methylphenylcyclobutanecarbonitrile, 29786-41-2; *p*-methylbenzyl cyanide, 2947-16-7; 1-*p*-nitrophenylcyclobutylcarbinol, 50921-42-1; 1-phenylcyclobutylcarbinyl acetate, 50921-43-2.

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(3) D. D. Roberts, unpublished observation.
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(22) Although this comparison may be questioned on the basis that release of strain may well contribute to the high reactivity[23,24] of the substrates listed in Table III, the 7-norbornyl system is considered most suitable[24] for comparing edge participation by the various neighboring groups listed in Table III.
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(36) Roberts and Watson[1f] previously demonstrated that a longer retention time and an absorption maximum at 280 mμ were characteristic of the para isomer of methyl 1-nitrophenylcyclopropylcarboxylate.
(37) Near the end of this series of experiments it was found that dilution of the 2-ml aliquot with 5 ml of acetic acid solvent followed by titration as with acetolysis samples gave much sharper end points.

Crystal and Molecular Structure of Cephalotaxine *p*-Bromobenzoate

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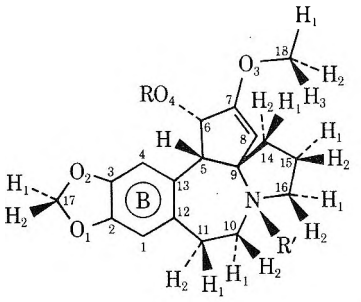
An X-ray study on the title compound verifies the constitution and relative configurations proposed for cephalotaxine and its esters, and shows for the first time the absolute configuration (5*S*). The conformation of the cephalotaxine portion of the molecule closely resembles that of the racemic methiodide, and is probably favored as well in the natural antileukemic cephalotaxine esters.

Several natural esters of cephalotaxine (I) have been found to be potent antileukemic agents, *e.g.*, homoharringtonine (II), which is undergoing preclinical testing.[1] An X-ray study has been carried out on the methiodide III, formed by reacting cephalotaxine (I, optically active) with methyl iodide at room temperature and recrystallizing from warm methanol.[2] Unexpectedly, the methiodide III was found to be racemic, indicating that the configurations at *all four* chiral centers are subject to change during the warming (no doubt *via* intermediates in which the C-9–N bond has cleaved), and thus no firm conclusions regarding the stereochemistry of cephalotaxine (I) could be drawn from the methiodide X-ray study. Two recent syntheses of racemic cephalotaxine (I), however, have lent some support to the view that its *relative* configurations are the same as those found in the racemic methiodide III.[3] We wish to report the results of an X-ray study on the title compound (IV), undertaken to check the proposed constitution and relative configurations and to establish the absolute configuration.

Experimental Section

Cephalotaxine *p*-Bromobenzoate (IV). A 2.05-g sample of *p*-bromobenzoyl chloride was added to a solution of 1.065 g of ce-



	R	R′
I	H	..
II	$C_9H_{17}O_4$—	..
III (racemic)	H	Me (+ on N, I⁻)
IV	Br—	..

phalotaxine (I), mp 136–137°, $[\alpha]_D$ −188° ($CHCl_3$), in 15 ml of dry pyridine. The reaction mixture was allowed to stand overnight and then evaporated to a red-brown syrup. This was taken up in a mixture of $CHCl_3$ and H_2O, NH_4OH was added, and the solution was extracted repeatedly with $CHCl_3$. The combined $CHCl_3$ extracts yielded 2.2 g of crude product. Chromatography on 50 g of Brockmann Grade III neutral alumina, eluting with ether and collecting 30-ml fractions, gave *p*-bromobenzoylcephalotaxine (IV, 1.35 g, 80%), concentrated in fractions 2–5. After recrystallization from ether, IV had mp 220–221° and $[\alpha]_D$ −289° ($CHCl_3$).

A sample of this derivative was saponified and gave back cephalotaxine (I), mp 134–136°, $[\alpha]_D$ −187° ($CHCl_3$).

Collection and Reduction of the Data. Oscillation and Weissenberg photographs of a needle of dimensions 0.2 × 0.3 × 0.5 mm indicated space group $P2_12_12_1$. The cell parameters were found by least squares to fit the settings for the four angles of eight reflections on a Picker-FACS-1 diffractometer (Cu Kα, λ 1.54178 Å, graphite monochromator) to be a = 7.055 (3), b = 17.494 (8), c = 18.192 (8) Å, ρ_c = 1.47, ρ_{obsd} = 1.44 g/ml, and Z = 4. Intensity data were collected using a scintillation counter with pulse-height analyzer, θ–2θ scan technique, 2°/min scan rate, 10-sec background counts, attenuators when the count rate exceeded 10^4 counts/sec, and 2° scan range with a dispersion factor allowing for α_1–α_2 splitting at large 2θ values. Of 1964 independent reflections measured, 1859 > $3\sigma(F)$ were considered observed. Three standard reflections were monitored every 50 measurements to check the crystal alignment and the stability; no decrease in the intensity of the standards was observed. Lorentz and polarization corrections were applied to the data, but no correction was made for absorption.

Solution and Refinement. The bromine coordinates were found both from an E map obtained using the MULTAN[4] program and from Patterson peaks. The calculation of structure factors with phases from the bromine atom gave an R value ($R = \sum||F_o| - |F_c||/\sum|F_o|$) of 0.41. All the nonhydrogen atoms were located from the Fourier map computed with bromine phases only. Four cycles of isotropic least-squares refinement of nonhydrogen atoms reduced R to 0.128, and then two anisotropic cycles to 0.076. A difference Fourier map gave all of the hydrogen positions. One more cycle of least-squares refinement in which nonhydrogen atoms were refined anisotropically and hydrogen atoms isotropically reduced R to 0.046. Refinement was terminated at this stage, since the variations in parameters were less than the standard deviations. The scattering factors used throughout were those of Hanson, Herman, Lea, and Skillman.[5] No correction was applied for extinction.

Absolute Configuration. Using anomalous dispersion corrections of −0.9 for $\Delta f'$ and 1.5 for $\Delta f''$ for scattering of Cu X-rays by Br, structure factors were calculated for each enantiomer for all reflections. The reflections were sorted on D values.[6] Nine of the more intense reflections with $D \geq 10$ were measured along with their negatives in 2θ. All nine showed differences in the direction expected if the absolute configuration depicted in IV is correct.

Table I
Fractional Coordinates and Estimated Standard Deviations

Atom	x/a	y/b	z/c
Br	0.3357 (2)	−0.1817 (1)	0.5582 (1)
O-1	0.5995 (9)	−0.0881 (3)	0.1306 (4)
O-2	0.9112 (8)	−0.0667 (3)	0.1270 (3)
O-3	0.8487 (8)	0.2497 (3)	0.4607 (2)
O-4	0.8022 (7)	0.1053 (2)	0.3938 (3)
O-5	1.0603 (8)	0.0337 (4)	0.4105 (4)
N	0.6188 (9)	0.2457 (3)	0.2137 (3)
C-1	0.5208 (11)	0.0225 (5)	0.2091 (5)
C-2	0.6398 (11)	−0.0238 (4)	0.1715 (4)
C-3	0.8372 (11)	−0.0101 (4)	0.1686 (4)
C-4	0.9132 (10)	0.0511 (4)	0.2016 (4)
C-5	0.8834 (9)	0.1704 (4)	0.2756 (4)
C-6	0.9072 (9)	0.1655 (4)	0.3599 (4)
C-7	0.8319 (10)	0.2394 (4)	0.3872 (4)
C-8	0.7637 (10)	0.2839 (4)	0.3360 (4)
C-9	0.7914 (10)	0.2505 (4)	0.2606 (4)
C-10	0.4449 (11)	0.2175 (5)	0.2465 (5)
C-11	0.4707 (11)	0.1416 (5)	0.2837 (5)
C-12	0.5989 (10)	0.0864 (4)	0.2430 (4)
C-13	0.7985 (10)	0.1022 (4)	0.2399 (4)
C-14	0.9186 (11)	0.3015 (4)	0.2128 (4)
C-15	0.7867 (18)	0.3515 (7)	0.1671 (7)
C-16	0.5921 (13)	0.3207 (6)	0.1783 (6)
C-17	0.7773 (13)	−0.1185 (5)	0.1055 (5)
C-18	0.7822 (12)	0.3222 (5)	0.4888 (4)
C-19	0.8894 (11)	0.0417 (4)	0.4163 (4)
C-20	0.7600 (11)	−0.0120 (4)	0.4506 (5)
C-21	0.5620 (10)	−0.0022 (4)	0.4427 (5)
C-22	0.4378 (11)	−0.0532 (5)	0.4763 (5)
C-23	0.5096 (13)	−0.1123 (5)	0.5152 (4)
C-24	0.7036 (13)	−0.1233 (5)	0.5240 (5)
C-25	0.8240 (13)	−0.0735 (5)	0.4902 (5)
H–C-1	0.391 (8)	0.015 (3)	0.195 (3)
H–C-4	1.046 (8)	0.057 (3)	0.195 (3)
H–C-5	0.997 (8)	0.177 (3)	0.253 (3)
H–C-6	1.050 (8)	0.162 (3)	0.371 (3)
H–C-8	0.719 (8)	0.338 (3)	0.343 (3)
H-1–C-10	0.381 (9)	0.257 (3)	0.293 (3)
H-2–C-10	0.365 (9)	0.224 (3)	0.204 (3)
H-1–C-11	0.358 (9)	0.112 (3)	0.286 (3)
H-2–C-11	0.515 (8)	0.153 (3)	0.331 (3)
H-1–C-14	0.980 (9)	0.271 (3)	0.179 (3)
H-2–C-14	1.017 (9)	0.339 (3)	0.247 (3)
H-1–C-15	0.809 (10)	0.395 (4)	0.206 (4)
H-2–C-15	0.820 (10)	0.374 (4)	0.116 (4)
H-1–C-16	0.527 (9)	0.352 (4)	0.215 (4)
H-2–C-16	0.523 (10)	0.313 (4)	0.130 (4)
H-1–C-17	0.796 (9)	−0.179 (3)	0.130 (3)
H-2–C-17	0.761 (9)	−0.145 (3)	0.048 (3)
H-1–C-18	0.816 (9)	0.318 (3)	0.545 (3)
H-2–C-18	0.675 (9)	0.323 (3)	0.476 (3)
H-3–C-18	0.819 (9)	0.369 (3)	0.458 (3)
H–C-21	0.523 (8)	0.042 (3)	0.418 (3)
H–C-22	0.299 (9)	−0.041 (3)	0.467 (3)
H–C-24	0.773 (8)	−0.167 (3)	0.557 (3)
H–C-25	0.950 (9)	−0.073 (3)	0.503 (3)

Results and Discussion

Table I shows the observed atomic coordinates. As can be seen by comparing the ORTEP[7] drawing in Figure 1 with formula III, cephalotaxine *p*-bromobenzoate (IV) has the same relative configurations (5*S*,6*S*,9*R*) as racemic cephalotaxine methiodide (III).[2] Even the spatial arrangement of groups about nitrogen is similar (*R* configuration in III), leading to essentially the same conformation for III and IV, the only cephalotaxine derivatives for which the conformation has been determined. In view of this finding, of the structural closeness between IV and the natural cephalotaxine esters (*e.g.*, II), and the observation that this conformation provides ample space for the variety of carboxylate portions of the natural esters, *it is very likely*

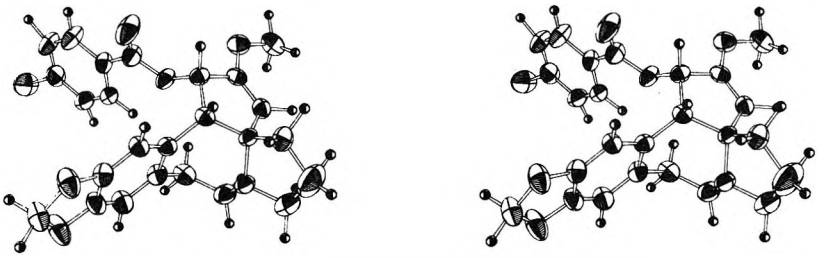


Figure 1. Stereoscopic view of a cephalotaxine *p*-bromobenzoate molecule. Hydrogen atoms are shown as spheres, and other atoms as 50% probability ellipsoids.

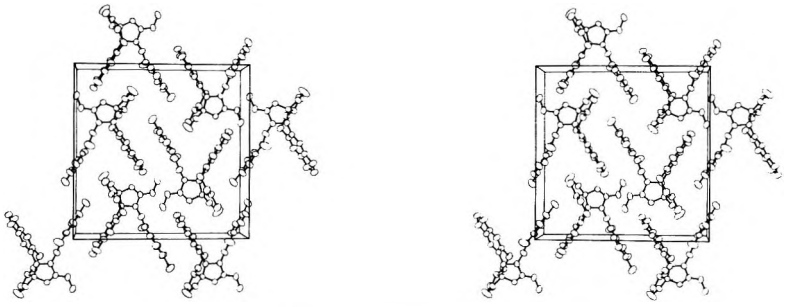


Figure 2. Stereoscopic view of a unit cell, *a* axis projection, with the *b* axis vertical and the c axis horizontal.

that the cephalotaxine portions of the natural antileukemic esters (e.g., II) also prefer this conformation. In this conformation, the seven-membered ring approximates a boat shape with the nitrogen at the prow. The methoxyl group lies essentially in the plane of the olefinic bond and bent toward C-8, with the rotation about the O-3–C-18 bond providing staggering between the methyl hydrogens and C-7. In the ester grouping, rotation about the bonds to O-4 puts the carbonyl oxygen (O-5) close to the hydrogen at C-6; the attached aromatic ring (F) is twisted 15° from the C-19–O-4–O-5 plane.

The absolute configuration from anomalous dispersion by bromine is as shown in IV; from chemical interconversions mentioned earlier, cephalotaxine (I) and its antileukemic esters (*e.g.*, II) share this configuration.

Figure 2 shows the packing diagram. The shortest intermolecular distances between nonhydrogen atoms are C-22–O-5 (3.292 Å), C-18–O-3 (3.432 Å), C-8–O-1 (3.456 Å), and C-18–O-5 (3.489 Å).

Acknowledgments. We thank the Public Health Service (CA-10944) for financial aid, and the University of Arizona Computer Center for computer time.

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Supplementary Material Available. Tables of temperature factors, bond distances, bond angles, least-squares planes, absolute configuration results from pair measurements, and structure factors will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-1269.

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Nuclear Magnetic Resonance Spectral Analysis of the Ergot Alkaloids[1]

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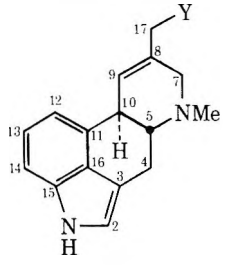
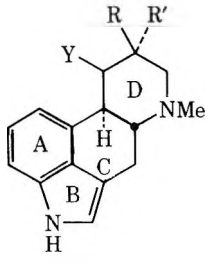
A full analysis of the pmr chemical shifts and coupling characteristics of the ergot alkaloids agroclavine, elymoclavine (and its acetate), festuclavine, and fumigaclavine B is described and some earlier assignments relating to their stereochemistry are revised. The ^{13}C nmr spectra of the ergoline bases methyl lysergate, its dihydro product, ergonovine, ergonovinine, ergotamine, ergotaminine, ergokryptinine, agroclavine, elymoclavine acetate, and festuclavine, their derivatives and models were recorded and their chemical shifts assigned. The cmr analysis confirms the stereochemistry of the alkaloids and the pmr signal assignment in the case of elymoclavine acetate. Pmr and cmr analyses of fumigaclavine B establish the stereochemistry of this rare alkaloid.

The hallucinogenic activity of some lysergic acid derivatives[3] and the antitumor activity of various ergolines[4] have reawakened recently interest in the structure[5-7] and biosynthesis[8] of the ergot alkaloids. The complete absence of available ^{13}C nmr spectral data on this alkaloid family and the disagreement between ^{1}H nmr spectral data on some clavine members of the group[7] with their established stereochemistry[9,10] necessitated a general nmr study of the ergot alkaloid system. As a consequence the complete pmr analysis of four clavines—agroclavine (**1a**), elymoclavine (**1b**) (and its acetate **1c**), festuclavine (**2a**), and fumigaclavine B (**2c**)—and cmr analysis of selected members of the clavine and lysergic acid types of ergot alkaloids were undertaken.



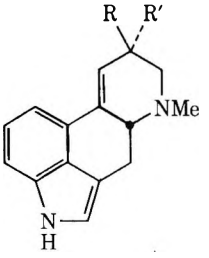
1a, Y = H
b, Y = OH
c, Y = OAc



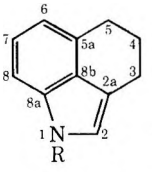
2a, R = Me; R′ = Y = H
b, R = CO_2Me; R′ = Y = H
c, R = H; R′ = Me; Y = OH

Proton magnetic resonance spectra at 220 MHz were run on deuteriopyridine solutions of agroclavine (**1a**) and elymoclavine acetate (**1c**) and on a deuteriochloroform solution of elymoclavine (**1b**). The interrelationship of the hydrogens of rings C and D was established by analysis of the spin–spin coupling characteristics deduced from the spectral fine structure, intensity distribution and width of the complex, but nearly first-order multiplets. The identification of the C-5 and C-7 hydrogens was confirmed by the observation of an expected deshielding effect exerted by the neighboring positive nitrogen on the addition of trifluoroacetic acid to the solution of agroclavine (**1a**).[11] The chemical shifts and coupling constants of the three compounds are listed in Table I. The coupling constant for the hydrogens at the bridgehead carbons 5 and 10 proved to be 9.5 Hz, consistent with their being cis and nearly eclipsed or trans with a dihedral angle of somewhat less than 180°. Since the constraint of the indole ring upon ring C does not tolerate an eclipsed, cis arrangement, the coupling data prove a trans C/D stereochemistry. This result is in agreement with stereostructure **1** for clavines on the basis of chemical interconversions.[9,12,13] While it is in contradistinction to stereochemical arguments based on an earlier pmr study of agroclavine (**1a**) and elymoclavine (**1b**),[7] the previous analysis involved incorrect chemical shift assignment of the 4α, 4β, and 5 hydrogens.

Inspection of the 220-MHz pmr spectra of deuteriochloroform solutions of festuclavine (**2a**) and fumigaclavine B (**2c**) and analysis by the above procedure yielded shift and coupling data for these ergot alkaloids (Table I). The coupling patterns indicate the natural bases to possess trans C/D configurations. Festuclavine (**2a**) exhibits an equatorial C-8 methyl group in accord with chemical findings,[12b,14] while fumigaclavine B (**2c**) shows its 8-methyl and 9-hydroxy functions to be axially oriented. Fumigaclavine B (**2c**) had been considered to possess a H-5/H-8 cis configuration,[15] *i.e.*, an equatorial 8-methyl orientation, on the basis of its base-induced dehydration leading to lysergine (**3a**). However, this experiment does not prove the configuration of the *C*-methyl group in **2c**, since the powerful base needed to execute the dehydration can be expected also to epimerize the C-8 hydrogen of the product and lysergine (**3a**) would be predicted to be more stable than isolysergine (**3b**). This argument is buttressed strongly by the observation of the base-catalyzed isomerization of agroclavine (**1a**) into a mixture of lysergines affording preponderantly lysergine (**3a**).[13]



3a, R = Me; R′ = H
b, R = H; R′ = Me
c, R = CO_2Me; R′ = H
d, R = $CONHCH(CH_3)CH_2OH$; R′ = H
e, R = H; R′ = $CONHCH(CH_3)CH_2OH$
f, R = CO⊣; R′ = H
g, R = H; R′ = CO⊣



4a, R = H
b, R = Me

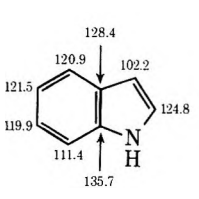
The analysis of the ergot alkaloid family by the natural abundance ^{13}C nmr spectral method was initiated by an inspection of the proton-decoupled and single-frequency off-resonance decoupled cmr spectra of the tricyclic models **4a**[16] and **4b**, prepared from **4a** by treatment with sodium hydride and methyl iodide. Assignment of the carbon shifts of the two compounds relies heavily on a comparison with the reported δ values for indole (**5**) and its 3- and 4-methyl derivatives, **6** and **7**, respectively.[17] Carbons 2, 8, and 8a are apparent from the expected shift pertur-

Table I
^{1}H Chemical Shifts and Coupling Constants

	1a[a]		1b		1c[b]		2a		2c	
	δ	J	δ	J	δ	J	δ	J	δ	J
4α	2.78	dd 15, 12	2.89	dd 15, 12	2.74	dd 15, 12	2.68	dd 15, 11.5	2.58	dd 11, 11
4β	3.31	dd 15, 4	3.37	dd 15, 4	3.27	dd 15, 4	3.39	dd 15, 4.5	3.29	dd 11, 2
5	2.52	ddd 12, 9.5, 4	2.68	ddd 12, 9.5, 4	2.53	ddd 12, 9.5, 4	2.10	ddd 11.5, 9.5, 4.5	2.66	ddd 11, 11, 2
7α	3.24	d 17	3.65	d 17	3.37	d 17	2.95	d[c] 11	3.38	d 12
7β	2.93	dd[c] 17, 4	3.08	dd[c] 17, 4	2.95	dd[c] 17, 4	1.87	t 11	2.82	dd 12, 4
8							2.01	ddd 12, 11, 6.5	2.15	m
9α	6.18	s[c]	6.80	s[c]	6.47	s[c]	2.63	dd[c] 12, 3.5	4.51	s[c] $W_{1/2}$ 6
9β							1.08	q 12		
10	3.74	dd[c] 9.5, 4	4.00	dd[c] 9.5, 4	3.76	dd[c] 9.5, 4	2.97	ddd 12, 9.5, 3.5	2.58	d 11
17	1.77	s	4.45	s	4.66 4.46	AB 12	0.99	d 6.5	1.25	d 7
NMe	2.49	s	2.45	s	2.48	s	2.45	s	2.39	s

[a] Signals of the 4β, 5, 7α, 7β, and NMe hydrogens in $CDCl_3$ with added trifluoroacetic acid appear at 3.19, 2.68, 3.33, 3.13, and 2.56 ppm, respectively, all other signals remaining virtually unchanged. [b] Acetate methyl hydrogens at 2.04 ppm. [c] Broad signal.

bation of N-methylation.[17] Carbons 2a and 5a are deshielded each by *ca.* 10 ppm with respect to C-3 and C-5 of indole (**5**) in analogy with the *ca.* 9 ppm Δδ value for methylation of these indole carbons. While the C-7 shift is close to that of the equivalent center in indole (**5**) and 4-methylindole (**7**), C-6 is shielded anomalously by 7 ppm in comparison to C-5 of **7**. This strong abnormality, also encountered by C-2 (Δδ 4.4 ppm with **6**) and to a smaller extent by most of the aromatic carbons, is due to the strain imposed on the indole nucleus by the trimethylene bridge, an effect reminiscent of the 9-ppm shielding experienced by the ortho methines C-2 and C-7 on conversion of 1,8-dimethylnaphthalene into the strained acenaphthene.[18] Carbon 8b is the only remaining aromatic center, while C-4 is the highest field methylene in view of its feeling the least number of β effects among the three methylenes. Differentiation of the benzylic methylenes relies tentatively on the expected perturbation of their shifts upon imposition of another ring on C-4 and C-5 in the creation of the ergot alkaloid system (*vide infra*). All δ values of tricycles **4a** and **4b** are depicted on formulas 8 and **9**, respectively.



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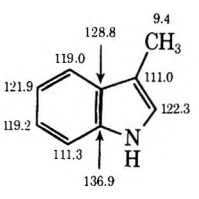

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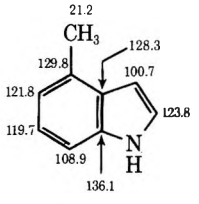

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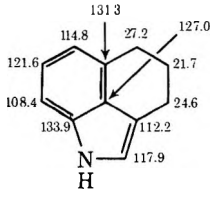

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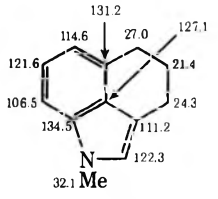

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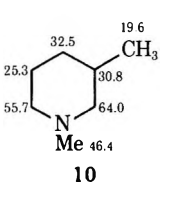
With the chemical shifts of the model **4a** (**8**) in hand and with the recognition of all nonaromatic carbons of agroclavine (**1a**) and elymoclavine acetate (**1c**) being environmentally unique, the cmr analysis of these clavines is easy and dependent on the application of simple chemical-shift theory.[19] Carbon 12 of these compounds feels the shielding peri effect on the imposition of a new ring onto model **8** (Table II).[20]

The carbon shift analysis of festuclavine (**2a**) and methyl 9,10-dihydrolysergate (**2b**) is facilitated by the determination of the C-4 resonance of the clavines **1a** and **1c** (*vide supra*), since the δ values of C-4 and the aromatic carbons would be expected to remain unchanged for compounds of identical C/D ring juncture. Application of standard shift theory[19] elucidates all chemical shifts of the environmentally unique, ring D carbons of festucalvine (**2a**) and methyl 9,10-dihydrolysergate (**2b**) except C-8 and C-10. Differentiation of this carbon pair relies on the shift constancy of C-10 in the two alkaloids (Table II).

While the cmr data discussed thus far are consistent only for a common configuration of the C/D ring juncture among compounds **1a**, **1c**, **2a**, and **2b**, the relative stereochemistry of the bridgeheads required further elaboration. The following interpretation of stereochemically significant features of the ring D carbon shifts of festuclavine (**2a**) and comparison with the shifts of 1,3-dimethylpiperidine (**10**)[21] proves a C-5/C-10 trans stereochemistry for the four substances. On the assumption of festuclavine (**2a**) having its ring D in a chair conformation and of 1,3-dimethylpiperidine (**10**) being in a similar conformational constraint with its methyl groups preponderantly equatorially oriented, the alkaloid can be assessed to have an equatorial methyl group and C-7 and C-8 unencumbered by nonbonded interactions with ring C carbons. This limits festuclavine (**2a**) to the conformational representation **11**.



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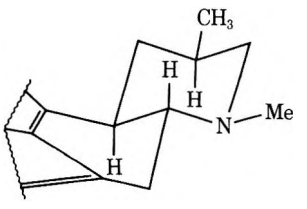

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The chemical shift assignment of all carbons of fumigaclavine B (**2c**) except of its nonaromatic methines follows previous arguments, while the shift analysis of these methines is interwoven intimately with the stereochemistry of their substituents. The identity of the C-4 methylene shift with that of all clavines **1** and **2** is suggestive of a C/D trans configuration.[22] The C-7 signal in the spectrum of **2c** being 8 ppm upfield of that in the festuclavine (**2a**) spectrum is compatible only with the summation of a

Table II
^{13}C Nmr Chemical Shifts of Clavine and Lysergic Acid Systems

	1a[a]	1c[b]	2a[b,c]	2b[d]	2c[a]	3c[b]	3d[d]	3e[d]	3f-12[d]	3g-13[d]	3g-14[d]
C-2	118.3	117.9	117.7	118.4	117.9	118.2	119.1	119.0	119.4	119.7	119.4
C-3	111.2	111.3	110.5	109.9	110.6	110.2	108.9	108.9	108.8	109.0	108.2
C-4	26.4	26.4	26.6	26.4	26.6	26.9	26.8	26.9	26.6	26.9	26.7
C-5	63.6	63.4	66.7	66.4	60.7	62.6	62.6	62.0	62.4	61.7	61.9
C-7	60.2	56.8	65.0	58.3	56.9	54.6	55.5	54.0	55.1	53.0	53.7
C-8	131.9	130.9[e]	30.2	39.3	35.8	41.8	42.8	~42.2	42.5	41.8	~42.2
C-9	119.4	124.8	36.2	30.3	68.1	117.6	120.1	119.0	118.3	118.1	117.6
C-10	40.8	40.5	40.4	40.7	41.4	136.0	135.0	136.1	136.0	137.1	136.7
C-11	131.9	131.3[e]	132.7[e]	132.0	130.8	127.6	127.4	127.6	127.1	127.9	126.7
C-12	112.0	112.2	112.0	112.0	112.9	112.0	111.0	111.0	111.0	111.4	111.5
C-13	122.0	122.6	122.0	122.0	122.0	122.9	122.4	122.1	122.2[e]	122.4	122.2
C-14	108.4	108.7	108.3	108.7	108.0	109.4	109.0	109.8	110.2	110.3	110.2
C-15	134.0	133.4	133.1	133.2	134.0	133.7	133.7	133.7	133.8	133.8	133.6
C-16	126.6	126.1	125.9	125.8	122.9	125.9	125.8	125.7	125.9	126.1	125.8
C-17	19.9	66.2	19.3	173.6	16.5	172.4	171.2	172.1	174.3	175.3	175.8
NMe	40.2	40.5	42.7	42.4	42.9	43.4	43.4	43.6	43.4	42.5	42.6
Me		20.6		51.5		51.9	17.4	17.2			
C=O		170.7									
NCH							46.4	46.2			
OCH_2							64.4	64.3			

[a] In pyridine-d_5 solution. [b] In $CDCl_3$ solution. [c] δ(pyridine-d_5) = $\delta(CDCl_3) \pm 0.3$ ppm except for C-13 and C-16, which are 120.8 and 121.7 ppm, respectively. [d] In DMSO-d_6 solution. [e] Signals in any one column may be reversed.

Table III
^1H–^{13}C Chemical Shift Correlation of Elymoclavine Acetate (1c)

	$\delta(^{13}C)$	Calcd $\delta(^1H)$[a]	Exptl $\delta(^1H)$[b]
Ac Me	20.6	2.04[b]	2.04
C-4	26.4	2.99	3.01[c]
NMe	40.5	2.49	2.48
C-10	40.5	3.69	3.76
C-7	56.8	3.22	3.16[d]
C-5	63.4	2.50	2.53
C-17	66.2	4.56	4.56[e]

[a] Each value is ± 0.05 ppm. [b] From Table I. [c] The average of 3.27 and 2.74 ppm. [d] The average of 3.37 and 2.95 ppm. [e] Center of gravity of AB pair of doublets.

γ effect of 5 ppm by an axial 9-hydroxy group and a reduced β effect of 3 ppm by the reorientation of the 8-methyl group from an equatorial into an axial conformation. The presence of an axial hydroxy function in fumigaclavine B (**2c**) is in consonance with the abnormally high-field resonance of C-5 ($\Delta\delta$ 5.9 ppm with C-5 of **2a**). Identification of the latter leads to the immediate shift designation for C-9 in view of this oxymethine being expected to exhibit a low-field signal. The cancellation of a γ effect by an axial β effect on C-10 produces nearly the same chemical shift for this methine in festuclavine (**2a**) and fumigaclavine B (**2c**). Finally, C-8 is allotted its shift by being the remaining methine. All these arguments support strongly stereostructure **2c** for fumigaclavine-B.

While both the ^1H and ^{13}C nmr spectra of the clavines **1** and **2** now showed the substances to belong to the C/D trans series, the recent misinterpretation of the pmr spectra of **1a** and **1b**[7] necessitated careful checking of the above ^1H nmr results. As a consequence a cmr method of analysis was used to determine the chemical shifts of the nonaromatic hydrogens of elymoclavine acetate (**1c**) and their relationship to specific carbon shifts.[23] This method is based on a graphical technique[23] involving the plotting of residual splitting observed in a series of single-frequency, off-resonance, decoupled cmr spectra spanning the pmr spectral region of interest against the decoupling frequency. The pairs, trios, and quartets of resultant straight lines corresponding to methine, methylene, and methyl resonances, respectively, intersecting at the locus at which the residual splitting constant and concomitantly the distance between the frequencies of a specific hydrogen and the applied radiation equal zero yield the δ values of hydrogens bound to specific carbons.[24] While the technique leads to the same information obtainable by specific hydrogen decoupling experiments, it has the advantage of defining all hydrogen resonances without prior knowledge of the pmr spectrum and otherwise time-consuming optimization of carbon signals.

The calculated ^1H δ values depicted in Table III were acquired by assigning to the known hydrogen resonance of the unambiguous acetate methyl group the measured decoupling frequency at the time of total collapse of the fine structure of the carbon signal at 20.6 ppm into a singlet and then adding to this frequency the measured difference (in hertz) of its value and that of the frequency of the locus of multiplet collapse of each nonaromatic carbon signal. The ^1H shift data of Table III are based on the experimental results shown in Figure 1. The nonequivalent, methylene carbon signals of C-4 and C-7 require special treatment. Were narrow line width associated with their residual splitting multiplets, their one-bond ^1H–^{13}C coupling could be expected to be reflected solely by the diagonal and parallel, dashed, vertical lines in their plot in Figure 1. Since in practice not all long-range ^1H–^{13}C couplings are eliminated in the single-frequency, off-resonance, decoupled cmr spectra and the signals display bandwidths of several hertz, the central components of the reduced splittings cannot be analyzed individually. However, the individual hydrogen resonances can be determined in view of their being equidistant from the frequency representing the confluence of the diagonal lines in Figure 1. The magnitude of the bandwidths of the C-4 and C-7 signals is described by the size of the separation of the dashed, vertical lines in their plots and the center of the broad signals by the solid vertical lines.

A large number of ergot alkaloids are based structurally on the lysergic acid system (**3**). An analysis of the cmr spectra of five natural products, ergonovine (**3d**), ergonovinine (**3e**), ergotamine (**3f-12**), ergotaminine (**3g-13**), and ergokryptinine (**3g-14**), was undertaken and modeled after the chemical shift assignment of methyl lysergate (**3c**). The latter was easy in view of the uniqueness of each nonaromatic carbon center. All chemical shifts of the model and the alkaloids are listed in Table II. Expectedly, conjugation of the ring D double bond with the indole nucleus

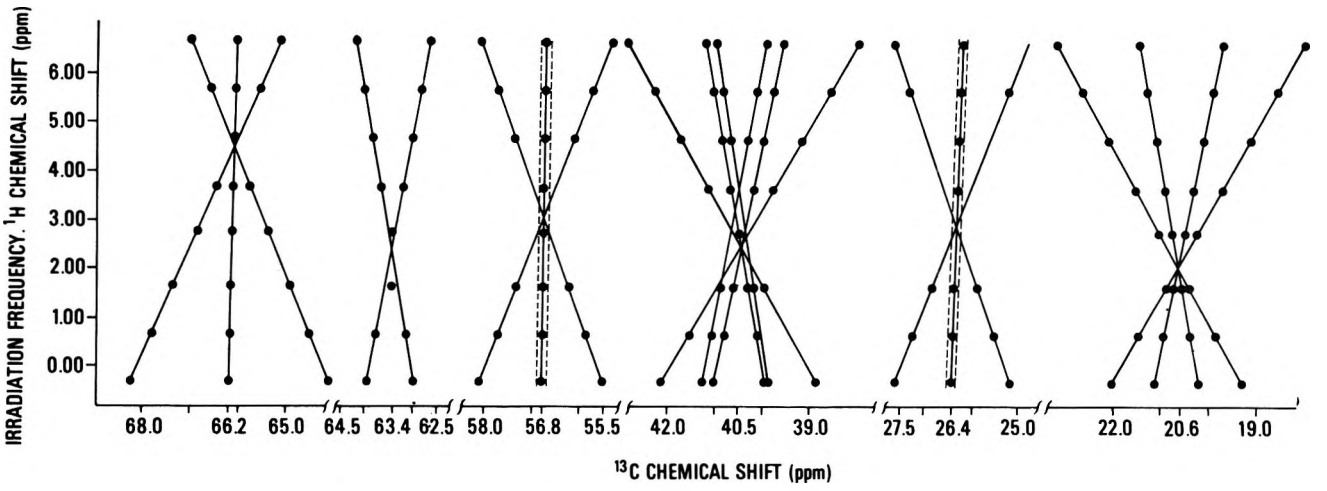
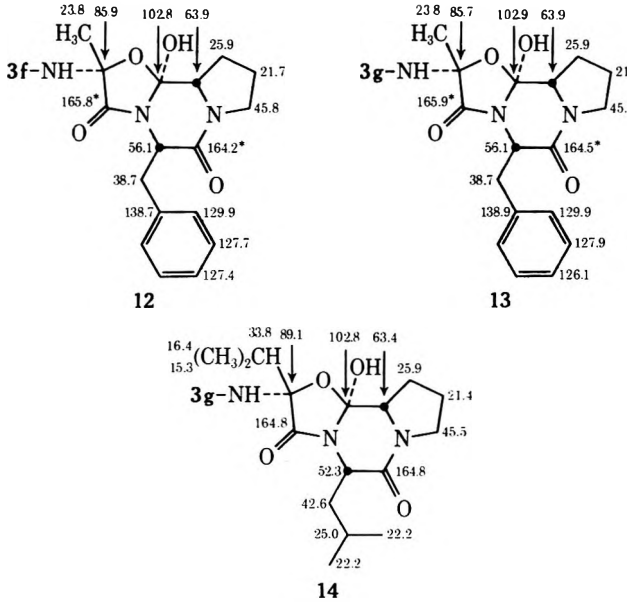


Figure 1. ^{1}H–^{13}C chemical shift correlation for elymoclavine acetate (**1c**).

modifies the C-11 and C-14 shifts.[19] As the $\Delta\delta$(C-7) for methyl lysergate (**3c**) and its dihydro derivative (**2b**) indicates, the introduction of a double bond into the piperidine nucleus shields the homoallyl carbon (*i.e.*, C-7).[25] While a difference of the chemical shift of C-8 for the quasi-equatorial (**3d, 3f-12**) and quasi-axial C-8 carboxamido compounds (**3e, 3g-13, 3g-14**) is noticeable, it is minimal and hence of little stereochemically diagnostic value. However the $\Delta\delta$(C-7) is sterically more revealing.

Application of chemical shift theory and recourse to carbon shift data of peptides[26] allow the assignment of the aminopropanol carbons of ergonovine (**3d**) and ergonovinine (**3e**) (Table II) as well as the environmentally diverse carbons of the peptide portions of ergotamine (**3f-12**), ergotaminine (**3g-13**), and ergokryptinine (**3g-14**). The shifts of the latter are designated on formulas **12**, **13**, and **14**, respectively.



Experimental Section

The pmr spectra were recorded on a Varian HR-220 spectrometer at 16°. The pmr δ values in Tables I and III are in parts per million downfield from TMS (used as internal standard). The J values in Table I are in hertz. The cmr spectra were obtained on a Varian DP-60 spectrometer operating in the Fourier transform mode at 15.08 MHz and 25–40° and on a Varian XL-100-15 Fourier transform spectrometer at 33°. The cmr δ values of Tables II and III and on formulas **5–10** and **12–14** are in parts per million downfield from TMS [δ(TMS) = δ($CDCl_3$) + 76.9 = δ(pyridine-d_5 C-4) + 134.6 = δ(DMSO-d_6) + 39.5 ppm], those of formulas **5–7** having been converted from the CS_2 scale [δ(TMS) = δ(CS_2) + 192.4 ppm].[17] Starred δ values within any one formula may be reversed.

1-Methyl-1,3,4,5-tetrahydrobenz[*cd*]indole (9). A 50% dispersion of sodium hydride in mineral oil, 435 mg, was added to a stirring solution of 1.45 g of **8** in 25 ml of dry dimethylformamide under nitrogen and the mixture was stirred while being cooled in ice for 15 min. A solution of 1.30 g of methyl iodide in 25 ml of dimethylformamide was added and the stirring mixture was allowed to warm to room temperature during 20 min. Cold water was added and the mixture was extracted with ethyl acetate. The extract was washed with water, dried over sodium sulfate, and evaporated. Vacuum distillation of the product yielded **9**, bp 169–172° (8 Torr).

Anal. Calcd for $C_{12}H_{13}N$: C, 84.17; H, 7.65; N, 8.18. Found: C, 83.99; H, 7.78; N, 8.27.

Registry No.—**1a**, 548-42-5; **1b**, 548-43-6; **1c**, 5080-45-5; **2a**, 569-26-6; **2b**, 35470-53-2; **2c**, 6879-93-2; **3c**, 4579-64-0; **3d**, 60-79-7; **3e**, 479-00-5; **3f-12**, 113-15-5; **3g-13**, 639-81-6; **3g-14**, 511-10-4; **8**, 826-67-5; **9**, 50921-47-6.

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Nuclear Magnetic Resonance Spectroscopy. Carbon-13 Chemical Shifts of Chlorinated Organic Compounds[1a]

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The ^{13}C chemical shifts of a variety of perchlorocarbons, their hydrogen-substituted derivatives, and chlorocarbon ketones have been determined and assigned to specific carbons by high-resolution nuclear magnetic resonance spectroscopy. The assignment of ^{13}C resonances for these substances was often aided by ^{13}C–^1H couplings and Overhauser enhancements observed in the carbon spectra of the hydrogen-substituted derivatives. Correlations between ^{13}C chemical shifts and structure were found for simple molecules and these correlations appear to provide the possibility of reasonable structural assignments for complex perchlorocarbons.

Chlorocarbon chemistry is growing in interest and importance,[2] and because the number of techniques for structural analysis of this type of substance is limited, we have investigated the degree to which ^{13}C nmr (cmr) spectra might be useful in this difficult area.

Detection and interpretation of the cmr resonances of chlorocarbons is substantially harder than for hydrocarbons of corresponding structures because of the absence of Overhauser enhancement of the ^{13}C signals associated with proton decoupling and the lack of spin–spin splitting information, as can be obtained for hydrocarbons by off-resonance decoupling. Nonetheless, we have been able to find correlations between ^{13}C chemical shifts and structural features for chlorocarbons and it is possible that cmr spectra may, in the long run, prove nearly as useful in the chlorocarbon area as ^{19}F spectra have been in the study of fluorocarbon structures.

Experimental Section

Chlorocarbons. *cis*- and *trans*-1,2-dichloroethylene, trichloroethylene, tetrachloroethylene, 1,1,1-trichloroethane, hexachloroethane, hexachloropropene, 1,1-difluorohexachloropropane, 1,1,1-trifluoropentachloropropane, hexachlorobutadiene, and hexachlorocyclopentadiene were commercial samples. All of the other chlorocarbons used in this study were generously provided by Professor R. West (University of Wisconsin) and Dr. V. Mark (Hooker Research Center).

Cmr Spectra. Cmr spectra were obtained for ^{13}C in natural abundance using a Varian DFS-60 spectrometer[3] operating at 15.08 MHz. For the hydrogen- and fluorine-substituted chlorocarbons, cmr spectra were determined both with and without proton or fluorine noise decoupling.[4] The preferred solvent was chloroform, which provides resonances for a proton field-frequency lock and internal ^{13}C reference. However, dioxane, cyclohexane, benzene, or tetrachloroethylene were sometimes used. Sweep rates of 40 Hz sec^{-1} or less were employed, which allowed the use of a high radiofrequency power level without saturation of the ^{13}C resonances.[5] The chemical shifts were reproducible to ±1.0 ppm. This variation in chemical shift with solvent, while relatively large, is not so large as to vitiate the structural correlations to be described later. Chemical shifts measured relative to internal standard were corrected to carbon disulfide as internal reference by the relation $\delta_C^{CS_2} = \delta_C^{INT} + N$, where N is 165.8 ppm for cyclohexane, 126.2 ppm for dioxane, 115.4 ppm for chloroforms, 64.6 ppm for benzene, and 71.0 ppm for tetrachloroethylene in a 1:1 tetrachloroethylene–dioxane mixture. Coupling constants and line widths are believed accurate to ±3 Hz. All chemical shifts obtained in this study are presented in Tables I–III. If it is desired that the shifts be referenced to tetramethylsilane (TMS), they can be corrected by the relation $\delta_C^{TMS} = 192.8 - \delta_C^{CS_2}$.

Results and Discussion

Assignments. The bulk of the compounds we have investigated are perchloroalkenes and cycloalkenes which are available in considerable profusion.[2] For these compounds, it is easy to distinguish between the resonances of the double-bond carbons, which fall between 50 and 75 ppm, and those of the single-bond carbons, which come between 90 and 120 ppm. It is interesting that the 50–75-ppm range of the alkenic carbon resonances for perchloroalkenes is not substantially different from the 40–80-ppm range of the corresponding resonances of ordinary alkenes,[6] although the alkane carbons of the perchlorocarbons are shifted some 50 ppm downfield relative to hydrocarbons by the substituent effect of the chlorines.

With the start provided by the differences between double-bonded and single-bonded carbons and taking advantage of symmetry or spin–spin splittings where present, it is possible to assign unambiguously the resonances of many of the compounds shown in Table I, which is arranged to highlight the structural features of each compound for future comparisons. The resonances of the more complicated compounds were assigned (where possible) so as to be consistent with the general pattern of correlation of chemical shifts with structures, as will be discussed below.

A. Single-Bonded Carbon Chemical Shifts. The data of Table I show that the chemical shift of a single-bonded carbon is strongly influenced by the nature of the directly bonded atoms. The single-bonded carbons are here classified as trichloromethyl (CCl_3), dichloromethylene (CCl_2), or chloromethine (CCl). Each class is then subdivided according to the number of directly attached double-bonded or single-bonded carbons. The chemical shift of each subgroup falls within a relatively narrow range, as illustrated in Figure 1.

1. The CCl_3 Carbon. Chemical shifts for trichlorometh-

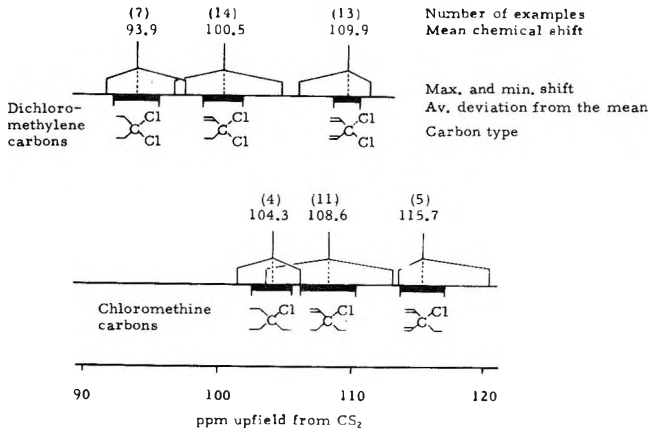
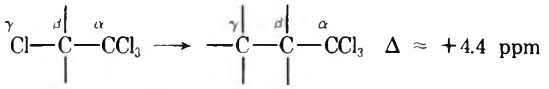


Figure 1. Correlation of ^{13}C chemical shifts of dichloromethylene and chloromethine carbons in fully chlorinated compounds, with degree of substitution. The number of examples is shown in parentheses along with the position of the mean chemical shift of each structural type. The observed range of shifts is shown by the light lines, while the heavy bars are centered on the means and cover the range of average deviation.

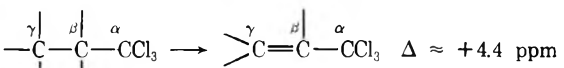
yl carbons of five compounds are given in Table IV. The resonances for compounds **6** and **7** were assigned by virtue of the shift change on substitution of a fluorine atom by chlorine and by the ^{13}C–^{19}F coupling constant, both of which diminish with increase in the number of intervening bonds. The two signals were assigned for octachloropropane (**8**) on the basis of the expected intensity ratio 2:1. Further confirmation for these assignments is given by the chlorocarbon hydrides, **49** and **50**, from the one-bond ^{13}C–^{1}H coupling constant, and the cmr-shift change produced by substitution of a chlorine for a hydrogen, which diminishes with an increase in the intervening number of bonds.

The signal at 95.6 ppm for chlorocarbon **21** is assigned to the CCl_3 carbon, because the signal at 115.2 ppm is logically assigned to C-5 in order to be consistent with the shift of 119.7 ppm for C-5 in chlorocarbon **37**. Finally, the signal due to the CCl_3 carbon (C-6) in chlorocarbon **22** is at 104.7 ppm, which is consistent with the assignments for the three CCl_2 carbons (C-3, C-4, C-5) as shown below.

An examination of Table IV shows that the atoms at both the β and γ positions can influence the trichloromethyl carbon shift. Thus, the trichloromethyl carbon chemical shift is readily correlated with the hybridization of the β-carbon atom and the number of γ-chlorine and carbon atoms. An increase in the shielding at the trichloromethyl carbon of about 4.4 ppm is observed for each γ-chlorine atom that is replaced by a carbon atom.



A similar upfield shift is observed for the structural change

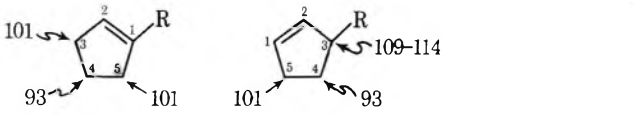


2. The CCl_2 and CCl Carbons. Chemical shifts for dichloromethylene and chloromethine carbons are presented in Table V. These shifts are classified according to the type of β and γ atoms, and are arranged in subclasses according to the number of β sp^2- and sp^3-hybridized carbons.

Here, as noted for the CCl_3 carbon, an upfield shift of 5–8 ppm is associated with each change of a β sp^3 carbon to β sp^2 carbon atom. A β chlorine atom is more deshielding than a β carbon by 8–10 ppm. There does not appear to be a consistent correlation for the γ atom shift. It is observed that the chemical shifts of the CCl_2 and CCl carbons fall within narrow limits for each subgroup of β carbon atoms and there is relatively little overlap between the subgroups for the dichloromethylene carbon, or between the subgroups for the chloromethine carbon shifts. However, there is considerable overlap in the chemical-shift ranges between the subgroups for the two different classes (CCl_2 or CCl) of carbon. While this is a potential limitation to the analysis of complex structures, most of the compounds studied here have sufficiently few sp^3 carbons that their resonances can usually be assigned by comparison with the chemical shifts predicted from the semiempirical correlations shown in Figure 1.

Chlorocarbons **22**, **30**, and **44** are cyclopentenyl structures, and the number of lines in the cmr spectra is consistent with an unsymmetrical 1- or 3-cyclopentenyl derivative, represented as isomers **a** and **b**.

Predicted chemical shifts, ppm



22a **22b** R = CCl_3
30a **30b** R = CCl=CCl_2
44a **44b** R = 1-cyclopentenyl

The observed resonances (see Table I) are most consistent with isomers **22a**, **30a**, and **44a**. For compound **22**, the sp^3 carbon resonance at 104.7 ppm is assigned to the trichloromethyl carbon. The nature of the substituent R appears to have no significant effect on the sp^3 carbon chemical shifts for these compounds.

The molecular formula ($C_{10}Cl_{10}$) for chlorocarbon **41** suggests six double-bond equivalents. In the observed cmr spectrum, there are three sp^3 and two sp^2 carbon signals, all of equal intensity. We consider two possible structures, **41a** and **41b**.

41a **41b**

For structure **41b**, the quaternary carbon (C-1) resonance would be predicted to be at about 119 ppm (the chloromethine carbon resonances with one β sp^2 carbon and two β sp^3 carbons should come at about 109 ppm, plus an additional 10 ppm for the substitution of the β chlorine by a β sp^3 carbon). The chemical shift for C-5 in structure **41b** should be 90–95 ppm, consistent with the observed chemical shift for C-7 in norbornene derivatives. Thus, structure **41b** is not in agreement with the observed shifts of 107.2, 112.0, and 101.6 ppm. The chemical shifts predicted for structure **41a**, on the other hand, are in reasonable agreement with experiment (109, 109, and 104 ppm for C-1, C-4, and C-5, respectively). Structure **41a** has subsequently been proved to be correct.[7]

The cmr spectra of the chlorocarbons **32** and **33** (isomeric bicyclo[3.3.0]octatrienes, C_8Cl_8) show eight signals. The chemical shifts predicted for four possible structures, a–d, of these isomers are as shown. The predicted shifts for a are in close agreement with those observed for **32**, with the signals at 110.4 and 106.2 ppm assigned to C-3 and C-8, respectively.[8] The shifts predicted for b are consistent with signals at 115.7 and 100.4 ppm for **33**.

Table I: ^{13}C Chemical Shifts of Chlorocarbons[a]

Structure		Formula	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10
C=C	**1**	C_2Cl_4	75.4									
CF—CF	**2**	$C_2Cl_4F_2$	72.6[b] [308, 35]									
C—C	**3**	C_3Cl_6	87.5									
	4	C_3Cl_4	70.0		130.4							
	5	C_3Cl_6	65.5	60.7	99.9							
	6	$C_3Cl_6F_2$	64.7 [307]	95.8 [27.5]	92.6							
	7	$C_3Cl_5F_3$	71.6 [287]	100.3 [32]	93.3							
	8	C_3Cl_8	91.4[c]	89.8[c]								
	**9**	C_4Cl_6	(65.5	66.1)								
	10	$C_4Cl_4F_4$	78.8[e,f] [300, 15]		104.4[e] [15]							
	11	C_4Cl_6	58.7		100.7							
	**12**	C_4Cl_{10}	(89.9	89.3)								
	13	$C_3Cl_2F_6$	90.1[b,g] [?, 24]	87.6[b,g] [262, 24]	65.0[b] [28]							
	14	C_5Cl_6	(60.8	61.8)			110.6					
	15	C_5Br_6	(62.8	70.0)			135.7					
	16	C_6Cl_8	57.6		99.9	93.4						
	17	C_6Cl_6	61.4	75.0			55.6	62.0				
	18	C_6Cl_6	(56.7	61.3)[d]			83.3[d]					
	19	C_6Cl_8	59.8	103.3			65.5					
	20	C_6Cl_8	(55.2)	110.7	57.1			(56.0)				
	21	C_6Cl_8	(59.8	62.1)			115.2	95.6				
	22	C_6Cl_{10}	(50.8	55.9)	99.6*	92.2	101.1*	104.7				

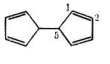
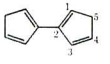
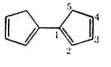
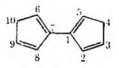
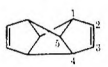
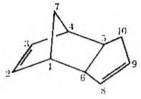
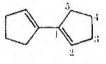
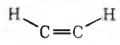
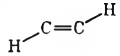
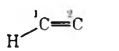
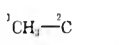
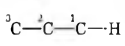
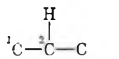
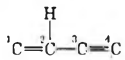
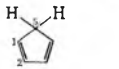
	**23**	$C_6Cl_4F_4$	82.4 [257, 28]	66.6 [30]	60.4						
	**24**	C_7Cl_8	113.9	(55.3	59.4)	104.9	110.8	(59.4	60.4)		
	**25**	C_7Cl_8	106.8	55.4					79.7		
	**26**	C_7Cl_8	(54.3	59.7	62.0	64.6*)	110.6	65.9*	75.0		
	**27**	C_7Cl_8	(54.7	57.2	58.3	64.7*)	110.6	64.7*	74.2		
	**28**	C_7Cl_8	(57.7	58.1	63.0)				107.6		
	**29**	C_7Cl_{10}	113.4	(53.0	60.6)	102.0	106.4	97.6	97.6		
	**30**	C_7Cl_{10}	52.4	58.0	99.9	92.4	101.0	64.3	75.0		
	**31**	C_7Cl_{18}	105.4 104.1[e]	55.7 54.5[e]			95.4 94.2[e]		95.4 94.2[e]		
	**32**	C_8Cl_8	(52.0	53.0)	110.4	(57.7	59.6	65.1	65.3)	106.2	
	**33**	C_8Cl_8	115.7	(46.6	57.5	60.5	60.7	65.9	67.8)	100.4	
	**34**	C_8C_{10}	103.8	56.3	59.3	100.4					
	**35**	C_8Cl_{10}	(54.8	56.0)	96.8	94.9	113.9	(56.4	58.3)	111.6	
	**36**	C_9Cl_{10}	(50.0	57.6	58.1	62.7)	110.2	65.0*	74.5**	66.0*	75.3**
	**37**	$C_{10}Cl_{10}$	(60.8	61.8)			119.7				
	**38**	$C_{10}Cl_{10}$	(51.8	61.1	64.3	67.0)	110.5				
	**39**	$C_{10}Cl_{10}$	(54.3	54.5	60.4	64.7)	109.4				

Table I (Continued)

Structure		Formula	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10
	**40**	$C_{10}Cl_{10}$	(49.9	54.9	55.9	59.4)	109.7	(61.9	62.9	64.5	66.5)	110.4
	**41**	$C_{10}Cl_{10}$	112.0*	(59.1	64.1)	107.2*	101.6					
	**42**	$C_{10}Cl_{12}$	109.0*	(51.5	57.4)	109.5*	104.0	106.1	94.9	(54.1	60.9)	99.5
	**43**	$C_{10}Cl_{12}$	107.5*	(52.7	54.3)	108.6*	105.2	106.4	87.4	(56.4	58.7)	97.5
	**44**	$C_{10}Cl_{14}$	(48.3	61.8)	99.7*	91.6	100.7*					

[a] The ^{13}C chemical shifts are in parts per million upfield from CS_2 and, unless otherwise stated, were measured from internal chloroform as solvent; the asterisks denote pairs of resonances which have been assigned to be consistent with other data; however, there is a possibility that the assignments could be interchanged; the parentheses enclose values of double-bonded carbon resonances which could not be specifically assigned; the brackets contain the ^{13}C–^{19}F coupling constants in hertz. [b] Measured from internal cyclohexane as solvent. [c] Measured from internal dioxane as solvent. [d] Measured from internal chloroform in 1:1 chloroform–dioxane as solvent. [e] Measured from internal tetrachloroethylene in 1:1 C_2Cl_4–dioxane as solvent. [f] Large Overhauser enhancement in ^{19}F noise-decoupled cmr spectrum. [g] Small Overhauser enhancement in ^{19}F noise-decoupled cmr spectrum.

Table II: ^{13}C Chemical Shifts of Chlorocarbon Hydrides[a]

Structure		Formula	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10
	**45**	$C_2Cl_2H_2$	72.3 [206, 32.5]									
	**46**	$C_2Cl_2H_2$	72.6 [208, ~1]									
	**47**	C_2Cl_3H	76.0 [200.5]	67.4 [8]								
	**48**	$C_2Cl_3H_3$	132.8 [134]	82.9 [5]								
	**49**	C_3Cl_7H	117.8[b] [186]	93.5[b]	91.3[b]							
	**50**	C_3Cl_7H	96.9[b]	113.8[b] [166]								
	**51**	C_4Cl_6H	69.4*	72.7 [169.8]	(69.1*	63.0)						
	**52**	$C_5Cl_4H_2$	67.6[g] [8]	64.6 [4.4]			145.7[f] [136]					

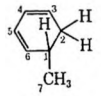
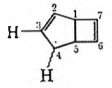
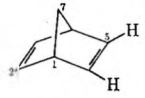
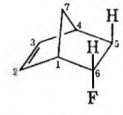
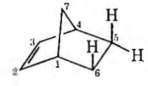
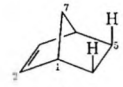
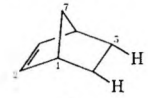
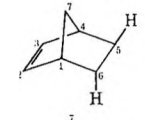
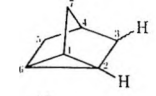
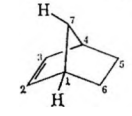
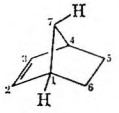
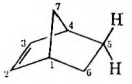
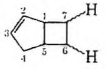
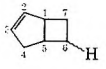
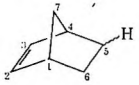
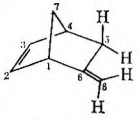
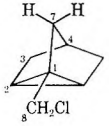
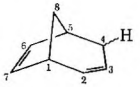
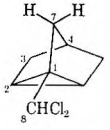
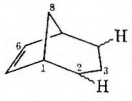
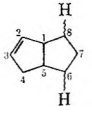
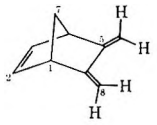
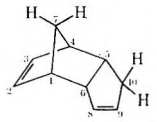
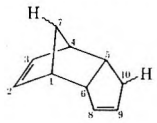
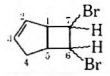
	**53**	C_5Cl_7H	56.9		105.9[g]	115.2[f] [162]			
	**54**	$C_6Cl_5H_3$	(58.1	65.4)			122.9[g]	168.7[f] [113]	
	**55**	$C_7Cl_4H_6$	155.5[c,f] [135]	153.5[c,f] [135]	(65.5	69.0	69.0	58.6)[c]	176.1[c,e,f] [130]
	**56**	$C_7Cl_6H_2$	111.6	57.3[g]	64.8[f] [179.5]	128.8[f] [164.5]	115.1[g]	(58.1	61.2)
	**57**	$C_7Cl_6H_2$	109.1[g] [10]	55.0			51.7[f] [191.5, 4.5]		76.5
	**58**	$C_7Cl_6FH_3$	111.1[c] ^1H ^{19}F [20]	(59.8	62.9)[c]	114.6[c]	149.9[c,f] [142] [23]	97.4[f] [174] [204]	91.9
	**59**	$C_7Cl_7H_3$	112.0[c] ^1H ^{19}F [20]	60.3	61.9	110.7	129.7[f] [163] [15]	100.9[f] [170] [216]	94.4
	**60**	$C_7Cl_7H_3$	109.7[c]	61.6[c]	60.3[c]	115.0[c]	147.6[f] [143]	131.5[f] [163]	91.8
	**61**	$C_7Cl_8H_2$	110.3	60.3			128.1[f] [166]		93.8
	**62**	$C_7Cl_8H_2$	111.3	58.0			131.2[f] [168]		93.8
	**63**	$C_7Cl_8H_2$	111.6	(58.6	59.5)	110.8	123.8[f] [167]	126.1[f] [169]	93.2
	**64**	$C_7Cl_8H_2$	133.2[g]	153.2[f] [191]	128.8[f] [164]	114.6[g]	98.9*	135.1[g]	101.1*
	**65**	$C_7Cl_8H_2$	129.4[c,g,*] [166]	(58.5	61.4)[c]	111.6[c]	98.0[c]	101.7[c]	128.6[c,g,*] [165]

Table II (Continued)

Structure		Formula	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10
	**66**	$C_7Cl_8H_2$	123.7[c,g,*] [165]	(61.0	59.8)[c]	105.2[c]	95.8[c]	100.4[c]	122.4[c,g,*] [165]			
	**67**	$C_7Cl_8H_2$	104.9[c,*]	58.6[c]	59.4[c]	115.7[c]	138.1[c,f] [145]	105.3[c,*]	92.5[c]			
	**68**	$C_7Cl_9H_2$	119.8[g]	55.0	60.3	101.2	111.5[g]	128.9[f] [168]	128.9[f] [168]			
	**69**	C_7Cl_9H	113.1	54.7	59.2	100.9	111.7[g]	122.5[f] [161.5]	105.4[g]			
	**70**	C_7Cl_9H	105.1	(56.9	59.6)	110.9[g]	119.6[f] [167.6]	101.3[g]	94.3			
	**71**	$C_8Cl_6H_4$	108.7[c]	62.1[c]	60.6[c]	114.7[c]	152.1[c,f] [140]	52.5[c]	91.2[c]	81.4[c,f] [160]		
	**72**	$C_8Cl_8H_4$	154.9[c] 154.6[d]	131.5[c] 131.4[d]	99.7[c] 99.2[d]	116.5[c] 116.2[d]			150.9[c,f] [147] 150.9[d,f]	154.9[c,f] [154] 154.6[d,f]		
	**73**	C_8Cl_9H	110.8	63.7 [8]	61.9 [6]	127.1[f] [164]	111.6[g] [7]	(59.7	56.2)	93.8		
	**74**	$C_8Cl_9H_3$	149.6[c] 149.3[d]	131.5[c] 131.9[d]	99.9[c] 99.6[d]	116.6[c] 116.3[d]			153.3[c,f] [145] 153.3[d,f]	126.9[c,f] [180] 126.5[d,f]		
	**75**	$C_8Cl_{10}H_2$	112.3[f]	122.3[f] [159]	102.1[g] [5]			60.8		92.6		
	**76**	$C_8Cl_{10}H_2$	111.6[g]	58.0	58.0	98.8	107.3[g]	118.7[f,*]	99.9	119.7[f,*]		

	**77** $C_9Cl_6H_4$	109.9[b]	60.9[b]			53.5[b]		90.9[b]	84.2[b,f] [163]		
	**78** $C_{10}Cl_8H_4$	115.8[g,*]	(60.1[g] [10]	60.6) [10]	116.6[g,*]	112.2	103.2	133.1[f] [146]	(55.9	60.1[g]) [10]	145.1[f] [138]
	**79** $C_{10}Cl_{10}H_2$	110.3[g,*]	(60.9[g] [7]	63.0[g]) [6]	110.9[g,*]	110.5	106.4	113.8[f] [161]	58.2	57.9[g]	127.8[f] [168]
	**80** $C_7Br_2Cl_6H_2$	120.1[g]	(55.6	59.6)	101.3	110.8[g]	139.6[f,*] [170]	141.6[f,*] [170]			

[a] See footnote *a*, Table I; square brackets contain the $^{13}C-^{1}H$ coupling constants in hertz. [b] Measured from internal dioxane as solvent. [c] Measured from internal cyclohexane as solvent. [d] Measured from internal benzene as solvent. [e] Only the two center lines of the expected quartet were observed. [f] Large Overhauser enhancement in proton-decoupled cmr spectrum. [g] Small Overhauser enhancement in proton-decoupled cmr spectrum.

Table III: ^{13}C Chemical Shifts of Chlorocarbon Ketones[a]

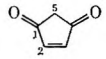
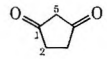
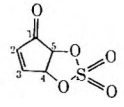
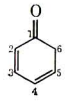
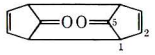
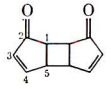
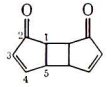
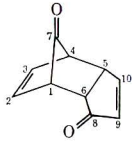
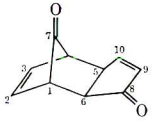
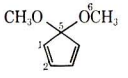
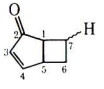
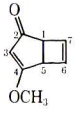
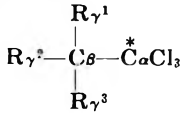
Structure	Formula	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10
	**81** C_3Cl_6O	102.6	17.3								
	**82** C_4Cl_4O	18.8	58.7	26.0	103.0						
	**83** $C_5Cl_4O_2$	13.3	44.1			122.5					
	**84** C_5Cl_6O	14.7	61.8	35.7	102.4	105.4					
	**85** C_5Cl_6O	10.0	116.4	56.0							
	**86** $C_5Cl_6O_2$	10.6	105.4			125.7					
	**87** $C_5Cl_4O_5S$	17.0	56.2	38.1	90.2	95.5					

Table III (*Continued*)

	**88**	C_6Cl_6O	17.2[b]	49.1	(57.7	64.3	66.4)	116.0			
	**89**	C_7Cl_6O	119.0	10.8	60.8*	36.0	117.0	56.7	61.3*		
	**90**	C_8Cl_6O	(48.5	22.8	52.1	60.7	66.1)	106.1	(67.4	69.3)	
	**91**	$C_{10}Cl_8O_2$	121.7	56.0			14.2				
	**92**	$C_{10}Cl_8O_2$	122.3	10.9	55.6	34.1	116.9				
	**93**	$C_{10}Cl_8O_2$	122.1[e]	11.3[e]	54.7[e]	37.2[e]	114.3[e]				
	**94**	$C_{10}Cl_8O_2$	119.8	(61.3 | 61.3)	115.6	114.8	117.8	13.2*	12.0*	(53.4)	36.8
	**95**	$C_{10}Cl_{10}O$	111.3	(56.1 | 55.5)	108.5*	108.6*	117.0	94.7	12.3	(55.1)	36.5
	**96**	$C_7Cl_4H_6O$	(63.8 | 64.3)			88.3	141.2				
	**97**	C_7Cl_7HO	120.9[g]	7.8	57.2	34.7	114.7	105.0	125.7[f] [162.5]			
	**98**	$C_8Cl_5H_3O$	119.9*	9.4	85.6	21.4	119.3*	(58.0 | 59.0)	131.4 [150]		

[a] See footnote *a* and *e–g*, Table I. [b] Measured from internal dioxane as solvent.

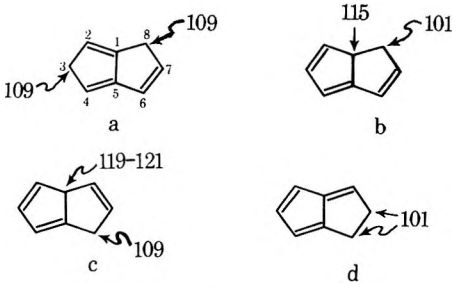
Table IV
^{13}C Chemical Shifts[a] for the Trichloromethyl Carbon



Compd	Carbon	Cβ	R¹	R²	R³	*CCl₃, ppm	Δppm
3	1, 2	sp³	Cl	Cl	Cl	87.5	
							3.9
8	1, 3	sp³	C	Cl	Cl	91.4	
							4.2
21	6	sp³	C	C	Cl	95.6	
							4.3
5	3	sp²	C=		Cl	99.9	
							4.8
22	6	sp²	C=		C	104.7	

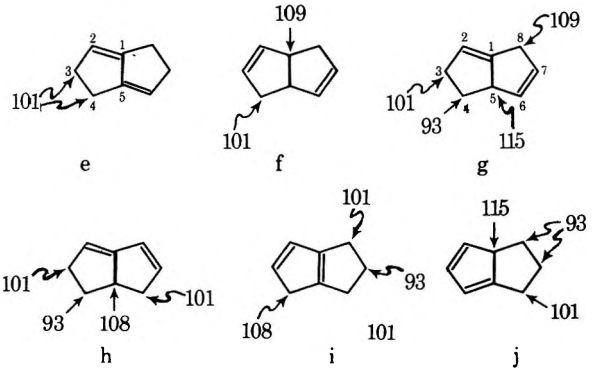
[a] See footnote *a*, Table I.

Predicted chemical shifts, ppm



The cmr spectra of **34** and **35** (isomeric bicyclo[3.3.0]octadienes, C_8Cl_{10}) show two and four sp³ carbon resonances, respectively. Of the set of possible structures e–j, **34** has the symmetrical structure e or f, with e being more consistent with the shifts of 100.4 and 103.8 ppm. Chlorocarbon **35** must have one of the unsymmetrical structures g–j, and the predicted shifts for g are in best agreement with the observed shifts. Thus, the observed resonances are assigned to C-5 at 113.9 ppm, C-8 at 111.6 ppm, C-3 at 96.8 ppm, and C-4 at 94.9 ppm.

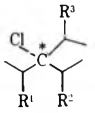
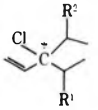
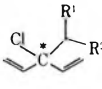
Predicted chemical shifts, ppm



The C-7 resonances for octachloro- (**25**) and hexachloro-5,6-dihydronorbornadiene (**57**) are at 79.7 and 76.5 ppm, respectively, and appear abnormally deshielded for dichloromethylene carbons. The C-7 resonance for the parent hydrocarbon, norbornadiene, has also been observed at low field.[9] These low-field shifts may be due to extra ring strain in the dienes as compared to norbornene derivatives.

The cmr spectrum of **64** shows examples of the resonances due to dichloromethylene carbons (C-5 and C-7) with a β cyclopropyl group which are assigned at 98.9 and 101.1 ppm, respectively. These resonances are only slightly affected by hydrogen substitution at C-2 and C-3, as will be shown later. It appears (see Table V) that a β sp² carbon and cyclopropyl carbon have a similar effect upon the dichloromethylene carbon shift. This observation is borne out by resonances of C-3 and C-5 for **72** and **74** which come at 99.7 and 99.9 ppm, respectively.

Table V
^{13}C Chemical Shifts[a] for Dichloromethylene and Chloromethine Carbons

	Compd	Carbon	*CCl₂, ppm[b]	R¹	R²	R³
	**44**	4	91.6	Cl		
	22	4	92.2	Cl		
	30	4	92.4	Cl		
	16	4	93.4	Cl		
	35	4	94.9	C		
	31	5, 6	95.4	C		
	29	6, 7	97.6	C		
	**35**	3	96.8	Cl	Cl	
	22	3	99.6 (101.1)	Cl	Cl	
	44	3	99.7 (100.7)	Cl	Cl	
	30	3	99.9	Cl	Cl	
	16	3, 5	99.9	Cl	Cl	
	11	3, 4	100.7	Cl	Cl	
	43	10	97.5	Cl	C	
	42	10	99.5	Cl	C	
	29	4	102.0	Cl	C	
	24	4	104.9	Cl	C	
	44	5	100.7 (99.7)	C	Cl	
	30	5	101.0	C	Cl	
	22	5	101.1 (99.6)	C	Cl	
	19	2, 3	103.3	C	Cl	
	**28**	7	107.6	Cl		
	40	10	110.4	Cl		
	32	3	110.4	Cl		
	38	5	110.5	Cl		
	14	5	110.6	Cl		
	26	5	110.6	Cl		
	32	8	106.2	C		
	39	5	109.4	C		
	40	5	109.7	C		
	36	5	110.2	C		
	27	5	110.6	C		
	20	2, 5	110.7	C		
	35	8	111.6	C		
	**29**	5	106.4	C	Cl	Cl
	42	5	104.0	C	C	Cl
	43	5	105.2	C	C	Cl
	41	5	101.6	C	C	C
	**24**	5	110.8	C	Cl	
	29	1	113.4	C	Cl	
	34	1	103.8	C	Cl	
	42	1	109.0 (109.5)	C	Cl	
	42	4	109.5 (109.0)	C	Cl	
	43	1	107.5 (108.6)	C	Cl	
	43	4	108.6 (107.5)	C	Cl	
	42	6	106.1	C	C	
	43	6	106.4	C	C	
	41	1	112.0 (107.2)	C	C	
	41	4	107.2 (112.0)	C	C	
	**21**	5	115.2	Cl	Cl	
	35	5	113.9	C	Cl	
	33	1	115.7	C	Cl	
	24	1	113.9	C	C	
	37	5	119.7	C	C	

[a] See footnote *a*, Table I. [b] Parentheses enclose assignments which may be interchanged.

3. The CH Group. Substitution of hydrogen for chlorine in the perchlorocarbons can aid in assignment of the resonances by giving ^{13}C–^{1}H couplings, and by producing recognizable shifts of the carbons relative to the parent compound. Thus, there is a large upfield shift for the carbon directly attached to hydrogen compared to the parent perchlorocarbon, while the carbons β to the CH group experi-

Table VI
^{13}C Chemical-Shift Changes between Perchlorocarbons and Chlorocarbon Hydrides

	Perchlorocarbon to monohydro derivative				Monohydro to vicinal dihydro derivative					Monohydro to *gem*-dihydro derivative		
Carbon	70–31	53–16	69–29	79–43	68–69	60–67	61–70	62–70	63–70	67–70	78–79	72–74
1	γ −0.3		γ −0.3	β +2.8	β +6.7	β +4.8	β +5.2	β +6.2	β +6.5	γ −0.2	β +5.5	β +5.3
3		β +6.0										
4	β +5.5	α +21.8	γ −1.1	β + γ +2.3	δ +0.3	γ −0.7	γ −0.6	γ +0.4	γ −0.1	β +4.8	β + γ +5.7	
5	α +24.2		β +5.3	β + γ +5.3	γ −0.2	β +9.5	β +8.5	β +11.6	β +4.2	α +18.5	β + γ +1.7	
6	β +5.9		α +24.9	γ + γ 0.0	β +6.4	α +26.2	α +26.8	α +29.9	α +24.8	β +4.0	γ + γ −3.2	γ 0.0
7	γ −1.1		β +7.8	α +26.4	α +23.5	γ −0.7	γ −0.5	γ 0.5	γ −1.1	γ −1.8	α +19.3	γ −2.4
8												α +28.0
10				α +30.3							α +17.3	

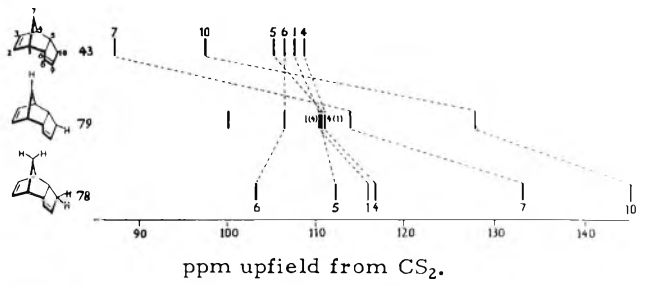


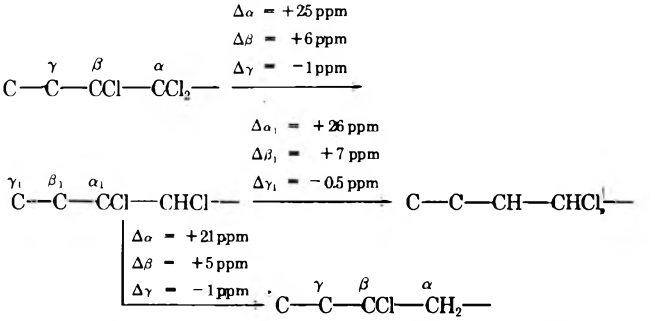
Figure 2. Variation in ^{13}C chemical shifts for successive substitution by hydrogen in *endo*-perchlorocyclopentadiene dimer.

ence a smaller upfield shift. The one-bond ^{13}C–^{1}H coupling further aids in assignment and the directly bonded carbon resonance shows substantial Overhauser enhancement for proton-decoupled spectra. The β carbon usually has only a small Overhauser enhancement and sometimes an observable, but small, two-bond ^{13}C–C–^{1}H coupling.

The six sp^3 carbon resonances of the exo and endo isomers of hexachlorocyclopentadiene dimer (**42** and **43**) were assigned with the aid of the cmr spectra of the *endo*-7,10-dihydro and *endo*-7,7,10,10-tetrahydro derivatives **78** and **79**. The chemical-shift assignments for compounds **43**, **78**, and **79** are summarized in Figure 2 (see also Table VI). The C-7 and C-10 resonances are readily identified by the large upfield shift (17–30 ppm) for the introduction of each hydrogen, and by the enhanced signal intensity in proton-decoupled spectra. The C-1, C-4, and C-5 resonances are identified by much smaller upfield shifts (2–6 ppm) for each proton introduced at C-7 or C-10, and small Overhauser enhancements. The γ carbon (C-6) is but little affected by substitution of chlorine by hydrogen and, for compound **78**, actually experiences a small downfield shift. The signal at 105.2 ppm in **43** is assigned to C-5 (predicted shift 104 ppm) while the signals at 107.5 and 108.6 ppm are assigned to C-1 and C-4 in general agreement with other bridgehead carbon assignments in other norbornene derivatives. Assignments for the exo isomer **42** were made in a corresponding way.

The five sp^3 carbon resonances of decachlorobicyclo[3.2.0]heptene (**29**) are in reasonable agreement with the predicted shifts. Analysis of the cmr spectra of the 6-hydro (**69**), 6,7-dihydro (**68**), and 6,7-dibromo-6,7-dihydro (**80**) derivatives allows a fairly definite set of assignments for compound **29**. The variations in chemical shifts for this group of compounds are summarized in Figure 3 (see also Table VI). High-field resonances and Overhauser enhancements indicate those carbons with directly bonded protons (C-6 for **69**, and C-6 and C-7 for **68**). The resonances due to C-5 and C-7 of **69** and C-1 and C-5 of **68** are identified by an upfield shift (6–8 ppm relative to **29**) and small Overhauser enhancements. The signal due to C-4 is least affected by hydrogen substitution at C-6 and C-7, and for **69** and **68**, a small downfield shift (−1.1 ppm) is observed. The mode of synthesis of **69** suggests the hydrogen to be either at C-6 or C-7, and having the hydrogen at C-6 is more consistent with the cmr data. The highest field resonance (113.4 ppm) for **29** can only be the C-1, and if the hydrogen in **69** were at C-7, an upfield shift for the C-1 resonance would be expected, but is not observed.

Table VI shows the chemical-shift variations for substitution of chlorine by hydrogen in chlorocarbons. The average chemical-shift changes at the α, β, and γ carbons for substitution by a single proton are approximately +25, +6, and −1 ppm, respectively. Substitution by a second proton to yield a vicinal dihydro derivative results in similar average α, β, and γ carbon shift increments. For substitution by a second proton to yield a geminal dihydro derivative, the average α, β, and γ carbon shift increments are +21, +5, and −1 ppm, respectively.



In a study of norbornene hydrocarbons, sterically induced shifts have been attributed to the C-7, C-5, and C-6 carbons.[9a] The C-7 chemical-shift variations with hydrogen substitution at C-5 and C-6 for the chloronorbornenes do not appear due to steric factors, but correlate well with the number rather than with configuration (exo or endo) of the hydrogens at C-5 and C-6, with an additive downfield "γ-shift parameter" at C-7 for each hydrogen. The chemical-shift change at C-7 per exocyclic double bond is −1.3 ppm for the change from **67** to **71**, and −2 ppm for the change from **31** to **77**.

B. The sp^2 Carbon Chemical Shifts. The sp^2 alkenic carbon resonances occur in the range 50–75 ppm. However, certain assignments are generally only possible for

Table VII
^{13}C Chemical Shifts of Some Alkenic Carbons in Perchlorocyclopentenes[a]

Compd		sp² carbon shift		Δδ	Mean sp² carbon shift
	**16**	C-1	57.6		
	**20**	C-3	57.1	−0.5	
	**53**	C-1	56.9	−0.7	
	**22**	C-1	50.8	−6.8	53.4
		C-2	55.9	−1.7	
	**30**	C-1	52.4	−5.2	55.2
		C-2	58.0	+0.4	
	**44**	C-1	48.3	−9.3	55.0
		C-2	61.8	+4.2	

[a] See footnote *a*, Table I.

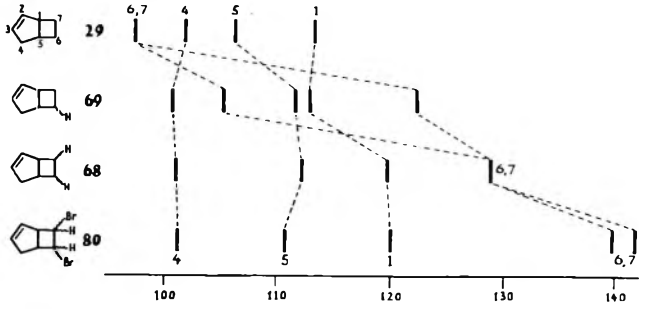
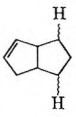
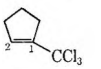
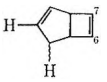


Figure 3. Variation in ^{13}C chemical shifts for successive substitution by hydrogen in perchlorobicyclo[3.2.0]hept-2-ene.

Table VIII
^{13}C Chemical Shifts of Alkenic Carbons in Perchlorocycloalkenes[a]

Compd		sp² carbon shift		Mean	
	**16**	C-1	57.6		
	**29**	C-2	53.0	56.8	
		C-3	60.6		
	**69**	C-2	54.7	56.9	
		C-3	59.2		
	**68**	C-2	55.0	57.6	
		C-3	60.3		
	**80**	C-2	55.6	57.6	Average = 57.4 ppm
		C-3	59.6		
	**24**	C-2	55.3	57.4	
		C-3	59.4		
	**34**	C-2	56.3	57.8	
		C-3	59.3		
	**76**	C-2	58.0	58.0	
			58.0		
	**22**	C-1	50.8	53.4	
		C-2	55.9		
	**30**	C-1	52.4	55.2	Average = 54.5 ppm
		C-2	58.0		
	**44**	C-1	48.3	55.0	
		C-2	61.8		
	**11**	C-1	58.7		
	**24**	C-6	(59.4)	59.9	
		C-7	(60.4)		Average = 59.4 ppm
	**56**	C-6	(58.1)	59.7	
		C-7	(61.2)		

[a] See footnote *a*, Table I.

simple molecules. For more complex molecules, the only helpful data involve comparisons with model compounds and with sp² carbon resonances for hydrocarbons. For this reason, the sp² carbon resonances assigned in Table I seem reasonable and internally consistent; however, these assignments cannot be considered unequivocal. In general, sp² carbon chemical shifts in hydrocarbons do not appear sensitive to conjugation.[10] Similar effects are observed here for the sp² alkenic carbon resonances in the chlorocarbons. For hydrocarbons, replacement of a vinylic proton by carbon results in deshielding of the α sp² carbon resonance and shielding of the β sp² carbon resonance.[11] For chlorocarbons, there is a corresponding deshielding change of the α sp² carbon shift on replacement of chlorine by carbon. The β sp² carbon seems to be erratic in experiencing a smaller shielding or deshielding effect.

The data in Tables VII and VIII give a mean value of the sp² alkenic carbon shift in a five-membered ring of 57.4 ± 0.5 ppm, when chlorine is the only substituent. A carbon substituent at an alkenic carbon in the chlorocyclopentenes causes a larger chemical-shift difference between the two sp² carbon resonances, but the mean shift is nearly constant at 54.5 ppm.

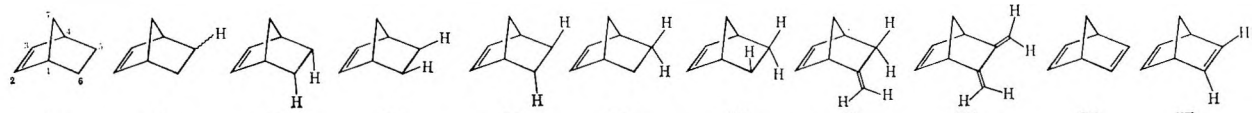
The position of the vinyl substituent for the perchlorovinylcyclopentadienes, **26, 27,** and **36,** does not seem to be deducible from the cmr chemical-shift data. However, the relatively constant chemical shifts of 64–65 and 74–75 ppm observed for some sp² carbon resonances in chlorocarbons **26, 27, 30,** and **36** suggest that these resonances be assigned to the sp² carbons of the vinyl substituents themselves.

The number of resonances in the cmr spectrum of the divinyl derivative **36** indicates unsymmetrical substitution (1,2- or 1,3-divinyl). There is no compelling evidence to assign the higher field resonance (74–75 ppm) to the terminal sp² carbon, except by comparison with the sp² carbons in unsaturated hydrocarbons.[9]

The resonances for the sp² carbons in the chloronorbornenes are tentatively assigned in Table IX. The sp² carbon resonances for the exo 5,6-dihydro derivative **61** are shielded relative to those for the endo derivative **62.** The measurable three-bond ^{13}C–^{1}H couplings were used to assign the sp² carbon resonances of chlorocarbons **60, 67,** and **71** (see below).

C. ^{13}C–^{1}H Coupling Constants. As mentioned previously, the ^{13}C–^{1}H coupling constants in chlorocarbon hydrides provide an additional tool for the cmr spectral analysis. The observed coupling constants are summarized in Table X. The one-bond ^{13}C–^{1}H coupling constants for sp³-hybridized carbons carrying one proton are about the same whether the carbon is attached to chlorine or to ei-

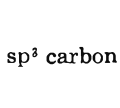
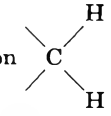
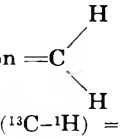
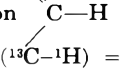
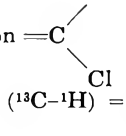
Table IX
^{13}C Chemical Shifts[a] for C-2, and C-3, C-7 in Some Chlorinated Norbornenes



	31	70	62	61	63	67	60	71	77	25	57
C-7	95.4	94.3	93.8	93.8	93.2	92.5	91.8	91.2	90.9	79.7	76.5
$\Delta\delta/H^b$		−1.1	−0.8	−0.8	−1.1	−1.4	−1.2				−1.6
C-2	55.7	56.9	58.0	60.3	58.6	58.6	61.6	62.1	60.9	55.4	55.0
C-3	55.7	59.6	58.0	60.3	59.5	59.4	60.3	60.6	60.9	55.4	55.0

[a] See footnote *a*, Table I; also Figure 4. Where C-2 and C-3 are not identical by symmetry, the assignments are tentative. [b] The C-7 shift relative to C-7 in compound **31** for the norbornenes, and C-7 in compound **25** for the norbornadiene, divided by the number of protons at C-5 and C-6.

Table X
One-Bond ^{13}C–^{1}H Coupling Constants for Chlorocarbon Hydrides

Compd	Carbon	$^{1}J(^{13}C-^{1}H)$, Hz	
75	2, 4	159	
79	7	161	
69	6	161.5	
53	4	162	
60	6	163	
64	3	164	
73	4	164	
56	4	164.5	
65	7	165	
66	1	165	sp³ carbon
50	2	166	
61	5, 6	166	
66	7	165	Mean $^{1}J(^{13}C-^{1}H)$ = 165 ± 6 Hz
63	5(6)	167	
70	5	167.6	
62	5, 6	168	
68	6, 7	168	
79	10	168	
63	6(5)	169	
80	6, 7	170	
52	5	136	
78	10	138	
71	5	140	
60	5	143	sp³ carbon
67	5	145	
74	7	145	
78	7	146	Mean $^{1}J(^{13}C-^{1}H)$ = 142 ± 5 Hz
72	7	147	
Ethylene		157[c]	
71	8	160	
Vinyl chloride	2	160–161[c]	sp² carbon
77	8, 9	163	
Vinylidene chloride	2	166[c]	Mean $^{1}J(^{13}C-^{1}H)$ = 161 ± 5 Hz
1,2,3,4-Tetrachlorobenzene	5	171.9[a]	
2,4,6-Trichloroaniline	3	170.1[a]	
1,3,5-Trichlorobenzene	6	172.2[a]	sp² carbon
2,3,5,6-Tetrachloronitrobenzene	4	175.0[a]	
56	3	179.5	Mean $^{1}J(^{13}C-^{1}H)$ = 174 ± 6 Hz
[**57**	5, 6	191.5][b]	
Vinyl chloride	1	195.0[c]	
47	1	200.5	
45		206	sp² carbon
46		208	
			Mean ^{1}J $(^{13}C-^{1}H)$ = 202 ± 7 Hz
64	2	191	
			sp³ carbon
			Mean $^{1}J(^{13}C-^{1}H)$ = 191 Hz

[a] J. Goldstein and G. S. Reddy, *J. Chem. Phys.*, **36**, 2644 (1962). [b] Not included in the mean value. [c] G. Govil, *J. Chem. Soc. A*, 1420 (1967).

ther sp^2 or sp^3 carbons. The average value of this type of coupling was 165 ± 6 Hz. The *gem*-dihydro carbons show an average value $^{1}J(^{13}C-^{1}H)$ = 142 ± 5 Hz. The difference between the average values for the coupling constants at these two carbon types is 24 Hz, which compares with the differences in $^{1}J(^{13}C-^{1}H)$ of 28-31 Hz for chloromethanes.[12] The larger coupling constant (191 Hz) for the cyclopropyl derivative **64** is consistent with the increased

value for $^1J(^{13}C-^1H)$ in the cyclopropane hydrocarbon.[13]

The one-bond sp^2 carbon–proton coupling constants fall into three distinct classes. Cyclic double-bond sp^2 carbons ($^1J(^{13}C-^1H)$ = 174 ± 6 Hz), terminal double-bond sp^2 carbons bonded to one proton $^1J(^{13}C-^1H)$ = 202 ± 7 Hz), and terminal double-bond sp^2 carbons bonded to two protons ($^1J(^{13}C-^1H)$ = 161 ± 5 Hz). These couplings are comparable to one-bond sp^2 carbon–proton coupling constants in hydrocarbons;[14] thus, the terminal sp^2 carbon of styrene has $^1J(^{13}C-^1H)$ = 161 Hz,[13a] and the sp^2 carbons of cyclohexene have $^1J(^{13}C-^1H)$ = 170 Hz.[15]

Chlorocarbon **51** is a monohydro derivative of hexachlorobutadiene. It is not possible to assign the proton to C-1 or C-2 from chemical-shift data alone; however, $^1J(^{13}C-^1H)$ = 169.8 Hz seems incompatible with the proton at C-1, but is reasonable for the proton at C-2 (see Table X). The observed coupling constant $^1J(^{13}C-^1H)$ = 191.5 Hz for hexachloro-5,6-dihydronorbornadiene (**57**) is larger than expected, possibly because ring strain produces greater s character in the alkenic C(–H) orbitals which should be reflected[16] in an increased $^1J(^{13}C-^1H)$.

Figure 4 shows the sp^2 carbon resonances observed for chlorocarbon hydrides **60**, **67**, and **71**. The broader of the resonances in the proton-decoupled spectra is assigned to C-3 for both **67** and **71**. This assignment is subject to the assumption that the three-bond $^{13}C-^1H$ coupling constant is not zero, while a four-bond coupling is not observable. The spectra shown in Figure 4 were measured at 20 Hz sec^{-1} sweep rate, and, while the three-bond couplings are not resolved, the participating sp^2 carbon resonances are measurably broader. The partial resolution of the three-bond $^{13}C-^1H$ coupling at the sp^2 carbons for **60** was reproducible, although the assignments are not conclusive because of the rapid sweep rates employed.

D. Chlorocarbon Ketones. The cmr chemical-shift data for the chlorocarbon ketones are summarized in Table III. Carbonyl carbon resonances are observed at 9–23 ppm, and other sp^2- and sp^3-hybridized carbon resonances are observed in the usual regions, as previously discussed.

1. The sp^3 Carbon Chemical Shifts. It is possible to correlate the chemical shifts of a carbon (the β' carbon) directly bonded to a carbonyl carbon with that of a carbon (the β carbon) directly bonded to a dichloromethylene carbon (see Table XI).[17]

The assignments of the resonances for C-1 and C-5 of the ketone **89** were made with the aid of the substituent chemical-shift parameters in Table XI, in conjunction with the assignments shown in Table I for **24**. For chlorocarbon ketone **98**, the chemical shifts for C-1 and C-5 are very similar (119.9 and 119.3 ppm) and, for ketone **89**, the corresponding shifts are C-1 and C-5, 119.3 and 117.0, respectively. If the C-4 methoxy substituent of ketone **98** has a shielding effect at C-5, with negligible effect at C-1, then there is further evidence for the assignment of C-1 of **89** to the resonance at 119.0 ppm. For this reason, the C-1 resonance is assigned to higher field than the C-5 resonance in **92** and **93**, and the C-6 resonance to higher field than the C-5 resonance in **94** and **95**.

The diketone **94** has been assigned as the endo (rather than exo) isomer on the basis of the better correlation between the observed chemical shifts and the shifts predicted from *endo*-perchlorocyclopentadiene dimer **43**, with the substituent chemical-shift parameters presented in Table XI. The indication that ketone **95** is the exo isomer is the greater similarity between the C-7 chemical shift for the ketone and *exo*- (rather than *endo*-) perchlorocyclopentadiene dimer **42**.

2. The sp^2 Carbon Chemical Shifts. The alkenic sp^2 carbon resonances in the β' and γ' unsaturated ketones[17] are observed at ~34 and 55–60 ppm. The lower field signal is assigned to the γ' alkenic carbon by analogy with the corresponding hydrocarbon ketones.[18] The deshielding effect of the methoxy substituent on the C-4 resonance of **98** (compare with **89**) is also consistent with ^{13}C shifts in hydrocarbon β',γ' unsaturated ketones.[18] In many cases, the β' alkenic carbon resonance cannot be distinguished from other alkenic carbon resonances in the same molecule. However, the low-field alkenic carbon resonance (*ca.* 34 ppm) and carbonyl carbon resonance (9–23 ppm) readily characterize a β',γ' unsaturated chlorocarbon ketone.

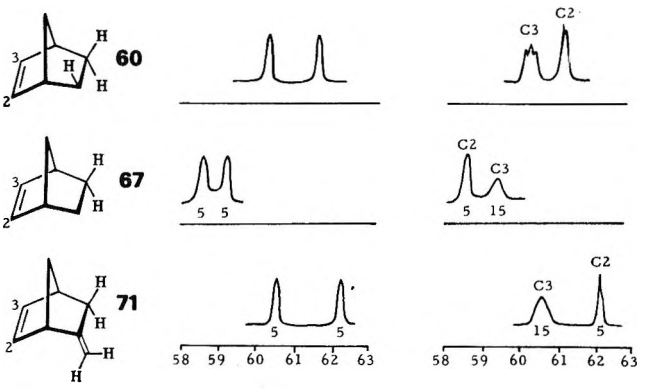
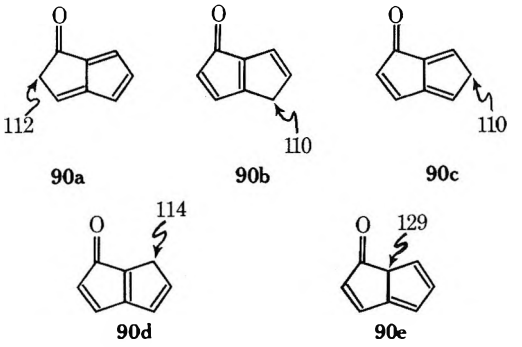


Figure 4. Schematic proton-coupled (right) and -decoupled (left) ^{13}C spectra of **60**, **67**, and **71** at 15.0 MHz. The numbers directly under the peaks are approximate line widths at half-height.

Ketone **90** is an isomer of hexachloro-2-oxobicyclo[3.3.0]octatriene with the possible structures **90a–e**.

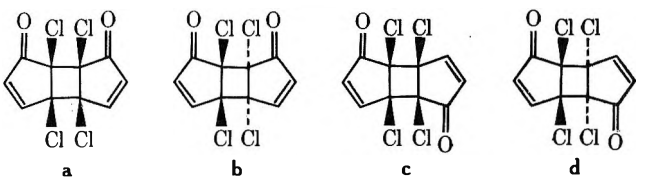
Predicted chemical shifts, ppm



90a **90b** **90c** **90d** **90e**

The cmr spectrum of chlorocarbon ketone **90** does not show a low-field alkenic carbon resonance characteristic of a β',γ' unsaturated ketone. The sp^3 carbon resonance is observed at 106.1 ppm. On the basis of the predicted chemical shifts for the sp^3 carbon resonance, structure **90b** or **90c** seems most reasonable for **90**. In the absence of a better correlation for sp^2 carbon chemical shifts in conjugated systems, it is not possible to assign a more specific structure to ketone **90**.

There are four possible structures (**a–d**) for the isomeric diketones **92** and **93**, and the cmr chemical-shift data do not, at this time, permit one to distinguish between them.

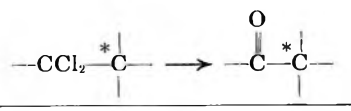


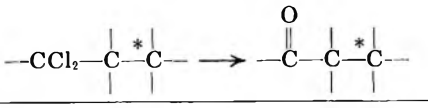
a **b** **c** **d**

92 and **93**

Registry No.—**1**, 127-18-4; **2**, 76-12-0; **3**, 67-72-1; **4**, 6262-42-6; **5**, 1888-71-7; **6**, 661-96-1; **7**, 1652-89-7; **8**, 594-90-1; **9**, 87-68-3; **10**, 336-50-5; **11**, 6130-82-1; **12**, 6820-74-2; **13**, 706-79-6; **14**, 77-47-4; **15**,

Table XI
Comparison of ^{13}C Chemical Shifts of Carbons Adjacent to a Carbonyl and a Dichloromethylene Group





Carbon	Δδ, ppm	Carbon	Δδ, ppm
C-1 (**81**)–C-1 (**8**)	+11.2	C-4 (**84**)–C-3 (**16**)	+2.5
C-2 (**85**)–C-3 (**16**)	+16.5		
C-5 (**84**)–C-4 (**16**)	+12.0		
[C-5 (**83**)–C-4 (**16**)]/2[a]	+14.5		
[C-5 (**86**)–C-4 (**16**)]/2[a]	+16.1		

[a] An additive effect is assumed for the two carbonyl groups in compounds **83** and **86**.

14310-17-9; **16**, 706-78-5; **17**, 6317-25-5; **18**, 1128-20-7; **19**, 1680-65-5; **20**, 3424-05-3; **21**, 6928-57-0; **22**, 50565-48-5; **23**, 50565-49-6; **24**, 34004-45-0; **25**, 15725-07-2; **26**, 50565-47-4; **28**, 21703-93-5; **29**, 50565-50-9; **30**, 50565-51-0; **31**, 2626-30-4; **32**, 27376-18-7; **33**, 37820-33-0; **34**, 50558-31-1; **35**, 50558-34-4; **36**, 50479-39-5; **37**, 2227-17-0; **38**, 27425-40-7; **39**, 27425-42-9; **40**, 27425-41-8; **41**, 33234-21-8; **42**, 2626-29-1; **43**, 27425-43-0; **44**, 27396-27-6; **45**, 156-59-2; **46**, 156-60-5; **47**, 79-01-6; **48**, 71-55-6; **49**, 594-89-8; **50**, 3849-33-0; **51**, 21400-41-9; **52**, 695-77-2; **53**, 50565-55-4; **54**, 16177-47-2; **55**, 50565-56-5; **56**, 50565-57-6; **57**, 3389-71-7; **58**, 14446-77-6; **59**, 50565-58-7; **60**, 2440-02-0; **61**, 2439-87-4; **62**, 38672-05-8; **63**, 2439-88-5; **64**, 50565-59-8; **65**, 28021-60-5; **66**, 26770-94-5; **67**, 50565-60-1; **68**, 50565-61-2; **69**, 50565-62-3; **70**, 35960-34-0; **71**, 4659-42-1; **72**, 50565-63-4; **73**, 50565-64-5; **74**, 50565-65-6; **75**, 50565-66-7; **76**, 50479-40-8; **77**, 6914-86-9; **78**, 50565-67-8; **79**, 29272-51-3; **80**, 50565-68-9; **81**, 116-16-5; **82**, 3200-96-2; **83**, 15743-13-2; **84**, 2514-52-5; **85**, 15743-12-1; **86**; 50565-69-0; **87**, 50565-70-3; **88**, 21306-21-8; **89**, 23326-66-1; **90**, 50565-71-4; **91**, 50565-72-5; **92**, 50565-73-6; **94**, 50565-74-7; **95**, 50565-75-8; **96**, 2207-27-4; **97**, 50565-76-9; **98**, 50479-41-9.

References and Notes

(1) (a) Supported by the National Science Foundation, and by the Public Health Service, Research Grant No. GM-11072 from the Division of General Medical Services. Some of the data in this paper has been reported earlier by V. Mark and E. D. Weil, *J. Org. Chem.*, **36**, 676 (1971). (b) NATO Postdoctoral Fellow, 1970–1972.
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(5) Care should be taken in interpreting integrated signal intensities which might be obtained for cmr spectra measured by the CAT technique with fairly rapid sweeps and high power levels. Under these conditions (which tend to optimize the signal to noise ratios for a given total time of observation), we have found very substantial and disturbing deviations from the predicted integrals on samples of known structure. After considerable hassling over the source of the difficulty, it was finally traced to the relatively long relaxation times of carbon in chlorocarbons which, with rapid sweeps, may not permit return of the equilibrium magnetization between sweeps. We have been able to show with the aid of a program for numerical integration of the Bloch equations developed here by Donald W. Roberts, somewhat along the lines of that described by R. Ernst and W. A. Anderson, *Rev. Sci. Instrum.*, **36**, 1696 (1965), that the first in a rapid series of sweeps gives normal integrals, but further sweeps do not, and, after three or four sweeps, a quasi-equilibrium is set up, which leads to an overall accumulation of signal intensities which may give up to 100% errors in relative signal integrals.
(6) D. E. Dorman, M. Jautelat, and J. D. Roberts, *J. Org. Chem.*, **36**, 2757 (1971).
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(10) One obvious exception is the unusual low-field resonance at 75.0 ppm in the spectrum of **17** which we originally assigned to C-6, but which, from the work of J. B. Grutzner, reported by E. T. McBee, E. P. Wesseler, R. Hurnaus, and T. Hodgins, *J. Org. Chem.*, **37**, 1100 (1972), clearly seems to arise from C-2. This shift is some 15 ppm upfield of any other =CCl– cyclopentene carbon resonance we have measured, and it is interesting that no comparable shift occurs in **14**, **20**, **21**, or **22**.
(11) (a) R. A. Friedel and H. L. Retcofsky, *J. Amer. Chem. Soc.*, **85**, 1300 (1963); (b) K. S. Dhami and J. B. Stothers, *Can. J. Chem.*, **43**, 510 (1965).
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(13) (a) N. Muller and D. E. Pritchard, *J. Chem. Phys.*, **31**, 768 (1959); (b) J. J. Burke and P. C. Lauterbur, *J. Amer. Chem. Soc.*, **86**, 1870 (1964).
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(17) For an explanation of the notation, see the footnote to Table IV.
(18) D. H. Marr and J. B. Stothers, *Can. J. Chem.*, **43**, 596 (1965).

Spectral Comparison of Steric Inhibition of Resonance in Some Hindered *p*-Arylacetophenones as Neutrals and as Gaseous Ions

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The infrared and ultraviolet absorption spectra of a series of *p*-phenylacetophenones substituted ortho to the aryl–aryl bond indicate steric inhibition of interaction between the rings by the substituent. The mass spectra, within error limits established earlier for multiple substitution, indicate that steric inhibition of resonance is not important in the ions.

The remarkable correlation of ion intensities in the mass spectra of acylbenzenes with Hammett σ constants[1] is probably the result of a correlation of onset potentials for formation of the pertinent ions unobscured by the various factors which cannot be correlated by such constants and which apparently are unimportant in the acylbenz-

enes.[2] Ion intensities in these systems, then, serve in the general case as an empirical gauge of ion energetics for processes associated with their formation.[3]

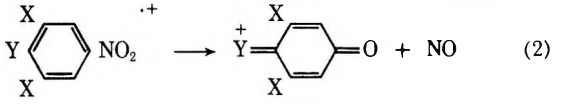
One of the poorest correspondences between solution behavior and mass spectral behavior is found for the *p*-phenyl substituent.[1] The ion abundances for the reactant and product in eq 1 have a ratio suggesting, on compari-

$$p\text{-}C_6H_5C_6H_4COC_6H_5\cdot^+ \longrightarrow C_6H_5CO^+ + C_{12}H_9\cdot \qquad (1)$$

son with similar reactions in other acylbenzenes, that the *p*-phenyl substituent is more electron donating in this sort of cleavage than it is in the dissociation of *p*-phenylbenzoic acid in water, the reaction which defines the Hammett substituent constant. It was suggested[1] that the origin of this behavior might be the same as that of the increased electron donation by the *p*-phenyl substituent in solution reactions when electron demand on the reaction center is high: variable response of the *p*-phenyl substituent as the requirement for resonance stabilization becomes more important and overcomes repulsion between ortho hydrogen atoms of the two rings.[4,5]

A comparison of the energetics of rotation about the bond between the two aromatic rings in *p*-phenylacetophenone and 2-fluoro-4′-acetylbiphenyl, as calculated by the semiempirical INDO method, reinforces this view.[6] In the molecular ion as compared to the neutral compound, there is a lower energy barrier to rotation and the ion can assume a more nearly planar configuration. Consideration of the likely energy distribution in *p*-arylacetophenones[6] suggests that the most important factor governing ion abundances in these compounds is again onset potentials, as in the general case, and not some peculiarity of the internal energy distribution of the ion. The problem can therefore be discussed in terms of activation energies.

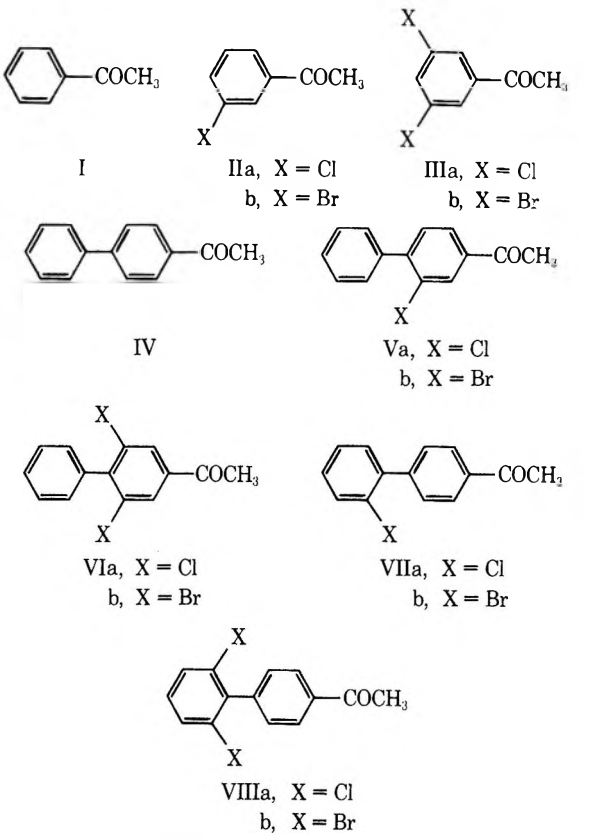
Empirical observations of effects on ion abundances consistent with steric inhibition of resonance have been made in the mass spectra of nitrobenzenes.[7,8] The process in eq 2 is important when Y is small or when X is hydro-



(2)

gen, but, for the special combination when Y is as large as dimethylamino and X is as large as the chloro, bromo, or methyl substituents, eq 2 is only of slight importance. We thought it important to determine, therefore, whether in this same fashion blocking groups on either side of a *p*-phenyl substituent could influence the reactivity of this group in a process where substituent effects can be monitored successfully, *viz.*, cleavage of acylbenzenes. Studies of the effect of multiple substitution in acylbenzenes have shown that multiple substitution in the absence of steric interaction gives an additive substituent effect for this cleavage.[9] Deviations from additivity then could be ascribed to steric interactions, provided that they are qualitatively consistent with such an interpretation and that they are not so small as to be ambiguous. The size of the deviation to be considered significant has been discussed.[9]

Accordingly, the following scheme for comparison of substituent effects was proposed. The compounds I–IV form the set to which the more highly substituted compounds can be compared. Compounds V and VI may be compared with II and IV and III and IV, respectively. If substituent effects are additive, as they are when there is no chance for steric interaction in other model systems,[9] then there is no steric interaction in compounds V and VI; on the other hand, substantial deviation from strict additivity compatible with the reduction of the substituent effect found in IV will indicate steric interaction. Within



rather wide limits[9] it may be possible, if the latter case obtains, to evaluate the effective size of the blocking groups X in V and VI. Compounds VII and VIII do not have immediately obvious model compounds with which they can be compared. However, the electronic effect of blocking groups so far removed from the reaction site (*i.e.*, the ring C–acyl C bond) is expected to be less than it is in II and III and might be sufficiently small that it can be ignored within the error limit expected, 0.12 log unit or twice the standard deviation of model systems.[9] Another estimate of the small effect of a halogen substituent in this position can be gained from the INDO charge distribution in the molecular ions of IV and 2-fluoro-4′-acetylbiphenyl (VI, X = F).[6]

In any case, many of these are new compounds and it is advisable to have experimental data for the neutral molecules with which the mass spectral data can be compared. We report here the carbonyl stretching frequencies in the infrared spectra of I–VIII and ultraviolet data as measures of the behavior of the neutral molecules.

Some of the compounds were prepared by Friedel–Crafts acetylation of substituted biphenyls. The others had to be prepared by a longer route usually involving an unsymmetrical Ullmann coupling of a *p*-halobenzoate ester and a halobenzene with nitro groups adjacent to halogens, conversion of nitro groups to halogens, and conversion of the methoxycarbonyl group to the acetyl group.

Experimental Section

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Satisfactory combustion analyses were obtained for all new compounds (Va, Vb, VIa, VIIa, VIIb, VIIIa, VIIIb, IX, X, XII, XIII, XIV, XVI, XVII, XVIII, XX) except VIb, whose high- and low-resolution mass spectra indicated no impurities.

Spectra. Infrared carbonyl stretching frequencies were measured on a Perkin-Elmer 267 grating spectrophotometer and calibrated against polystyrene. A matched set of 1.0-mm NaCl cells was used; the solvent was CCl_4. Ultraviolet spectra were obtained on a Cary 14 instrument with hexane as solvent in 1-cm cells. Proton magnetic resonance spectra (for confirmation of substitu-

tion patterns) were obtained on a JEOLCO C-60 HL spectrometer with tetramethylsilane as standard. Low-resolution mass spectra were obtained on a Hitachi RMU-6E single-focusing instrument using 75-eV electrons (emission current 80 μA). The source pressure was always in the range 5–10 × 10^{-7} Torr; the source temperature was 185 ± 5°. Four replicate determinations gave a reproducibility of at least 3%; day-to-day variation was <5%. High-resolution mass spectra (for analysis of composition and inspection for interfering fragment ions) were obtained on an MS902 instrument at the Research Triangle Center for Mass Spectrometry, supported by a grant from the Biotechnology Resources Branch of the Division of Research of the National Institutes of Health (RR-330).

Purification. Gas–liquid chromatography was performed on a Perkin-Elmer 900 gas chromatograph using a 4 ft × 0.25 in. stainless steel column packed with 3.8% OV-17 on AWS Chromosorb W support at temperatures from 140 to 220°. Collected peaks were chromatographed on Mallinckrodt ChromAR sheet 500 and ChromAR sheet 1000 with hexane as eluting solvent, using long- and short-wavelength ultraviolet lamps for detection. Peaks deemed singular were submitted for high-resolution mass spectral analysis.

Synthesis. 2-Chloro-4′-acetylbiphenyl (VIIa). This compound was prepared by a Friedel–Crafts reaction of acetyl chloride (3.1 g, 40 mmol) and 2-chlorobiphenyl (7.4 g, 40 mmol) in the presence of $AlCl_3$ (5.8 g, 44 mmol) in 100 ml of CS_2. After 2 hr most solvent was distilled and the mixture was poured on ice–concentrated HCl (100 g/10 g); this mixture and washing were extracted with benzene and the benzene solution was washed with H_2O, 10% NaOH, and H_2O, dried, and treated with charcoal, yield 6.5 g (72%), mp (from MeOH) 48–51°.

Anal. Calcd for $C_{14}H_{11}ClO$: monoisotopic mol wt, 230.0498. Found: 230.0503.

2-Bromo-4′-acetylbiphenyl (VIIb). This was prepared similarly to VIIa in 69% yield, mp (from MeOH) 92–95°.

Anal. Calcd for $C_{14}H_{11}BrO$: monoisotopic mol wt, 273.9993. Found: 273.9996.

Methyl 3-Nitro-4-phenylbenzoate (IX). A reaction mixture of methyl 3-nitro-4-bromobenzoate (5.18 g, 20 mmol), iodobenzene (9.8 g, 20 mmol), and copper bronze (2.4 g) was heated under a slight positive pressure of Ar at 190–195° for 7 hr, and the excess iodobenzene was distilled. The residue was extracted with benzene and the extract was chromatographed on activity I alumina with benzene; the combined yellow eluate yielded 5.03 g (98%) of product, mp 91–92°.

Anal. Calcd for $C_{14}H_{11}NO_4$: monoisotopic mol wt, 257.0688. Found: 257.0683.

Methyl 3-Chloro-4-phenylbenzoate (X). The reduction of IX (2.57 g, 10 mmol) with 10% Pd/C (0.2 g) in ethyl acetate–acetic acid (20 ml/15 ml) under 55–60 psi H_2 in a Parr apparatus for 8 hr gave 2.27 g of oily methyl 3-amino-4-phenylbenzoate (XI) after filtering, extraction of Pd/C with benzene, washing with $NaHCO_3$, drying, and evaporation. The amine (1.13 g, 5 mmol) was used directly in 60 ml of HCl (6 *N*) to generate the diazonium ion with $NaNO_2$ (0.35 g in 5 ml of water). After addition of CuCl (0.8 g) in HCl (concentrated, 5 ml) the mixture was vigorously stirred for 1 hr, warmed to 60° on the steam bath, poured into 100 ml of ice water, and stirred for 1 hr. The precipitate was filtered, washed, dried *in vacuo*, dissolved in benzene, and treated with charcoal to give product (57%).

2-Chloro-4-acetylbiphenyl (Va). This was prepared from X by the method of Corey and Durst[10] using the dianion of methanesulfin-*p*-toluidide at −78°. After decomposition with water, the sample was extracted with ether and washed with HCl, $NaHCO_3$, and NaCl solution. Drying over $MgSO_4$ and evaporation yielded an uncrystallizable oil purified by tlc, then glc.

Anal. Calcd for $C_{14}H_{11}ClO$: monoisotopic mol wt, 230.0498. Found: 230.0501.

Methyl 3-Bromo-4-phenylbenzoate (XII). A solution of XI (1.13 g, 5 mmol) in 24% HBr (30 ml) was diazotized at 0–5° by slow addition of $NaNO_2$ (0.35 g in 5 ml of water), and CuBr (1.15 g in 5 ml of 48% HBr) was added. The mixture was stirred for 1 hr, heated to 60°, poured into ice water, and stirred for 1 hr; the solid was filtered, washed with water, dried, dissolved in benzene, and treated with charcoal to give product (0.76 g).

2-Bromo-4-acetylbiphenyl (Vb). This was prepared from XII by the method of Corey and Durst[10] and worked up as in the preparation of Va; the product before chromatographic purification was treated with Girard T reagent to remove a small amount of unreacted XII. An uncrystallizable oil was finally obtained and purified by tlc, then glc.

Anal. Calcd for $C_{14}H_{11}BrO$: monoisotopic mol wt, 273.9993. Found: 273.9996.

Methyl *p*-(2,6-Dinitrophenyl)benzoate (XIII). Under a slight positive pressure of Ar, 2,6-dinitrochlorobenzene (2.02 g, 10 mmol), methyl *p*-iodobenzoate (2.88 g, 11 mmol), and copper bronze (5 g) were heated with stirring for 4 hr at 195–200°. After cooling and extracting with hot benzene, the solution was concentrated and chromatographed on activity I alumina with benzene until the eluent was no longer yellow. Evaporation and recrystallization from methanol gave 2.05 g (68%) of product, mp 127–128°.

Anal. Calcd for $C_{14}H_{10}N_2O_6$: monoisotopic mol wt, 302.0538. Found: 302.0532.

Methyl *p*-(2,6-Dichlorophenyl)benzoate (XIV). The reduction of XIII (4.06 g, 13.4 mmol) with 10% Pd/C (0.4 g) in ethyl acetate–acetic acid (40 ml/20 ml) under 55–60 psi H_2 for 20 hr in a Parr apparatus gave crude methyl *p*-(2,6-diaminophenyl)benzoate (XV), which was isolated by addition of 100 ml of benzene, filtering, washing three times with $NaHCO_3$, drying over $MgSO_4$, and flash evaporation. The oil (3.24 g, 100%) was used directly in further steps; 1.27 g (5.25 mmol) of the oil in acetic acid (25 ml) was added to $NaNO_2$ (0.85 g) in H_2SO_4 (8.5 ml). The temperature was kept below 30° during and for 1 hr after addition. The solution was poured slowly into a stirred solution of CuCl (1.08 g, 10.8 mmol) in HCl (concentrated, 10 ml) and stirred for 1 hr. After pouring on ice and letting stand for 2 hr, the solid was filtered, washed, dried, dissolved in benzene, treated with charcoal, and recovered by stripping solvent to give an uncrystallizable product (0.98 g, 67% theory).

Anal. Calcd for $C_{14}H_{10}Cl_2O_2$: monoisotopic mol wt, 280.0058. Found: 280.0064.

2′,6′-Dichloro-4-acetylbiphenyl (VIIIa). This was prepared from XIV by a procedure similar to that for preparing Vb; Girard T treatment was again used, and the final product was purified by tlc and glc, mp 48–51°.

Anal. Calcd for $C_{14}H_{10}Cl_2O$: monoisotopic mol wt, 264.0109. Found: 264.0109.

Methyl *p*-(2,6-Dibromophenyl)benzoate (XVI). This material was prepared from XV (3.2 g, 13 mmol) by a procedure similar to that for the preparation of XIV. Chromatography of the product on activity I alumina with benzene gave 0.73 g (15%) of product as an oil which could not be crystallized.

Anal. Calcd for $C_{14}H_{10}Br_2O_2$: monoisotopic mol wt, 367.9049. Found: 367.9045.

2′,6′-Dibromo-4-acetylbiphenyl (VIIIb). This was prepared from XVI by a procedure similar to that for preparing Vb; Girard T treatment was again used. The final product was purified by glc to give a colorless oil.

Anal. Calcd for $C_{14}H_{10}Br_2O$: monoisotopic mol wt, 351.9097. Found: 351.9094.

Methyl 3,5-Dinitro-4-phenylbenzoate (XVII). After flushing with Ar, methyl 3,5-dinitro-4-bromobenzoate (13.0 g, 50 mmol), iodobenzene (28.7 g, 140 mmol), and copper bronze (10 g) were heated at 195–200° for 5 hr. Excess iodobenzene was vacuum distilled and the residue was extracted with hot benzene; this benzene solution was filtered, treated with charcoal, and chromatographed on activity I alumina with benzene until the eluate was no longer yellow, yield 14.9 g (98%), mp 149–150° (from methanol).

Anal. Calcd for $C_{14}H_{10}N_2O_6$: monoisotopic mol wt, 302.0538. Found: 302.0535.

Methyl 3,5-Dichloro-4-phenylbenzoate (XVIII). The reduction of XVII (15.1 g, 50 mmol) with 10% Pd/C (0.57 g) in ethyl acetate–acetic acid (70 ml/35 ml) under 35–40 psi H_2 for 8 hr in a Parr apparatus gave crude methyl 3,5-diamino-4-phenylbenzoate (XIX), which was purified as XV was. This reaction was exothermic to the extent that the hydrogenation was stopped after the first 20 min for 1 hr, then resumed. The product (12.0 g, 99%) was an oil used directly in following steps. The preparation of XVIII from XIX was similar to that of XIV, yield 15%, mp 134–135°.

Anal. Calcd for $C_{14}H_{10}Cl_2O_2$: monoisotopic mol wt, 280.0058. Found: 280.0061.

2,6-Dichloro-4-acetylbiphenyl (VIa). This was prepared from XVIII by a procedure similar to that for preparing Va. A yellow oil was obtained, which was purified by glc, yield 54%.

Anal. Calcd for $C_{14}H_{10}Cl_2O$: monoisotopic mol wt, 264.0109. Found: 264.0111.

Methyl 3,5-Dibromo-4-phenylbenzoate (XX). The preparation of XX was similar to that of XIV, using a solution of CuBr in 48% HBr, yield 19%, mp 108–109°.

Anal. Calcd for $C_{14}H_{10}Br_2O_2$: monoisotopic mol wt, 367.9049.

Table I
Infrared, Ultraviolet, and Mass Spectral Data for Substituted p-Arylacetophenones and Related Compounds

Compd[a]	ν_{CO}, cm^{-1}	λ_{max}, nm[b]	ϵ_{max}	$[CH_3CO^+]/[M\cdot^+]$[c]	Log Z/Z_0
I	1692	278	1100	0.36	0
IIa (*m*-Cl)	1694	288	1.2×10^3	0.63	+0.24
IIb (*m*-Br)	1694	288	8.8×10^2	0.69	+0.28
IIIa (3,5-Cl_2)	1699, 1703	296	7.9×10^2	0.88	+0.34
IIIb (3,5-Br_2)	1698	297	1.8×10^3	1.10	+0.49
IV (*p*-Ph)	1689	276	2.3×10^4	0.18	−0.30
Va (3-Cl-4-Ph)	1694	268	2.0×10^4	0.35	−0.02
Vb (3-Br-4-Ph)	1692	266	1.2×10^4	0.43	+0.07
VIa (3,5-Cl_2-4-Ph)	1698	257	7.9×10^3	0.47	+0.11
VIb (3,5-Br_2-4-Ph)	1699	256	6.0×10^3	0.51	+0.15
VIIa [*p*-(2-ClPh)]	1691	261	1.6×10^4	0.28	−0.11
VIIb [*p*-(2-BrPh)]	1691	261	1.6×10^4	0.45	+0.09
VIIIa [*p*-(2,6-Cl_2Ph)]	1692	250	1.2×10^4	0.56	+0.19
VIIb [*p*-(2,6-Br_2Ph)]	1692	249	1.7×10^4	0.62	+0.23

[a] Numbered as a derivative of acetophenone for easy comparison. [b] For the longest wavelength transition. [c] $[CH_3CO^+]/[M\cdot^+] = Z$ for this study.

Found: 367.9054.

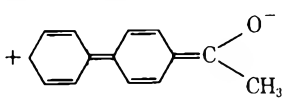
2,6-Dibromo-4-acetylbiphenyl (VIb). This was prepared from XX by a procedure similar to that for preparing Vb, using Girard T reagent, tlc and glc to yield an oil (64%).

Anal. Calcd for $C_{14}H_{10}Br_2O$: monoisotopic mol wt, 351.9097. Found: 351.9094.

Observed Halogen Exchange between Methyl 3-Nitro-4-bromobenzoate and Iodobenzene under Ullmann Conditions. A mixture of methyl 3-nitro-4-bromobenzoate (15.5 g, 60 mmol), iodobenzene (31.7 g, 156 mmol), and copper bronze (5.0 g) was heated under a slight positive pressure of Ar at 190–195° for 6 hr, at which time a large *m/e* 307 peak was observed in the mass spectrum of the crude reaction mixture; heating for an additional 3 hr increased the intensity of this peak relative to that of the starting materials' parent ions. On addition of 5.0 g more of copper bronze and heating at 190–195° for 6 hr, the peak at *m/e* 307 disappeared from the spectrum of the crude product, and on work-up a sample of IX (95% yield) was obtained whose mixture melting point with a sample of IX prepared by the previous route was undepressed.

Results and Discussion

The spectral data for compounds I–VIII are given in Table I. For the most part, the infrared stretching frequencies of the carbonyl group exhibit the trends expected within this series. For the exceptions, the errors are just outside the reproducibility of the data. A correlation is known[11] to exist between the carbonyl stretching frequencies of aromatic ketones and Hammett σ constants, and the data for compounds I, II, and IV bear out this correlation (for *m*-Cl, σ = +0.37; for *m*-Br, σ = +0.39; for *p*-Ph, σ = −0.01 and σ^+ = −0.17). Beyond this, a further shift to greater frequency is seen in the doubly substituted compounds IIIa and IIIb. If we compare the effect of the steric blocking of phenyl by adjacent halogen, and take as our basis the shift between IV and I, then we should compare the shift between V and II and the shift between VI and III. While the shift between IV and I is only 3 cm^{-1}, there is essentially no shift between V and II or VI and III, overall. This observation seems consistent with the interpretation of the shift in IV as a result of interactions of the type



which would be decreased by twisting of the biphenyl system when there are blocking groups in the ortho positions. In such cases, the effect of the phenyl group becomes small, so that the major electronic influence on the carbonyl frequency is that of the electron-withdrawing halogens.

There is no obvious model for gauging the interactions in the compounds with substituents in the far rings, VII and VIII. Since disubstitution (VIII) produces only a small shift from monosubstitution (VII), we may estimate that this increase is additive and a measure of the effect of going from no to one as well as from one to two halogens. We can calculate, then, that the hypothetical frequency of a nonresonating phenyl group is $\nu_{VII} - (\nu_{VIII} - \nu_{VII})$, or 1691 − 1, or 1690 cm^{-1}. More significantly, we have a gauge of the effect of substitution in the distant phenyl ring. Comparison of the shifts in VII and V, and of the shifts in VIII and VI, from the frequency of I shows that the interaction of the halogen with the carbonyl group in VII and VIII is very much damped. Assuming that the greatest portion of this interaction is inductive because of the twisting between rings which removes resonance interaction, we note that the damping is consonant with damping off of inductive effects through bonds as one moves further from the reactive center.

The ultraviolet data also exhibit a trend supporting the intervention of steric inhibition by blocking halogen atoms. As an example, let us assume that the dihedral angle between the rings in solution is the same as that found for biphenyl in heptane solution, 23°.[12] Examination of the ultraviolet spectra of II, III, chlorobenzene, bromobenzene, *m*-dichlorobenzene, and *m*-dibromobenzene shows no significant absorption (*i.e.*, no more than 3% of ϵ_{max}) at λ_{max} of the appropriate compound in Table I for which it would serve as a model of a locally excited state. Hence, the absorption at λ_{max} is due entirely or essentially entirely to the transition involving a molecule-encompassing orbital. Further evidence for this is given by the comparison of the spectra of I and IV. Finally, the influence of halogen on ϵ_{max} is small in compounds II, compared to I, and we extrapolate to hypothesize that the important effect of halogen on ϵ_{max} in compounds V–VIII is its influence on the dihedral angle θ, where it influences the absorptivity by the relation[13]

$$\cos^2\theta = \epsilon/\epsilon_0 \qquad (3)$$

where ϵ_0 is the molar absorptivity of hypothetical planar reference compound, taken here as planar IV. Taking this reference as the reference compound for all members of the series IV–VIII for the reasons cited above, we may calculate the dihedral angle θ in each compound. These values are given in Table II. For the most part, the data follow a trend of increasing angle with increasing steric interference, as expected. Deviations from the trend proba-

Table II
Values of the Dihedral Angle θ between the Aryl Rings of Substituted *p*-Arylacetophenones

Compd[a]	θ, deg
IV (*p*-Ph)	23
Va (3-Cl-4-Ph)	31
Vb (3-Br-4-Ph)	48
VIa (3,5-Cl_2-4-Ph)	57
VIb (3,5-Br_2-4-Ph)	62
VIIa [*p*-(2-ClPh)]	40
VIIb [*p*-(2-BrPh)]	40
VIIIa [*p*-(2,6-Cl_2Ph)]	48
VIIIb (*p*-(2,6-Br_2Ph)]	38

[a] Numbered as a derivative of acetophenone for easy comparison.

bly reflect the poorness of the assumptions and seem to be greater for the compounds substituted in the further ring.

The energy of the transition also increases in a steady fashion as the bulk of the blocking substituents increases, as inspection of the values of λ_{max} in Table I shows. This is less amenable to simple quantitative interpretation, but points to decreased interaction between rings in the blocked compounds as well.

Thus, both the infrared and the ultraviolet spectra of these compounds in solution point to steric inhibition of resonance by bulky substituents at the position adjacent to the bond between the rings.

The Z/Z_0 values from the mass spectra of the multiply substituted acetophenones (Table I) are estimated remarkably well by Z/Z_0 values calculated on the basis of additive effects of individual substituents. Thus, the value for Va, −0.02, is close to the value calculated from IIa and IV, −0.06; that for Vb, +0.07, is fairly close to the calculated value based on IIb and IV, −0.02. For the disubstituted compounds, VIa and VIb, the observed values of Z/Z_0 are +0.11 and +0.15, and the calculated values are +0.04 and +0.19. We estimate that removal of the resonance interaction would have reduced the value of the *p*-phenyl constituent of Z/Z_0 to $\rho\sigma = -0.01$, where ρ is taken from the earlier correlations of singly and multiply substituted compounds[1,9] and σ is taken from solution data for the *p*-phenyl substituent (it is the Hammett σ constant). Therefore, a set of calculated values nearly the same as the Z/Z_0 values of II and III would be predicted by the model in which interaction is similar to that in solution. This is clearly not the case. The data are much closer to the model in which effects are additive, and in fact we cannot distinguish between the experimental results and this model on the basis of the expected error level.[9]

There are no suitable models for the compounds substituted in the further ring, VII and VIII. The effects of substituents in VII and VIII generally appear to be similar to those in V and VI when the compounds are examined as a class.

The additivity of substituent effects in V and VI suggests that there are no important substituent interactions in these compounds. Thus, in the ion, hydrogen–chlorine and hydrogen–bromine interactions are not sufficient to remove the usual resonance effect of the *p*-phenyl group, and even more bulky blocking groups must be sought if one wishes to find evidence for twisting of the aryl rings.

While these results are unusual, they are not totally unexpected. Molecular orbital calculations indicate a reduced energy barrier to rotation in the *p*-arylacetophenone system when the molecule is ionized.[6] One previous study of hindrance of the *p*-dimethylamino group in acylbenzene ions also led to results indistinguishable from those calculated on the basis of additivity.[14] It is not clear why this latter functional group can be blocked by adjacent halogen in the nitrobenzene molecular ion,[7,8] and further studies of this class of compounds is underway.

It is appropriate now to add a few remarks derived from a deeper consideration of substituent effects.[2] Suppose, first, that the halogen substituent led to decreased interaction between the rings. The number of free rotors will be less in the ion. However, in the activated complex for acetyl ion formation, there will be less demand on the substituent for planarity with the reactive center, and the number of free rotors will increase. The *increase* for the substituted, hindered case will be less than the increase for the unhindered case. Then $k(E)$ will rise more abruptly with internal energy, producing a larger fragment ion current than a model ignoring this effect would predict. We do not observe an excess of fragment ion in the substituted compounds; so this model can be rejected as an influence or intensity. If we suppose that the halogen has no influence on the number of free rotors, as we do when we claim no change in interaction between substituents in the halogenated *p*-arylacetophenones, then the rate of rise of $k(E)$ in the halogenated and the model compound is similar and ion intensities may be correlated by the rule we observe to draw conclusions about the onset potential difference (activation energy).

Consider also the effect of a halogen substituent on the shape of the energy distribution in molecular ions. In many aromatic systems a band is found at 11.2 or 11.7 eV corresponding to ionization of lone-pair electrons of bromine or chlorine, respectively.[15] However, the appearance potential of $C_6H_5CO^+$ in acetophenone is 10.45 eV,[16] and the appearance potential of CH_3CO^+ is higher. Therefore, if contributions to ion intensity from the lone-pair band have an appreciable effect, they will raise $[CH_3CO^+]$, or the intensity of some other fragment, but not the intensity of the molecular ion; Z/Z_0 can be raised but not lowered. Again, since we do not observe an excess of fragment ion, this effect cannot be important.

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Registry No.—I, 98-86-2; IIa, 99-02-5; IIb, 2142-63-4; IIIa, 14401-72-0; IIIb, 14401-73-1; IV, 92-91-1; Va, 6908-81-2; Vb, 50987-24-1; VIa, 50987-25-2; VIb, 50987-26-3; VIIa, 3808-89-7; VIIb, 3808-91-1; VIIIa, 50987-27-4; VIIIb, 50987-28-5; IX, 39180-36-4; X, 50987-29-6; XI, 39180-37-5; XII, 50987-30-9; XIII, 50987-31-0; XIV, 50987-32-1; XV, 50987-33-2; XVI, 50987-34-3; XVII, 50987-35-4; XVIII, 50987-36-5; XX, 50987-37-6; acetyl chloride, 75-36-5; 2-chlorobiphenyl, 2051-60-7; methyl 3-nitro-4-bromobenzoate, 2363-16-8; iodobenzene, 591-50-4; 2,6-dinitrochlorobenzene, 606-21-3; methyl *p*-iodobenzoate, 619-44-3; methyl 3,5-dinitro-4-bromobenzoate, 23938-86-5.

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Infrared Studies of Anion Radicals. IV. Diketones[1a]

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The reduction of o-dibenzoylbenzene (II), o-dipentamethylbenzene (III), and benzil (IV) by sodium in THF were studied by ir in NaCl cavity cells. Two reduction stages were observed in each, the first containing an unreduced and apparently unchelated ketone; the second showed ketyl-like absorptions near 1520–1590 cm^{-1} [as compared with benzophenone (I) ketyl]. The latter are probably chelated species. Fully reduced III showed a characteristic C=C stretch at 1610 cm^{-1}.

Recent progress in the development of methods of studying anion radicals by infrared spectroscopy has provided a probe by which considerable information may be obtained concerning the nature of anion radicals.[1] This report is concerned with the infrared shifts observed in some diketones upon metal reduction. The advantage of ir in this area is the ability to observe some structure regardless of the diamagnetic or paramagnetic species formed. In addition, some correlation can be made with results from epr and other structural analyses in determining the species under observation.

The shifts observed are those of ketone and aryl absorptions in the 1800–1500-cm^{-1} range. With each compound in this work we find at least two absorptions occurring in this region, and, since these tend to shift about somewhat irregularly, we will not be concerned with their exact assignment, but rather with the general aspects of the spectra.

Reduction to the weakly ion-paired ketyl has been shown to have two effects in this region of the ir. First, weakening of the carbonyl bond to something more like a bond and a half lowers the normal ketone frequency about 100 cm^{-1} to around 1550 cm^{-1} (*e.g.*, see benzophenone, Figure 1[2] and Table I). Second, the aromatic 1600 cm^{-1} region vibrations are also "loosened" by the presence of the antibonding electron of the anion (or dianion) and are thrown down to approximately the same region, *i.e.*, the 1500's (see paper II of this series).

Experimental Section

Reductions were performed in sealed tubes by sodium metal mirrors in THF or DME solvent, by standard methods previously described.[1a] Perkin-Elmer 621 and 21 ir instruments were used for measurements, and concentrations required were about $5 \pm 5 \times 10^{-2}$ *M*. For low-temperature observations, a cold box was constructed of polystyrene foam using double KBr windows for insulation and pure solvent reference cells. Heat removal was effected by use of a coil of copper tubing into which was pulled liquid nitrogen (by means of an air pump) until the internal temperature desired was reached. Temperatures were measured by a thermocouple. Spectra tracings and apparatus diagrams are available in the microfilm edition. See paragraph at end of paper regarding supplementary material.

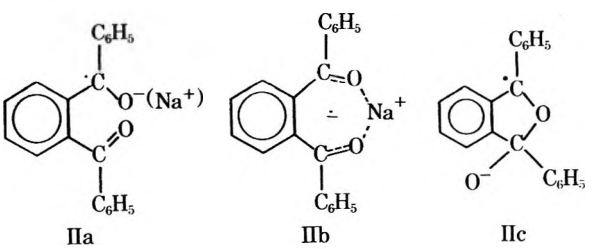
Results and Discussion

Benzophenone (I). This ketone was used as standard for comparison of the ir shift in the 1500–1900-cm^{-1} region as a known ketone → ketyl reaction. The ir shifts of the diketones upon reduction are shown in Table I. The reduction stages were followed by prominent changes in color. These changes are noted and generally conform to previously observed species, though not always structurally known ones. Several of the absorptions recorded did not lend themselves to interpretation, largely because at this stage of our knowledge of the ir of anion radicals we simply do not have enough data on charge-bearing species.

***o*-Dibenzoylbenzene (II).** The first conspicuous color change was to orange in the Na–DME reduction. The organic chemistry of this and other reduction species has been studied in some detail by Herold[3] and Novais.[4] Novais found that, over 3 days, with II in the presence of an excess of sodium, there were several color changes, orange → violet → red → brown, corresponding to several probable reactions. Our system was able to detect only the first two of these steps, because the strongly alkaline solution tends to erode both the salt cell and the epoxy glue fixing it to the Pyrex tube.

The first observable reduction stage of II gives several absorptions in the 1500–1900-cm^{-1} range which are attributed to at least one unreduced carbonyl group. This group is under considerable electron withdrawal resulting in absorptions (1805 and 1735 cm^{-1}) which are not characteristic of known ketyls like benzophenone. One possible structure for this species could be that of the singly reduced IIa, probably not chelated.

The second stage of reduction exhibits ir absorptions which are almost exactly those of benzophenone ketyl. For this reason the species may possibly be that of the chelate IIb or the intermediate IIc proposed by Novais.[4] With the present information we are not in a position to distinguish between these two possibilities; however, it is certain that there is no unreduced carbonyl present.



IIa IIb IIc

***o*-Dipentamethylbenzoylbenzene (III).** The highly sterically hindered structure of III forces it to undergo a somewhat different route from II in its reduction stages. Epr studies conducted on this diketone[5] show the color changes to be yellow (no epr spectra made) → brown (paramagnetic) → orange (diamagnetic). The final reduc-

Table I
Ir Absorptions of Ketones and Reduction Products[a]

Parent compd	Unreduced compd, cm^{-1} Ar	Unreduced compd, cm^{-1} C=O	First observable reduction stage, cm^{-1}	Second observable reduction stage, cm^{-1}
Benzophenone (standard) (I) (119-61-9)[b]	1605 ± 1, 1560 ± 1 d	1668 ± 1	(Purple) (3 to −26°) 1590 ± 5 (sh) 1562 ± 0.5 (16592-08-8)	
o-Dibenzoylbenzene (II) (1159-86-0)	1602 ± 1, 1586 ± 1 d	1668 ± 1	(Orange) (30 to −30°) 1805 ± 2 (s) 1735 ± 2 1668 ± 2 (w)[c] (50987-18-3)	(Purple) (33°) 1595 ± 5 (sh) 1552 ± 3 (s) 1520 ± 2 (w) (50987-20-7)
o-Dipentamethylbenzoylbenzene (III) (27928-29-6)	1600 ± 1	1653 ± 1	(Greenish-yellow) (30 to −30°) 1682 ± 4 1552 ± 8 (br) (50987-19-4)	(Brown) (30 to −30°) 1564 ± 2 (sh) 1515 ± 2 (s) 1462 ± 1 (?) (50987-21-8)
Benzil (134-81-6)	1600 ± 1, 1584 ± 1 d	1686 ± 1 1674 ± 2	(Purple) (17 to −25°) 1683 ± 2 (s) 1588 ± 2 (sh) (16827-94-4)	(Orange) (20 to −25°) 1618 ± 5 (sh) 1563 ± 8 (sh) (43049-35-0)

[a] Abbreviations used: sh, shoulder; br, broad; s, strong; w, weak; d, doublet generally found with ArC=O. [b] Registry numbers are in parentheses. [c] Probably residual unreduced II.

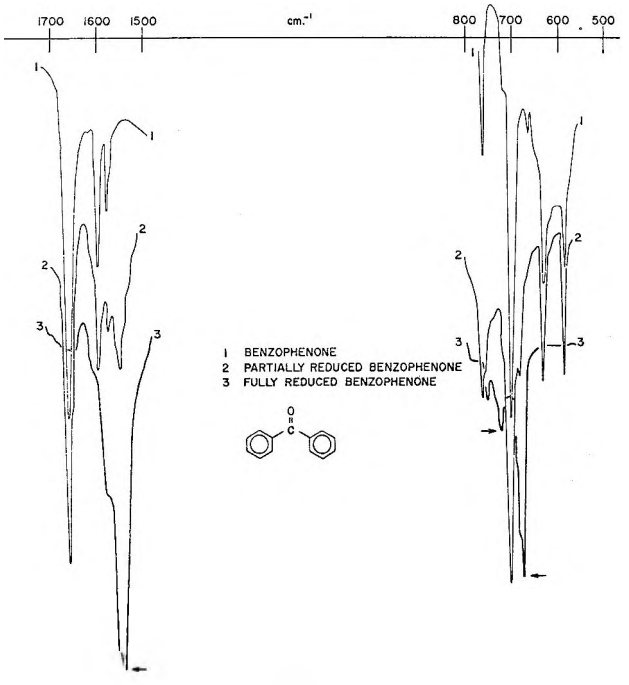
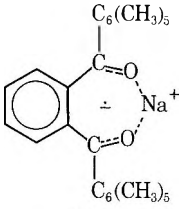


Figure 1.

tion stage was not obtainable in our cells for reasons explained above. The yellow-stage ir absorptions show the presence of an unreduced carbonyl and probably also a ketyl, similar in structure to IIa, but with considerably less electron withdrawal.

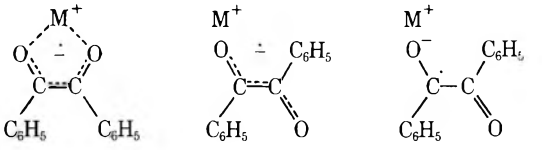
The second stage is most probably the metal chelate IIIa. The epr spectrum shows that only one Na metal cation is bonded to the chelate,[3c] and its ir absorptions



IIIa

are all within the usual ketyl range. The diketone III has been shown not to undergo molecular rearrangement during reduction, as does II.[3c]

Benzil (IV). Benzil has been shown by Bauld to form easily its anion (purple) and dianion (orange) with potassium in THF.[6] Both species were found to possess about 75:25 cis:trans structures (IVa and IVb; monoanion only shown).



IVa IVb IVc

Although we are accustomed in these cases to writing the carbonyl function as >C=O, the ir observations for the monoanion indicate that it may be more correct to show *one* of the carbonyls as essentially remaining in the keto form. This is surprising, in that it is to be expected that, with the sodium cation, even more cis chelate would be found than with potassium, and, in the chelate, both C–O functions should at least be nearly equivalent and considerably lower in frequency than a "pure" keto form.[7]

The dianion, however, seems quite regular, with the C=C stretching frequency being found at 1616 cm^{-1} and the typical ketyl-type frequency appearing at 1563 cm^{-1}.

Temperature Dependence. Since several authors[8] have noted some temperature variations in the ion pairs of ketyls, we found it of interest to investigate the possibility of a shift in the ketyl frequency with temperature owing to the proximity of the metal cation. Consequently, a cold chamber (see Experimental Section) was devised to provide a 60° lowering of temperature. The temperature ranges used are included in Table I. However, no shifts in any frequencies were to be found over a considerable range of temperature. Some slight variations were observed in intensity, but these must be deemed relatively unimportant.

The conclusion to be drawn from these observations must be that either the metal–oxygen bonds are so tight that in these compounds the temperature variations were not effective enough to shift the C–O absorption, or that

Table II
Ir Absorptions of Butanol Salts[a]

	K salt (neat), cm^{-1}	K salt (in DME), cm^{-1}
2-Butanol (50986-98-6)[b]	385 ± 5	450 ± 5 (w)
	410 ± 5	515 ± 5 (w, br)
	Other very weak peaks	
	2500–900, nearly 100% abs, no structure	2500–700, nearly 100% abs, no structure
	350 ± 10 (br)	<400 cutoff
	430 ± 5 (s)	435 ± 5 (w)
	485 ± 5 (br)	480 ± 5 (s)
		510 ± 5 (br)
		540 ± 5
2-Methyl-2-propanol (865-47-4)		570 ± 5
	2500–600, <100% abs, no sharp structures	2500–1500, <100% abs, no structure
	v br abs 1900–1600 and 1500–1000	
	3090 ± 5 (br, s)	3090 ± 5 (br, s)

[a] Some broad C–H stretching bands at *ca.* 2950, 2890, and 2800 cm^{-1} were present in all spectra. [b] Registry numbers are in parentheses.

they were so "loose" that our method (ir) is insufficiently sensitive to detect such a shift.

Some problems with water absorption (1635 cm^{-1}) on the cells were experienced, but these were overcome by exercising great care with humidity control.

Low-Frequency Absorptions. Several broad absorptions appeared in the lower frequency regions of the first reduction stages of the anions, but they were not analyzed: II, 1020–1060, 850–720 cm^{-1}; III, 1150, 1010 cm^{-1}; and IV, 695–760 cm^{-1}.

Absorptions of Metal Salts of Alcohols. In order to verify that no extraneous absorptions were to be found in the observing range of 1850–1500 cm^{-1}, 2-butanol and 2-methyl-2-propanol were reduced in exactly the same manner as the ketyls. The reductions by potassium were carried out both in DME and neat until no further OH absorptions (3300 cm^{-1}) were found. The results found are shown in Table II. No interfering absorptions at all were to be found in the 1850–1500-cm^{-1} regions, although several interesting but unassigned structures were to be found in the 600–400-cm^{-1} region. This region is being investigated further for possible oxygen–metal vibrations.

In this latter region, it was necessary to open the slits completely or use a 2X program, owing to the slight solubility of the salts in DME. However, the salts formed a gel which was present at all times in the sample beam.

The hydrogen pressure in the cell-tube system was calculated at slightly greater than 1 atm and presented no problem.

In conclusion, it has been shown that not only is it feasible to observe by ir the charged reduction species of diketones, but that considerable structural information may be derived from such studies. In all three diketones studied we have noted that the first reduction stage appears to have an unchelated, unreduced ketone function, while further reduction results in typical ketyl-like absorptions in the 1520–1590-cm^{-1} region.

Acknowledgments. The author is indebted to the Fundaçao Gulbenkian (Portugal) and the Consejo Nacional de Investigaciones Científicas y Técnicas (Venezuela) for financial assistance in this project. Also thanks are due to Dr. B. J. Herold for comments on the manuscript and to Maria C. Santos Viais and Elizabeth C. N. Fernandez Geraldes for assistance in taking several spectra.

Supplementary Material Available. Infrared absorption spectra tracings of compounds II, III, and IV, their reduction products, and the two alcoholate salts will appear following these pages in the microfilm edition of this volume of the journal. Also available in microfilm are detailed drawings of the cold box used for low-temperatures studies and of the sample reduction tube. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-1295.

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Direct Synthesis of Fluorocarbon Peroxides. I. Addition of Bis(trifluoromethyl) Trioxide to Selected Carbon–Carbon Multiple Bonds[1,2]

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The addition of bis(trifluoromethyl) trioxide, CF_3OOOCF_3, to a variety of carbon–carbon multiple bonds is reported. With ethylene, tetrafluoroethylene, chlorotrifluoroethylene, hexafluoropropylene, perfluorobutene-2, and perfluorocyclopentene the usual products are $CF_3OOCR_1R_2CR_3R_4OCF_3$ and $CF_3OCR_1R_2CR_3R_4OOCF_3$. These products form in 50–80% yield with alkenes which are not prone to radical polymerization. In the case of tetrafluoroethylene and chlorotrifluoroethylene, additional products containing 2 mol of alkene are observed as well as several trifluoromethyl ethers. The proposed reaction mechanism of initial addition of $CF_3O\cdot$ to the alkene is consistent with the observed products.

Fluorocarbon peroxides are an interesting class of potentially useful compounds. However, until quite recently, examples of these compounds were very limited because of the lack of any general synthetic methods. Previously, most compounds of this type were obtained by reactions involving the coupling of two oxy radicals to form a peroxide bond.[3] The utility of such reactions is severely limited by the apparent instability of most perfluoroalkoxy radicals. The synthesis of trifluoromethyl hydroperoxide in 1968[4] and subsequent development of its chemistry[5-9] indicated that a more successful route to fluorocarbon peroxides containing the CF_3OO group lay in the direct addition of this moiety to suitable substrates. Now several other methods of general synthetic value, in which the CF_3OO group is introduced as a unit, have been found. These involve reactions of fluoroperoxytrifluoromethane (CF_3OOF),[10] chloroperoxytrifluoromethane (CF_3OOCl),[11] and bis(trifluoromethyl) trioxide (CF_3OOOCF_3),[12] as shown in the following general equations.

$$CF_3OOF + R_1R_2C{=}CR_3R_4 \longrightarrow CF_3OOCR_1R_2CR_3R_4F$$

$$CF_3OOCl + R_1R_2C{=}CR_3R_4 \longrightarrow CF_3OOCR_1R_2CR_3R_4Cl$$

$$CF_3OOOCF_3 + R_1R_2C{=}CR_3R_4 \longrightarrow CF_3OOCR_1R_2CR_3R_4OCF_3$$

R = H, F, Cl, alkyl, or perfluoroalkyl

$$CF_3OOOCF_3 + X \longrightarrow CF_3OOXOCF_3$$

X = SO_2, SF_4, CO

In this paper, additions of CF_3OOOCF_3 to a variety of olefins, forming new compounds of the type $CF_3OOCR_1R_2CR_3R_4COCF_3$ and $CF_3OCR_1R_2CR_3R_4OOCF_3$, are described. Evidence is presented for the radical nature of these reactions involving the initial addition of $CF_3O\cdot$ to the alkene.

Results and Discussion

The addition of bis(trifluoromethyl) trioxide to alkenes is a new general route to fluorocarbon peroxides. Although we encountered one failure, that with cyclopentene, the others attempted did give the expected 1:1 addition products as shown in Table I. The molecular weight and ir data indicate the empirical formulas, while the nmr data in Table II identify the isomers present. The group shift for CF_3OO- at ϕ^* ~69 and CF_3O- at ϕ^* ~56 are quite characteristic of these new compounds. Decoupling of nmr spectra was particularly informative in deducing structures. The more stable, highly fluorinated alkenes, which are not as prone to polymerization, gave very good yields. The mechanism for formation of these products is probably a free-radical chain of the type shown.

$$CF_3OOOCF_3 \xrightarrow[\Delta]{\sim 70^\circ} CF_3OO\cdot + CF_3O\cdot \quad (1)$$

$$2CF_3OO\cdot \longrightarrow [CF_3OOOOCF_3] \longrightarrow CF_3OOCF_3 + O_2 \quad (2)$$

$$CF_3O\cdot + R_1R_2C{=}CR_3R_4 \longrightarrow CF_3OR_1R_2C{-}\dot{C}R_3R_4 \quad (3)$$

$$CF_3O\cdot + R_1R_2C{=}CR_3R_4 \longrightarrow R_1R_2\dot{C}{-}CR_3R_4OCF_3 \quad (4)$$

$$CF_3OR_1R_2C{-}\dot{C}R_3R_4 + CF_3OOOCF_3 \longrightarrow CF_3OR_1R_2C{-}CR_3R_4OOCF_3 + CF_3O\cdot \quad (5)$$

$$R_1R_2\dot{C}{-}CR_3R_4OCF_3 + CF_3OOOCF_3 \longrightarrow CF_3OOR_1R_2C{-}CR_3R_4OCF_3 + CF_3O\cdot \quad (6)$$

$$CF_3O\cdot + CF_3O\cdot + M \longrightarrow CF_3OOCF_3 + M^* \quad (7)$$

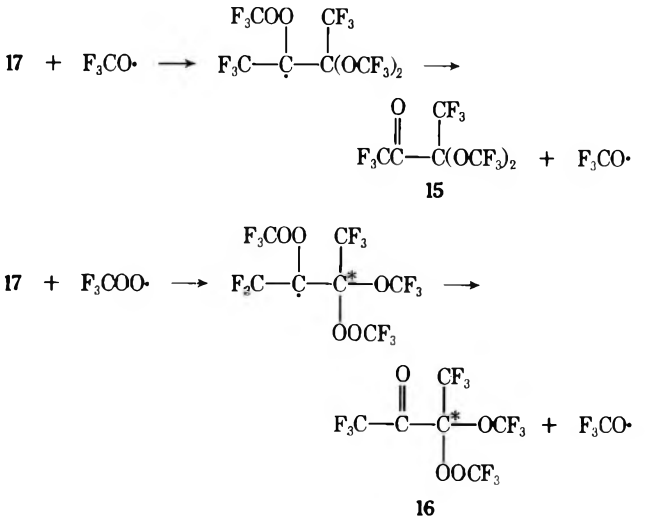
M = reactor walls or a gas

This mechanism is consistent with (1) the evidence for polymerization which suggests the presence of free radicals; (2) the necessity to heat the reactions to about 70°, at which temperature the trioxide decomposes slowly to CF_3OOCF_3 and O_2; (3) the known dissociation of peroxides, trioxides, and tetraoxides into oxy and peroxy radicals,[13] and (4) production of the observed new compounds.

Our choice of which compounds to designate erythro and threo between **11** and **12** and cis and trans between **13** and **14** is somewhat arbitrary. By application of Cram's rule, we have determined that the more abundant isomer between **11** and **12** should be erythro. Hence, we have designated **11** as *erythro*-1,2,3,3,3-pentafluoro-1-trifluoromethyl-2-(trifuoromethyldioxy)propyl trifluoromethyl ether. In the case of **13** and **14**, larger coupling constants are observed between ring substituents that are trans to each other. Hence, we have designated **14** *trans*-1,2,3,3,4,4,5,5-octafluoro-2-(trifluoromethyldioxy)cyclopentyl trifluoromethyl ether.

The reaction of CF_3OOOCF_3 with the perfluoroalkyne, $CF_3C{\equiv}CCF_3$, proceeds with extensive polymerization which may physically entrap the expected product making isolation impossible. The products we do observe, **15** and **16**, are not as well characterized as the products from reaction with alkenes. On the basis of its nmr, **16** could have the structure *trans*-$(CF_3O)(CF_3)C{=}C(CF_3)(OOCF_3)$ (**17**), although our molecular weight and ir data suggest the structure we have given. **17** is the initial hypothetical product resulting from addition of the elements of CF_3OOOCF_3 to $CF_3C{\equiv}CCF_3$ which could then undergo further reaction to give **15** and **16** as shown.

The incorporation of more than 1 mol of alkene in the products from reaction of CF_3OOOCF_3 with C_2F_3Cl and C_2F_4 results in nmr spectra that are difficult to interpret.



15

16

Nonetheless, the reaction and its mechanistic implications deserve further consideration. In a previous paper,[11] we postulated a mechanism for addition of CF_3OOOCF_3 to central atoms in which one initial step was addition of $CF_3OO\cdot$ to the central atom. The observed reaction products of C_2F_3Cl in this work make such a step improbable. In the reaction of C_2F_3Cl we observe 1:1 isomers, V and VI. If a step in their formation is $CF_3OO\cdot + C_2F_3Cl \rightarrow CF_3OOCFClCF_2\cdot$ and $CF_3OOCF_2CFCl\cdot$, then as 2:1 products we would expect to observe both $CF_3OOCFClCF_2(C_2F_3Cl)OCF_3$ (8, a mixture of isomers) and $CF_3OOCF_2CFCl(C_2F_3Cl)OCF_3$. The nmr of the 2:1 product shows only CF_3OO peaks split into doublets. We attribute this to the various isomers of 8. The ethers, 7, are also a mixture of isomers. These observations lead us to postulate the additional steps in the cases of C_2F_3Cl where $R_1 = R_2 = R_3 = F$ and $R_4 = Cl$ (similar considerations apply to the reaction with C_2F_4 with appropriate allowance for the higher symmetry of the alkene).

$$CF_3OCFCl\dot{C}F_2 + C_2F_3Cl \longrightarrow CF_3OCFClCF_2CF_2\dot{C}FCl \quad (8)$$

$$CF_3OCF_2\dot{C}FCl + C_2F_3Cl \longrightarrow CF_3OCF_2CFClCF_2\dot{C}FCl \quad (9)$$

$$CF_3OCFClCF_2CF_2\dot{C}FCl + CF_3OOOCF_3 \longrightarrow \mathbf{8} + CF_3O\cdot \quad (10)$$

$$CF_3OCF_2CFClCF_2\dot{C}FCl + CF_3OOOCF_3 \longrightarrow \mathbf{8} + CF_3O\cdot \quad (11)$$

$$2CF_3OCF_2\dot{C}FCl + M \longrightarrow \mathbf{7} + M^* \quad (12)$$

$$2CF_3OCFCl\dot{C}F_2 + M \longrightarrow \mathbf{7} + M^* \quad (13)$$

$$CF_3OCF_2\dot{C}FCl + CF_3OCFCl\dot{C}F_2 + M \longrightarrow \mathbf{7} + M^* \quad (14)$$

$$CF_3OCFClCF_2CF_2\dot{C}FCl + CF_3O\cdot + M \longrightarrow \mathbf{7} + M^* \quad (15)$$

$$CF_3OCF_2CFClCF_2\dot{C}FCl + CF_3O\cdot + M \longrightarrow \mathbf{7} + M^* \quad (16)$$

This chain process is a specific form of the general equations for addition to C–C double bonds. In it, CF_3OOOCF_3 is a good transfer agent because the rates of steps 5 + 6 and 10 + 11 are apparently greater than subsequent alkene addition steps would be. Consequently, telomers of relatively low molecular weight are observed. Although reaction of excess alkene with CF_3OOOCF_3 should result in formation of $CF_3O(C_2F_3Cl)_nOCF_3$, we did not attempt such a reaction because of experimental difficulties we would encounter attempting to characterize the products. Small amounts of these products may have been present under our conditions and were not identified.

The high yields we obtain with several of the alkenes tried demonstrates that the reaction is quite specific. We believe that this specificity is in steps 5, 6, 10, and 11 where reaction of a free radical with CF_3OOOCF_3 occurs

Table I
Reaction of CF_3OOOCF_3 with C=C and C≡C

Registry no.	$R_1R_2C{=}CR_3R_4$ R_1	R_2	R_3	R_4	α	CF_3OOOCF_3[a]	Conditions Temp, °C	Time, hr	Products No.	Mol wt (calcd)	Yield,[b] %	Bp, °C	Log $P_{(t)} = A - B/T - C/T^2$ A	B	C
74-85-1	H	H	H	H	4.46	4.46	65	3	**1**	211.8 (214.1)	14	73.9[c]	8.706	2022	
116-14-3	F	F	F	F	2.08	2.20	73	3	**2**	288.4 (286.0)	8	33.6	7.848	1542	
									3	345 (370)	2.5				
									4	360 (386)	9				
79-38-9	F	F	F	Cl	4.64	5.57	69	1	**5, 6**	300 (302.5)	4	54.8[c,d]	8.194	1743	
									7	412 (403)	4		21.3 t	19.7°[d]	
									8	423 (419)	3		16.8 t	20.0°[d]	
116-15-4	F	F	F	CF_3	4.24	4.49	67	3	**9, 10**	336.8 (336.0)	52	51.9[d]	61.118	488.60	18,300
360-89-4	F	CF_3	F	CF_3	3.90	4.43	67	4	**11, 12**	380.6 (386.0)	68	72.0[c,d]	6.6756	838.56	15,670
559-40-0	c-C_5F_8				4.85	5.97	67	8	**13, 14**	399.5 (398.0)	80	91.2[c,d]	5.2858	21.833	32,730
	c-C_5H_8				4.46	5.26	68	0.5							
692-50-2	$CF_3C{\equiv}CCF_3$				4.00	8.14	65	1.5	**15, 16**	360 (*cf.* text)	8				

[a] Amounts in millimoles. [b] Based on amount of alkene. [c] Extrapolated from values at lower temperatures. [d] Isomers present; refer to Table II.

Table II
Nmr Data

Compd	Formula[a]	Chemical shift[b] A	B	C	D	E	F	Selected coupling constants[c]
1	$CF_3OOCH_2CH_2OCF_3$ A B C D	68.56 m	4.555[d] m	4.307[d] m	62.51 m			AB = 0.8, BC = 3.42,[d] BC′ = 6.14[d] CD = 0.5, BB′CC′ = 1.66[d]
2	$CF_3OOCF_2CF_2OCF_3$ A B C D	68.69 t	96.37 q, q	87.03 q	55.98 t, t			AB = 4.4, BD = 0.6, CD = 9.0
3	$CF_3OCF_2CF_2CF_2CF_2OCF_3$ A B C C B A	55.80 t	85.84 m	126.12 m				AB = 9.2, BC = 0.4, BC′ = 7.5
4	$CF_3OOCF_2CF_2CF_2CF_2OCF_3$ A B C D E F	68.78 t	90.69 m	123.54 m	125.96 m	85.60 m	55.87 t	AB = 4.3, BC = 2.2, BD = 9.2, BE = 0.4, CE = 10.3, DE = 0.5, EF = 9.1
5	$CF_3OOC^*FClCF_2OCF_3$ A B CD E	68.45 d	83.09 m	84.60 m	84.6 m	56.37 d, t		AB = 5.1, BC = BD = 4.4, BE = 0.6, CE = DE = 9.1
6	$CF_3OOCF_2C^*FClOCF_3$ A BC D E	68.99 t	94.26 m	94.36 m	77.34 m	55.56 d, t		AB = AC = 4.5, BD = 4.0, CD = 5.0, BE = CE = 0.6, DE = 10.1
7	$(CF_3O)_2(CF_2{}^*CFCl)_2$ ABC	55.31 d	56.15 d	56.17 t				A = 10.0, B = 9.8, C = 9.0
8	$CF_3OOC^*FClCF_2(CF_2{}^*CFCl)OCF_3$ AB CDE	67.84 d	67.96 d	55.09 d	55.94 t	55.98 t		A = 4.8, B = 4.9, C = 10.2, D = 9.2, E = 9.0
9	$CF_3OOC^*F(CF_3)CF_2OCF_3$ A B C DE F	69.34 d	139.01 m	76.48 t	81.35[e] m	81.35[e] m	56.50 t	AB = 6.2, BD = BE = 4.8, CD = CE = 9.0, DF = CF = 9.0
10	$CF_3OOCF_2C^*F(CF_3)OCF_3$ A BC D E F	69.44 t	90.74[e] m	90.74[e] m	144.43 m	81.38 m	54.83 d, m	AB = AC = 4.4, BD = CD = 4.1, BE = CE = 8.6, BF = CF = 4.0, EF = 4.0
11	*erythro*-$CF_3OOC^*F(CF_3)C^*F(CF_3)OCF_3$ A B C D E F	68.69 d	154.53 m	74.15 sex, m	140.23 m	79.32 m	53.53 m	AB = 6.2, BF = 5.4, C = 11.5 d, C = 5.2 q, CF = 1.6, DF = 15.8, EF = 5.4
12	*threo*-$CF_3OOC^*F(CF_3)C^*F(CF_3)OCF_3$ A B C D E F	68.66 d	133.37 m	73.69 d, m	137.16 m	77.68 m	54.35 m	AB = 6.2, BF = 1.7, CF = 1.7, DF = 13.6, EF = 7.2
13	*cis*-$CF_3OOC_5F_8OCF_3$ A B	68.59 d	55.72 m					A = 6.6 d, B = 10.5 d, 8.5 d, 5.0 d, 2.2 d, AB ~0.2
14	*trans*-$CF_3OOC_5F_8OCF_3$ A B	68.60 d	55.14 m					A = 6.1 d, B = 12.0 d, 8.2 d, 5.0 d, 3.2 d, AB ~0.4
15	$(CF_3O)_2C(CF_3)C(O)CF_3$ A B C	54.35 q, q	76.53 m	73.61 q, sep				AB = 4.9, AC = 1.1, BC = 3.7
16	$CF_3OO^*C(OCF_3)(CF_3)C(O)CF_3$ A B C D	68.12 m	54.53 m	73.68 m	74.34 m			AB = 1.9, AC = 0.7, AD = 1.2, BC = 1.2, BD = 2.4, CD = 3.8

[a] An asterisk denotes a chiral center. In **7** and **8** the ABC, CDE, and AB refer to the different CF_3O and CF_3OO groups of the various isomers. [b] Values are ϕ^* for ^{19}F and δ for ^1H, both in parts per million, to center of peak or multiplet: d = doublet, t = triplet, q = quartet, sex = sextet, sep = septet, m = multiplet. [c] J_{AB} = 0.0 Hz is abbreviated AB = 0.0 and refers to coupling between fluorines designated A and B; A = 10.0, etc., refers to the fluorine designated A coupled to another unspecified fluorine(s). [d] Values are from computer-assisted solution of the experimental spectrum. [e] A difference between the fluorines of this CF_2 group could not be observed.

to abstract the CF_3OO moiety and generate a new radical, $CF_3O\cdot$. In the reaction of hexafluoropropene, formation of **9** in preference to **10** (71 to 29%) is suggestive. Addition of radicals to an alkene is predicted to occur so as to form the more stable free radical.[14] In this instance, formation of $CF_3OCF_2\dot{C}FCF_3$ should be preferred over formation of $CF_3OCF(CF_3)\dot{C}F_2$. This is consistent with the observed production of **9** and **10**, presumably by further reaction of the respective radicals above.

This role of CF_3OOOCF_3 as a transfer agent is perhaps better considered with greater perspective. The more common transfer agents are the halogens, and CF_3OOOCF_3 can be viewed as a halogenoid. It is a volatile compound but not as symmetric as the more common pseudohalogens such as $(CN)_2$, $(OCN)_2$, $(SCN)_2$, $(OSO_2F)_2$, etc. Salts with the formulas $MOCF_3$ are known and those of $MOOCF_3$ have been postulated.[7,15] The free acid, CF_3OOH, is known[4,5] and derivatives of CF_3OH are well known.[16] A halogenoid's radicals may react with other halogens, forming compounds such as CF_3OOF,[7] CF_3OF,[17] CF_3OOCl,[8] CF_3OCl,[18,19] etc. A halogenoid adds to alkenes and to central atoms in a low oxidation state. In this light, it is instructive to view CF_3OOCF_3 as an interhalogenoid.

All of the new peroxides obtained in this work are stable for prolonged periods at 22°. None have been observed to be explosive (Caution! potential explosive decomposition is possible for any of these compounds) and they are easily handled in both glass and metal equipment. While detailed stability studies have not been made on these new materials, their apparent high thermal stabilities clearly demonstrate the stabilizing effect of fluorine in such compounds Most hydrocarbon analogs of these compounds, if known, would not be expected to have high thermal stabilities in view of the C:O ratios. The addition of CF_3OOOCF_3 to olefins is clearly a new and useful reaction for the formation of fluorocarbon peroxides. In our opinion, extension of this reaction to many other alkenes is possible, particularly fluoroalkenes. Failure of this reaction to give the expected products will probably occur in some cases owing to carbon–carbon bond cleavage as observed with cyclopentene. However, moderation of the reaction conditions using radical initiators at lower temperatures might offer a method of overcoming these failures.

Experimental Section

General. All work was carried out on a standard vacuum line.[20] Quantities of reactants and products were measured either by direct weighing or by the relationship $n = PV/RT$, assuming ideal gas behavior. All reactions were carried out in 100–500-ml Pyrex bulbs fitted with a Kontes K-82600 Teflon-glass valve. Reaction products were usually given a preliminary separation through U traps cooled to an appropriate temperature. Following this, the products were separated *via* glc on a Victoreen Series 4000 gas chromatograph equipped for gas or liquid injection, sub- or superambient operation, thermal conductivity detection, and low-temperature collection. A 10 ft × 0.375 in. column of 304 stainless steel packed with 49% Halocarbon 11-21 polymer oil on acid-washed Chromosorb P was used in most cases. For less volatile products, a 1-ft column of similar construction was used.

Structural determinations were made on a Varian XL-100-15 nmr spectrometer. Interpretation of nmr spectra was aided by a computer program, LAOCOON 3.[21]

In reactions giving high yields, vapor pressures and boiling points of the products were measured by the method of Kellogg and Cady.[17] Similar data for other products were obtained by a static method. In either case, temperatures were measured with a calibrated iron–constantan thermocouple and pressures were measured with a Wallace and Tiernan Model FA 145 differential pressure gauge. This gauge was also used to measure pressures for molecular weight determinations by vapor density.

Infrared spectra were recorded on Perkin-Elmer Model 180 or Model 337 spectrometers. Mass spectra were obtained on an AEI MS9 spectrometer at 70 eV with a source temperature of 200°. The base peak in all instances was at m/e 69 (CF_3^+).

Reagents. Bis(trifluoromethyl) trioxide was prepared by reaction of a $CsOCF_3$–CsF mixture with OF_2 at 42° as previously described.[12,22] It was purified by repeated low-temperature trap-to-trap distillation until free from CF_3OOF as evidenced by ir at 950 cm^{-1} in a 10-cm cell at 100 Torr total pressure. Tetrafluoroethylene was prepared by thermal degradation of Teflon.[23] Chlorotrifluoroethylene, hexafluoropropene, perfluorobutene-2 (20.4% cis *via* nmr), perfluorocyclopentene, and hexafluorobutyne-2 were obtained from PCR, Inc. The C_2F_3Cl was passed through a −78° bath before use to remove its inhibitor; the others contained no such inhibitor and were used as received. Cyclopentene was obtained from Aldrich and used as received. Likewise, C_2H_4 from Matheson Gas Products was used as supplied.

The experimental conditions for preparation of these new ethers and peroxides are given in Table I. Nmr values characterizing the products are contained in Table II. No attempts were made to separate the various pairs of isomers encountered in this work. In all reactions, polymerization of the alkene or alkyne apparently occurred, as evidenced by the formation of a nonvolatile oil or white solid which was not characterized further. Several low molecular weight products were observed in these reactions as well. These included O_2 and CF_3OOCF_3 in all reactions with minor amounts of COF_2 and SiF_4. With C_2F_3Cl considerable CF_2CFClO was observed.

Reaction of C_2H_4. This reaction readily gives 2-[(trifluoromethyl)dioxy]ethyl trifluoromethyl ether (**1**) plus additional products, some of which were polymeric. Heteronuclear INDOR decoupling shows that both CH_2 groups are coupled to both CF_3 groups. Heteronuclear noise decoupling results in a symmetrical AA′BB′ ^1H spectrum whose computed solution is given in Table II: ir 2996 sh, 2968 m, 2944 m, 1469 m, 1414 m, 1378 m, 1339 m, 1280 vs, 1229 vvs, 1171 vs, 1119 m, 1080 m, 1050 m, 1009 m, 929 m, 879 m, 860 m, 820 m, 679 m, 619 m, 588 m, 510 cm^{-1} m.[20]

Reaction of C_2F_4. Extensive polymerization apparently occurs as evidenced by formation of a nonadhering white solid in the reaction. We have identified the following products: 1,1,2,2,-tetrafluoro-2-[(trifluoromethyl)dioxy]ethyl trifluoromethyl ether (**2**), ir 1382 m, 1290 vs, 1251 vvs, 1203 s, 1178 s, 1148 vs, 1089 s, 900 s, 803 m, 683 m, 671 m, 606 m, mass spectrum (selected values) m/e (rel intensity, assignment) 151 (2.0, $C_2F_5O_2$), 135 (11.4, C_2F_5O), 119 (14.6, C_2F_5), 97 (7.3, C_2F_3O); 1,1,2,2,3,3-hexafluoro-1,3-bis(trifluoromethoxy)propane, ir 1330 s, 1286 vs, 1268 sh, 1248 vvs, 1211 vs, 1197 sh, 1188 sh, 1182 vs, 1160 vvs, 1130 vs, 1096 m, 963 m, 928 m, 893 m, 861 m, 807 m, 793 m, 681 m, 657 m, 621 m, 586 cm^{-1} m; 1,1,2,2,3,3,4,4-octafluoro-4-[(trifluoromethyl)dioxy]butyl trifluoromethyl ether (**4**), ir 1365 m, 1289 vs, 1248 vvs, 1215 vs, 1185 sh, 1160 vvs, 1088 s, 958 m, 931 m, 913 m, 899 m, 883 m, 869 s, 841 m, 823 m, 793 s, 778 s, 728 m, 678 m, 653 m, 628 m, 610 m, 575 cm^{-1} m.[20]

Reaction of C_2F_3Cl. Extensive polymerization and formation of several new compounds are observed. We have identified the following: 2-chloro-1,1,2-trifluoro-2-[(trifluoromethyl)dioxy]ethyl trifluoromethyl ether (**5**) and 1-chloro-1,2,2-trifluoro-2-[(trifluoromethyl)dioxy]ethyl trifluoromethyl ether (**6**). The asymmetric carbon atom in these compounds results in the fluorines of the adjacent CF_2 group being nonequivalent. This nonequivalence gives rise to an ABX nmr spectrum: ir (85% **5**, 15% **6**) 1331 s, 1291 vs, 1274 s, 1248 vvs, 1212 vs, 1164 vs, 1152 s, 1073 s, 1000 m, 938 m, 919 m, 893 m, 865 m, 852 m, 818 m, 769 m, 746 m, 661 m, 605 m, 591 cm^{-1} m; mass spectrum m/e (rel intensity, assignment) 267 (1.0, $C_4F_9O_3$), 217 (0.7, $C_3F_6O_2Cl$), 201 (1.8, C_3F_6OCl), 167 (1.7, $C_2F_4O_2Cl$), 151 (2.9, $C_2F_5O_2$), 147 (2.6, C_3F_5O), 135 (16, C_2F_4Cl), 131 (1.9, C_3F_5), 119 (2.7, C_2F_5), 100 (1.5, C_2F_4), 97 (7.9, C_2F_3O), 85 (5.2, CF_3O, CF_2Cl).[20]

Dichlorohexafluoro-1,4-bis(trifluoromethoxy)butane (7). The possibility of three structural isomers, each having two asymmetric carbon atoms, gives rise to six possible structures. Since we observe a very complex nmr having at least three unique CF_3O groups, a more specific description of the product is not possible. The area ratio of the CF_3O groups (A:B:C) is 1:1.3:4.4 *via* nmr: ir of the mixture 1308 s, 1243 vvs, 1148 vs, 1069 m, 990 m, 960 m, 885 m, 864 m, 842 m, 813 m, 778 m, 681 m, 660 m, 609 cm^{-1} m.

Dichlorohexafluoro-4-[(trifluoromethyl)dioxy]butyl Trifluoromethyl Ether (8). As in the case of **7**, two asymmetric carbon atoms are present in the molecules. The nmr spectrum, although still very complex, does permit us to specify the molecules as

being 4-chloro-3,3,4-trifluoro, since the two CF_3OO peaks observed are split into 1:1 doublets. The area ratio of these CF_3OO peaks (A:B) is 1.4:1.0: ir of the mixture 1316 s, 1292 vs, 1245 vvs, 1195 sh, 1148 vs, 1073 sh, 999 m, 967 m, 882 m, 818 m, 779 m, 762 m, 716 m, 663 m.[20]

Reaction of C_3F_6. High yields of the 1:1 addition product are obtained in which both isomers are observed *via* nmr. We have identified 1,1,2,3,3,3-hexafluoro-2-[(trifluoromethyl)dioxy]propyl trifluoromethyl ether (**9**) and trifluoromethyl 1,2,2-trifluoro-1-(trifluoromethyl)-2-[(trifluoromethyl)dioxy]ethyl ether (**10**): ir (71% **9**, 29% **10**) 1338 s, 1328 s, 1291 vs, 1278 vs, 1255 vvs, 1225 s, 1212 vs, 1165 s, 1142 vs, 1110 s, 1035 m, 1018 m, 990 m, 938 m, 898 m, 862 m, 828 m, 772 m, 748 m, 714 m, 684 m, 676 m, 658 m, 624 m, 542 cm^{-1} m; mass spectrum *m/e* (rel intensity, assignment) 201 (1.6, $C_3F_2O_2$), 185 (1.2, C_3F_7O), 170 (2.5, $C_2F_6O_2$), 151 (1.3, $C_2F_5O_2$), 147 (5.1, C_3F_5O), 135 (14.5, C_2F_5O), 119 (3.3, C_2F_5), 97 (7.6, C_2F_3O).[20]

Reaction of C_4F_8. A high yield of the expected 1:1 addition product is obtained. Since there are two asymmetric carbon atoms, an erythro and threo structure can be formed and indeed two molecules containing six peaks each are observed in the nmr. The most obvious difference in their nmr spectra is the appearance of the CF_3 absorptions at 73.69 and 74.15 ppm. The former is basically a doublet; the latter is a sextet formed from an overlapping doublet of quartets, *erythro*-1,2,3,3,3-Pentafluoro-1-(trifluoromethyl)-2-[(trifluoromethyl)dioxy]propyl trifluoromethyl ether (**11**) and *threo*-1,2,3,3,3-pentafluoro-1-(trifluoromethyl)-2-[(trifluoromethyl)dioxy]propyl trifluoromethyl ether (**12**) had ir (67% **1**, 33% **12**) 1338 m, 1308 vs, 1287 vs, 1255 vvs, 1230 vs, 1201 vs, 1187 s, 1143 s, 1112 s, 1063 m, 1029 m, 964 m, 921 m, 890 m, 861 m, 768 m, 739 m, 690 m, 678 m, 652 m, 639 m, 620 m, 531 cm^{-1} m; mass spectrum *m/e* (rel intensity, assignment) 317 (0.2, $C_5F_{11}O_3$), 229 (0.2, $C_4F_7O_3$), 213 (0.2, $C_4F_7O_2$), 201 (3.7, $C_3F_7O_2$), 197 (0.3, C_4F_7O), 185 (5.2, C_3F_7O), 147 (0.9, C_3F_5O), 135 (0.8, C_2F_5O), 119 (2.0, C_2F_5), 116 (0.7, C_2F_4O), 97 (12.0, C_2F_3O), 78 (0.8, C_2F_2O).[20]

Reaction of c-C_5F_8. A very high yield of the expected 1:1 addition product is obtained. Nmr shows nearly equal amounts of the cis and trans products. Both show coupling between the CF_3O and CF_3OO groups. *cis*-1,2,2,3,3,4,4,5-Octafluoro-5-[(trifluoromethyl)dioxy]cyclopentyl trifluoromethyl ether (**13**) and *trans*-1,2,2,3,3,4,4,5-octafluoro-5-[(trifluoromethyl)dioxy]cyclopentyl trifluoromethyl ether (**14**) has ir (52% **13**, 48% **14**) 1322 s, 1291 vs, 1251 vs, 1241 sh, 1222 s, 1199 s, 1157 s, 1009 s, 979 s, 924 m, 877 m, 861 sh, 850 m, 749 m, 666 m, 620 m, 609 m, 585 m, 544 m, 522 cm^{-1} sh; mass spectrum *m/e* (rel intensity, assignment) 294 (0.2, $C_6F_{10}O_2$), 266 (2.2, $C_5F_{10}O$), 197 (2.3, C_4F_7O), 169 (4.3, C_3F_7), 166 (1.6, C_3F_6O), 159 (1.2, C_4F_5O), 150 (1.8, C_3F_6), 135 (1.4, C_2F_5O), 131 (8.1, C_3F_5), 119 (8.2, C_2F_5), 109 (1.9, C_3F_3O), 100 (5.2, C_2F_4), 97 (1.8, C_2F_3O), 93 (1.1, C_3F_3), 78 (1.3, C_2F_2O).[19]

Reaction of c-C_5H_8. Several attempts to observe the reaction of c-C_5H_8 with CF_3OOCF_3 were made, all without successful isolation of the expected product, $CF_3OOC_5H_8OCF_3$. Instead, ring opening apparently occurred with formation of many carbonyl containing compounds. The reaction contained considerable residue, presumably polymeric, which was not characterized.

Reaction of C_4F_6. The reaction proceeds with extensive polymerization. We were unable to isolate the expected product $C_2(CF_3OO)_2(CF_3O)_2(CF_3)_2$. We did observe two products which could not be separated on our gc column, presumably because of the C=O functions contained. 1,1,1,4,4,4-Hexafluoro-2,3-butanedione mono[bis(trifluoromethyl) acetal] (**15**) and 1,1,1,4,4,4-hexafluoro-2,3-butanedione mono[(trifluoromethyl)(trifluoromethoxy) acetal] (**16**) had ir (50% **15**, 50% **16**) 1790 s, 1286 vs, 1251 vvs, 1211 vs, 1202 vs, 1189 vs, 1139 vs, 1107 vs, 1080 s, 1061 s, 994 m, 931 s, 885 m, 789 m, 760 m, 734 m, 708 m, 680 m, 657 m, 610 m, 584 m, 553 m, 541 m, 515 m, 451 cm^{-1} m.

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Registry No.—**1**, 50921-48-7; **2**, 50921-49-8; **3**, 39479-36-2; **4**, 50921-57-8; **5**, 42028-66-0; **6**, 42028-65-9; **7**, 50921-20-5; 8 isomer A, 50921-50-1; 8 isomer B, 50921-52-2; **9**, 50921-52-3; **10**, 50921-53-4; **11**, 50921-74-9; **12**, 50921-75-0; **13**, 50921-76-1; **14**, 50921-77-2; **15**, 50921-54-5; **16**, 50921-55-6; bis(trifluoromethyl trioxide, 1718-18-9.

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Free Radical Chlorination of Alkanes by Thionyl Chloride

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The free radical chlorination reactions of thionyl chloride ($SOCl_2$) have been investigated. The reaction of thionyl chloride with alkanes proceeds when initiated with either light or benzoyl peroxide. The peroxide-initiated reactions had a chain length of about 2. Phenylazotriphenylmethane (PAT), 2,2′-azobis(2-methylpropionitrile) (AIBN), *tert*-butyl perpivilate, and di-*tert*-butyl peroxide all failed to form halogenated products. Under either photochemical or thermal conditions, the alkyl products were the chloride and the sulfonyl chloride. The selectivity for the photochemical reaction was approximately 3:1 for attack at tertiary to primary hydrogens. Relative reactivities of alkanes and substituted toluenes suggest that the hydrogen-abstracting species in both types of reaction are chlorine atoms.

The usefulness of thionyl chloride as an ionic chlorinating agent is well known.[1] However, the use of this material as a free radical chlorinating agent for alkanes has not been studied previously. As a result, it is the subject of this study.

The reaction of cyclohexane and thionyl chloride in the presence of benzoyl peroxide formed chlorocyclohexane as the major product. This reaction could be carried out without benzoyl peroxide by irradiation with tungsten lamps. In both reactions, in addition to the chlorocyclohexane, another product arising from hydrogen atom abstraction on the alkane was formed, cyclohexanesulfonyl chloride. In the thermal reaction, a chain length for the formation of the alkyl products was 1.7 ± 0.1. In the photochemical reaction, an approximate value for the quantum yield of 0.036 ± 0.009 was found for the region of 310–340 nm. In this region, the photolysis is on an end absorption of thionyl chloride.

The chlorination of 2,3-dimethylbutane by thionyl chloride in the presence of benzoyl peroxide formed a large number of products and these are reported in Table I. The major products arising from alkyl hydrogen abstraction are 2,3-dimethyl-2-chlorobutane and 2,3-dimethyl-1-butanesulfonyl chloride. The minor alkyl products are the primary chloride and the tertiary sulfonyl chloride. The tertiary sulfonyl chloride could also be a source of the tertiary chloride. Analysis of the reaction mixture showed that the concentration of 2,3-dimethyl-2-butanesulfonyl chloride decreased from a value of 0.069 *M* to 0.035 *M* at the same time that the amount of the tertiary chloride increased by 0.025 *M*. After a few days, the tertiary sulfonyl chloride could not be detected in the reaction mixture, while the amount of the primary sulfonyl chloride remained constant. The tertiary to primary selectivity of the hydrogen-abstracting species in these thermally initiated reactions was about 19:1. The three major volatile products arising from the peroxide were identified as benzene, chlorobenzene, and benzenesulfonyl chloride.

Other thermal free radical initiators were tried to see if they would also initiate these reactions. Phenylazotriphenylmethane, AIBN, di-*tert*-butyl peroxide, and *tert*-butyl perpivilate all failed to cause the formation of the alkyl chlorides or alkanesulfonyl chlorides. This selective behavior of free radical initiators has been noted elsewhere. Tanner[2] has reported that only benzoyl peroxide will cause the reaction to proceed for the free radical chlorination of alkanes by benzoyl peroxide–hydrogen chloride mixtures. Here it was postulated that the benzoyl hypochlorite, formed by addition of hydrogen chloride across the peroxide linkage, was the reactive intermediate.

A possible explanation of only benzoyl peroxide initiating the thionyl chloride reaction is that thionyl chloride is first reacting with the peroxide to form benzoyl hypochlorite and benzoyloxysulfinyl chloride. These two intermediates have been suggested previously by Pausacker for the thermal decomposition of benzoyl peroxide in the presence of thionyl chloride.[3] These two intermediates then thermally decompose to free radicals involved in the actual hydrogen-abstraction steps. This would also explain the very low value for the chain length; benzoyl peroxide is really a reactant and not just an initiator.

The decomposition of acyl hypohalites has been studied recently[4,5] and they are found to form alkyl halides when alkanes are present and/or in the absence of hydrogen-containing substrates, halobenzenes. These reactions are illustrated in Scheme I.

Scheme I

$$PhCO_2Cl \longrightarrow PhCO_2\cdot + Cl\cdot$$
$$PhCO_2\cdot \longrightarrow Ph\cdot + CO_2$$
$$Ph\cdot + PhCO_2Cl \longrightarrow PhCl + PhCO_2\cdot$$
$$Ph\cdot + RH \longrightarrow R\cdot + PhH$$

The benzoyloxysulfinyl chloride could be envisioned as a possible source for the formation of the sulfonyl chlorides, by a sequence similar to that above, and was considered by Pausacker to be the major source of benzenesulfonyl chloride.[3] If this were the case, one important reaction would be that shown in eq 1. The acyl radical

$$PhCO_2S(O)Cl + X\cdot \longrightarrow XSO_2Cl + PhCO\cdot \qquad (1)$$

would be expected to eliminate carbon monoxide and again be a source of phenyl radicals. This reaction, however, does not seem to be important, since no carbon monoxide was detected in the gaseous products by either ir or glpc.

Another possible source for the sulfonyl chlorides from the benzoyloxysulfinyl chloride could be by the sequence of Scheme II, where X is either an alkyl or aryl radical. The oxidation step could be accomplished by either the acyl hypochlorite or benzoyl peroxide. In the first case, the acid chloride would be formed, while, in the second, benzoic anhydride would result. The oxidation process would seem likely, since sulfinyl chlorides are known to be oxidized to the sulfonyl chlorides by hypohalite ions.[6]

Scheme II

$$X\cdot + PhCO_2S(O)Cl \longrightarrow XSOCl + PhCO_2\cdot$$
$$XSOCl + \text{oxidizing agent} \longrightarrow XSO_2Cl$$

A third pathway for the formation of the products would be similar to that reported for the Reed reaction.[7] Scheme III, where X is either an alkyl or aryl radical. These reactions could arise by a series of steps involving hydrogen abstraction by chlorine atoms initially formed from the acyl hypochlorite. In this case, hydrogen chloride

Table I
Reaction Mixture Composition for Representative Reactions of Thionyl Chloride with 2,3-Dimethylbutane[a]

Compd	Reactions with benzoyl peroxide 1	2	3	4[b]	Photochemical reactions 1	2
Benzene	0.034	0.045	0.020	0.004		
2-Chloro-2,3-dimethylbutane	0.185	0.195	0.348	0.00004	0.238	0.239
1-Chloro-2,3-dimethylbutane	0.014	0.023	0.026	0.00001	0.045	0.032
Chlorobenzene	0.050	0.023	0.056	0.002		
2,3-Dimethylbutane-1-sulfonyl chloride	0.025	0.038	0.083	0.110	0.405	0.360
2,3-Dimethylbutane-2-sulfonyl chloride	0.006	0.003	0.006	0.004	0.005	0.017
Benzenesulfonyl chloride	0.042	0.119	0.136	0.164		
Chlorinated benzoic acids[c]	0.073	0.087	0.036	0.002		
Benzoyl chloride–benzoic anhydride	0.410	0.508	0.715	0.293		
Thionyl chloride[d]	1.680	0.831	1.342	1.25	1.190	0.738
Benzoyl peroxide[d]	0.341	0.369	0.502	0.268		
Material balance phenyl	88	105	96	87		

[a] All concentrations are in moles per liter in 2,3-dimethylbutane. Experimental errors on all molarities are less than 6%. [b] SO_2 added to 1.77 *M*. [c] The ratio of the ortho:meta:para isomers was 1:1:1. [d] Starting concentrations.

Table II
Relative Reactivities of Several Substrates of Different Structures and Substituents toward Thionyl Chloride under Thermal and Photochemical Conditions, Compared with the Values Obtained for Chlorine

Substrate	Registry no.	Thionyl chloride[a]	Thionyl chloride[b]	Chlorine
		Cyclohexane as Standard		
Cyclohexane	110-82-7	1.00	1.00	1.00
Cyclopentane	287-92-3	2.32 ± 0.06	1.35 ± 0.13	0.82 ± 0.06
2,3-Dimethylbutane	79-29-8	6.88 ± 0.10	1.05 ± 0.11	0.75 ± 0.11
2,2,3,3-Tetramethylbutane	594-82-1	0.38 ± 0.05	0.42 ± 0.09	0.33 ± 0.10
Toluene	108-88-3	0.31 ± 0.05	0.41 ± 0.06	0.27 ± 0.08
1-Chlorobutane	109-69-3	0.36 ± 0.11	0.29 ± 0.09	0.25 ± 0.10
Perdeuteriocyclohexane	1735-17-7		0.85 ± 0.08	0.78 ± 0.08
		Toluene as Standard		
Toluene		1.00	1.00	1.00
p-Xylene[c]	106-42-3	1.60 ± 0.09	1.65 ± 0.19	1.60 ± 0.23
m-Xylene[c]	108-38-3	1.11 ± 0.9	1.13 ± 0.10	1.22 ± 0.22
p-Chlorotoluene	106-43-4	0.65 ± 0.09	0.46 ± 0.11	
m-Chlorotoluene	108-41-8		0.68 ± 0.15	0.59 ± 0.09

[a] Benzoyl peroxide present. [b] Photochemically. [c] Statistically corrected.

Scheme III

$$X\cdot + SO_2 \longrightarrow XSO_2\cdot$$
$$XSO_2\cdot + Cl_2 \longrightarrow XSO_2Cl + Cl\cdot$$

would be a major product and react with benzoyl peroxide to product the acyl hypochlorite and benzoic acid.[2] The benzoic acid formed would be converted into the acid chloride by the excess thionyl chloride present (eq 2). The

$$PhCO_2H + SOCl_2 \longrightarrow PhCOCl + SO_2 + HCl \qquad (2)$$

chlorine molecules would arise by the reaction of a positive halogen compound with hydrogen chloride. This type of process has been well studied in the case of *N*-chlorosuccinimide[8] and reported for *N*-chloro amines.[9,10]

An alternate or possible competing route for the formation of chlorine and sulfur dioxide could be the chain transfer of the radical, X, with thionyl chloride. The resulting previously unreported chlorosulfinyl radical, SOCl·, might be expected to be in equilibrium with sulfur monoxide and chlorine atoms, similar to that reported by Russell for the equilibrium of $SO_2Cl\cdot$ radicals.[11] If this equilibrium is involved, the sulfur monoxide is known to disproportionate into elemental sulfur and sulfur dioxide.[12,13] The sulfuryl chloride which has been detected as a reaction product could arise by the equilibrium involving sulfur dioxide and molecular chlorine.[11]

Of the three routes outlined for the formation of the products, we believe that the third pathway is operative. The amount of benzene, a product derived from hydrogen abstraction of phenyl radicals, is very low, approximately one-sixth the amount of alkyl products arising from hydrogen atom abstraction. The other hydrogen abstraction most likely is by chlorine atoms which favor the formation of hydrogen chloride, and as a result sulfur dioxide, by eq 2. As the sulfur dioxide concentration increases, the reactions in Scheme III should become more important. This scheme was confirmed by the fact that, in a set of reactions with sulfur dioxide added, the amount of the alkanesulfonyl chloride was greatly enhanced at the expense of the alkyl chloride (Table I, entry 4).[14] In these reactions, the radical formed by hydrogen abstraction would have a greater probability of attack on the sulfur dioxide than to chain transfer with the hypochlorite.

The values of the relative rates of reaction for a number of toluenes and alkanes were determined and are presented in Table II. The use of relative reactivities as a probe for the study of intermolecular selectivities of a specific radical has the advantage that the ratio of rate constants is obtained from the determination of the relative concentrations of the substrates and that this value is not affected by the subsequent fate of the intermediates or products involved. The values obtained for relative rates of reactions are similar to those for chlorine under photochemical conditions. The exceptions are 2,3-dimethylbu-

tane and cyclopentane. A possible explanation comes from the literature. It has been found previously in systems of benzoyl peroxide–hydrogen chloride that large amounts of reversible hydrogen abstraction from hydrogen chloride by alkyl radicals are present.[2] Reversible hydrogen abstraction has been shown to cause increased reactivities of certain compounds in relative rate determinations.[2,15] With iodobenzene dichloride, an increase in the reactivity of 2,3-dimethylbutane relative to cyclohexane has been noted.[15] Substrates containing halogens and/or aromatic rings, are not affected.[16]

The photochemical reaction was also studied to gain an insight as to the hydrogen-abstracting radical under these conditions. In the reaction of 2,3-dimethylbutane with thionyl chloride, only four products were detected, and these are reported in Table I. The tertiary to primary selectivity for the abstracting radical in the photochemical reaction was found to be 3.2:1.0 for the reaction run at 42°. This value for the selectivity is similar to that reported for molecular chlorine.[11,17]

To gain a better probe as to the nature of the abstracting species, the relative reactivities for the chlorination using thionyl chloride were obtained and reported in Table II.

The values in the table for thionyl chloride are similar to those reported for chlorine except for cyclopentane. A value for the primary:secondary:tertiary selectivity calculated from the relative reactivities is 1:3.6:16 for thionyl chloride compared to a selectivity of 1:4.6:14 for molecular chlorine. These values are similar to other values for the selectivity calculated from relative rates of reaction data for chlorine atoms.[17] The relative reactivities for the cyclohexane and perdeuteriocyclohexane allowed for the calculation of a deuterium isotope effect. This value is 1.25, which is within experimental error of the value obtained for molecular chlorine in this study and reported in the literature.[15,18]

The relative rates of reaction of thionyl chloride with the substituted toluenes allowed for a Hammett plot to be made. A ρ value of -0.70 was obtained for the reactions involving thionyl chloride, while a value of -0.76 was obtained for molecular chlorine. Both of the values compare very well with previous literature values for chlorine atoms as the hydrogen-abstracting species.[19,20]

The following mechanism (Scheme IV) is suggested from these hydrogen atom abstractions by the reactive intermediate from thionyl chloride. In the reaction of thionyl chloride with acids to form the acid chloride, α-chlorination has been noted. The chlorination has been suggested as arising from a mechanism involving chlorine molecules formed from the photolysis of thionyl chloride,[21] similar to that reported here in steps 1, 4, and 8.

Scheme IV

$$SOCl_2 \longrightarrow Cl\cdot + SOCl\cdot \quad (1)$$

$$RH + Cl\cdot \longrightarrow R\cdot + HCl \quad (2)$$

$$RH + SOCl\cdot \longrightarrow R\cdot + HCl + [SO] \quad (3)$$

$$2SOCl\cdot \longrightarrow SO_2Cl_2 + S \quad (4)$$

$$SO_2Cl_2 \longrightarrow Cl\cdot + SO_2Cl\cdot \quad (5)$$

$$SO_2Cl\cdot \longrightarrow Cl\cdot + SO_2 \quad (6)$$

$$RH + SO_2Cl\cdot \longrightarrow R\cdot + HCl + SO_2 \quad (7)$$

$$SO_2Cl_2 \longrightarrow SO_2 + Cl_2 \quad (8)$$

The calculated ρ value for thionyl chloride and the relative reactivities indicate that the major hydrogen-abstracting species is chlorine atoms. These could arise in the homolysis of the S–Cl bond of thionyl chloride. The abnormally high value for the relative reactivity of cyclopentane compared to that of the other compounds studied could be explained by abstraction by the $SO_2Cl\cdot$ radical (eq 3–5). This is supported by the relative reactivity of cyclopentane to cyclohexane found in the literature[22] for sulfuryl chloride as the chlorinating agent.

The well-known equilibrium of chlorine atoms with sulfur dioxide would favor hydrogen atom abstraction by chlorine atoms when deactivated substrates are employed. Cyclopentane has been shown by Bunce[23] to react more rapidly than statistics would suggest relative to cyclohexane with hydrogen-abstracting radicals that are more selective than chlorine. Such is the case with this substrate in the thionyl chloride reactions. With more reactive substrates, a larger amount of hydrogen abstraction would be by the $SO_2Cl\cdot$ radical, indicating that eq 7 is important only with this type of substrate. The slightly higher reactivity of 2,3-dimethylbutane than that of cyclohexane for thionyl chloride can also be explained along these lines.

In conclusion, it appears that the thermal reaction of thionyl chloride, benzoyl peroxide, and hydrocarbons proceeds by a nonchain process with chlorine atoms as the hydrogen-abstracting species. In the photochemical reactions, thionyl chloride again forms chlorine atoms, which are responsible for hydrogen atom abstraction.

Experimental Section

All compounds were commercially available unless otherwise indicated. Thionyl chloride was purified by either the method of Trager[24] or that of Friedman and Witter.[25] The primary sulfonyl chloride, 2,3-dimethylbutane-1-sulfonyl chloride, was prepared from the hydrocarbon and sulfonyl chloride with an excess of added sulfur dioxide, amide mp 47–48° (lit.[26] mp 48–49°). Cyclohexanesulfonyl chloride was prepared similarily, amide mp 90–91° (lit.[27] mp 93–94°).

General Procedure. Reactions were carried out in sealed Pyrex ampoules which had been doubly degassed by the freeze–thaw method. The ampoules were allowed to stand in a constant-temperature bath (98 ± 3°) for an appropriate period and were opened after being cooled to 77°K. A weighed amount of an appropriate standard was added to the opened tubes.

Photoinitiated reactions were also carried out in Pyrex ampoules as described above. These ampoules were placed in a water bath at 41 ± 0.5°; and photolyzed with two 150-W tungsten lamps. At appropriate times, the tubes were removed and treated as above.

All values obtained are the results of at least duplicate, and in many instances triplicate, experimental runs and subsequent analysis. Analysis was mainly be means of glpc on a Hewlett-Packard F & M Model 700 gc using either column A (6 ft × 0.25 in. 20% silicon gum rubber SE-30 on 60/80 Chromosorb W), column B (6 ft × 0.25 in. 20% DEGS on 60/80 acid-washed Chromosorb G), column C (6 ft × 0.25 in. 10% silicon gum rubber SE-52 on 60/80 Chromosorb G), or column D (6 ft × 0.25 in. 10% di-*n*-nonyl phthalate on 60/80 Chromosorb G). Products were identified by comparison of their glpc retention times with those of authentic samples. Samples were collected by preparative glpc and identified by comparison of their nmr, ir, and/or mass spectra with those of authentic samples. except for 2,3-dimethyl-2-butanesulfonyl chloride, which could not be isolated.

Yields reported are based either on the amount of benzoyl peroxide employed in the thermal reactions, or upon reacted thionyl chloride in the case of the photochemical reactions, unless otherwise stated.

Reaction of Thionyl Chloride with Cyclohexane. I. Solutions of equimolar amounts of thionyl chloride and benzoyl peroxide (0.33 *M*) in cyclohexane were heated at 98 ± 3° for 72 hr. After this time, 2,3-dibromobutane was added as an additional standard and the mixture was analyzed on column A or B isothermally at 80°, until the standard had come off the column. At this time, the temperature was turned to 160°. The only alkyl products obtained were chlorocyclohexane (60.5 ± 0.4%, chain length 1.00 ± 0.1) and cyclohexanesulfonyl chloride (17.9 ± 0.3%, chain length 0.65 ± 0.08). Three other volatile products were detected as arising from benzoyl peroxide, chlorobenzene (7.7 ± 0.1%), benzene (3.5 ± 0.1%), and benzenesulfonyl chloride (16.5 ± 0.3%).

II. In the photochemical reactions, a degassed solution of thionyl chloride (1.14 *M*) in cyclohexane was irradiated for 17.5 hr. Analysis was by glpc on either column A or column B isothermally at 80°, until the standard had come off the column, and then the temperature was increased to 160°. The only two products detected were cyclohexane (47.2 ± 1.0%) and cyclohexanesulfonyl chloride (40.0 ± 0.8%). These yields were based upon thionyl chloride reacted.

III. In separate triplicate reactions, degassed solutions of equimolar amounts of each of the following thermal free radical initiators and thionyl chloride in a 15 molar excess of cyclohexane were heated at 90° for 36 hr. The tubes were opened and the reaction mixtures were analyzed on column A and in II above. No detectable amounts of cyclohexanesulfonyl chloride or the chlorocyclohexane were found. The initiators used were tritylazobenzene, di-*tert*-butyl peroxide, 2,2′-azobis(2-methylpropionitrile), and *tert*-butyl perpivalate.

IV. Quantum Yield. Sealed, degassed ampoules of thionyl chloride (1.58 *M*) in cyclohexane were irradiated by two 150-W tungsten lamps in a bath maintained at 41.5 ± 1.0°. At the same time, a set of sealed degassed ampoules containing 2 ml of a benzophenone (0.35 *M*) in 2-propanol solution were also irradiated in the same bath with the same light source. The benzophenone–2-propanol tubes and the thionyl chloride tubes were removed at various times and cooled to 77°K. In the case of the chlorination tubes, analysis for alkyl products was made by glpc on column A as before. In order to analyze the actinometer reaction tubes, a modified method of Pitts[28] was employed. The quantum yield obtained was 0.0036 ± 0.009.

Reaction of Thionyl Chloride with 2,3-Dimethylbutane. I. Degassed solutions of approximately equimolar amounts of thionyl chloride and benzoyl peroxide in excess 2,3-dimethylbutane were heated at approximately 100° for 72 hr. Analysis by glpc on column A with 2,2-dibromobutane as the added standard indicated the presence of seven products. Four other compounds were found in the reaction mixture that could not be detected by glpc. These were benzoic acid and the 3-monochlorinated benzoic acids. These were identified and isolated by evaporation of the reaction mixture nearly to dryness. This was taken up in ether and washed successively with water, 10% sodium hydroxide, and 10% hydrochloric acid. The aqueous layers from the last two extractions were neutralized and extracted with ether. The ether was removed after drying over sodium sulfate. The water layer was evaporated to dryness. The only materials found in the three fractions were benzenesulfonyl chloride and the benzoic acids. The acids were identified by treatment with (1) diazomethane and glpc analysis on column D or (2) thionyl chloride followed by methanol and glpc analysis on column C.

To determine if the benzoic acids arose from either the acid chloride and/or the anhydride, a reaction tube was opened and the mixture was poured into methanol. Methyl benzoate was detected after the solution was heated under reflux for approximately 30 min, and then analyzed upon column C. Infrared spectral analysis indicated that the ratio of the anhydride to the acid chloride was 0.7.

The molar amounts of these products are listed for three representative reactions in Table I.

II. Degassed solution of thionyl chloride (about 1 *M*) in 2,3-dimethylbutane was irradiated for 1 week at 40°. Analysis by glpc on column A, using 1,2-dibromobutane as an added standard, indicated the presence of four products. The molar amounts of these compounds are also listed in Table I. These experiments were repeated using trichloroethylene as a chlorine trap after the method of Walling.[29] The results between these two experiments were within experimental error, although the yield was considerable less.

III. Gaseous Products. The reaction of thionyl chloride and benzoyl peroxide in 2,3-dimethylbutane was run in a degassed ampoule equipped with a break seal. After the reaction was complete, the reaction mixture was opened into a vacuum line and allowed to warm to room temperature. A gas-phase infrared spectrum was obtained on the gases, in a 10-cm gas infrared cell. By their characteristic absorptions, the following compounds were identified, although not quantitated: carbon dioxide,[30] sulfur dioxide,[30] and sulfuryl chloride.[31] The gaseous products were also analyzed on a Porapak Q glpc column. No detectable amount of carbon monoxide was present.

Competitive Reactions. Relative reactivities were determined by the methods previously reported from this laboratory[17,22] for the photochemical and thermal reactions. These values are reported in Table II. These experiments were repeated with trichloroethylene as a chlorine-atom trap, and the results were within experimental error of those obtained in the other reactions.

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Registry No.—Thionyl chloride, 7719-09-7.

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Stable Carbocations. CLXVII.[1] Protonation and Cleavage of Acetylsalicylic Acid and Isomeric Hydroxybenzoic Acids in FSO_3H-SbF_5 (Magic Acid) Solution

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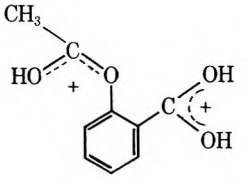
The protonation of monosubstituted benzene derivatives has been studied extensively by nuclear magnetic resonance spectroscopy.[3] The structure of protonated, disubstituted benzene derivatives, however, has received considerably less attention.[4] We wish to report now the pmr study of protonated acetylsalicylic acid and isomeric hydroxybenzoic acids in FSO_3H-SbF_5 (Magic Acid) solution. The relative biological activities of acetylsalicylic acid and salicylic acid, and the mechanism by which the former is hydrolyzed *in vivo*, have been extensively studied.[5] It was hoped that the *in vitro* observation and identification of the intermediates involved in the cleavage reaction would contribute to our better understanding of the mechanism of this biologically important hydrolysis.

Results and Discussion

Treatment of an SO_2ClF solution of acetylsalicylic acid (1) with excess FSO_3H-SbF_5 at −70° gave a solution whose pmr spectrum consisted of singlets at δ 3.44 (3 H), 12.64 (2 H), and 14.08 (1 H) and a multiplet between δ 7.92 and 8.97 (4 H). The two most deshielded singlets were differentiated on the basis of their relative intensities. The chemical-shift data indicate that acetylsalicylic acid in Magic Acid solution exists as the diprotonated species, **2**.



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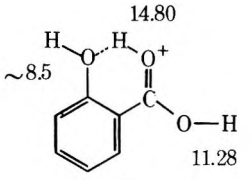

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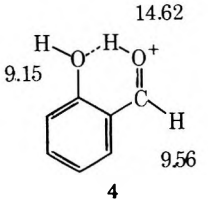
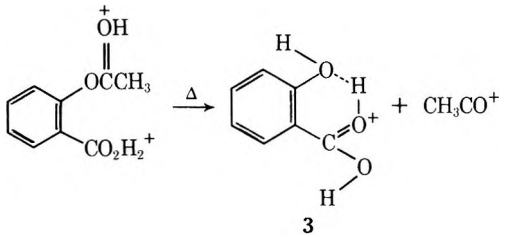


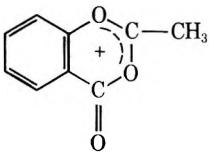
4

Warming the above solution to 0° resulted in a decrease in intensity of the singlet at δ 3.44 and the appearance of a singlet at δ 4.1, which is coincidental with the methyl proton resonance of an added sample of acetyl cation. It, therefore, seems that **2** on heating is cleaved, most likely by an $A_{AL}1$ mechanism,[3b] to the acetyl cation and protonated salicylic acid **3**.



3

No acetylsalicyloyl cation, which was recently shown by Ruchardt[6] to exist as the stable cyclic 2-methyl-4,5-benzo-1,3-diox-4-en-5-on-2-ylium ion (**5**), was observed in the system.



5

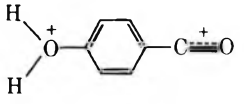
The above cleavage was confirmed in our studies by showing that the pmr spectrum of salicylic acid in excess FSO_3H-SbF_5 is identical with that of the ion resulting from cleavage of acetylsalicylic acid.

The pmr spectrum of salicylic acid in excess FSO_3H-SbF_5 at 0°, with SO_2ClF as the diluent, consists of a multiplet for the aromatic protons between δ 7.5 and 8.8 and a broad singlet at δ 11.7, resulting from rapid proton exchange of the OH protons with the acid solvent. On cooling to −108°, the exchange rate is sufficiently slowed to observe sharp singlets at δ 14.80 (1 H) and 11.28 (1 H) (besides the HSO_3F and H_3O^+ signals) and broad multiplets at δ 8.3–9.0 (3 H) and 7.5–8.2 (2 H). We propose that the spectrum at this temperature is that of monoprotonated salicylic acid **3**. For comparison we also obtained the pmr spectrum of protonated salicylaldehyde (**4**) in excess FSO_3H-SbF_5 at −120°. It shows doublets at δ 14.62 (1 H, J = 15 Hz) and 9.56 (1 H, J = 15 Hz), a singlet at δ 9.15 (1 H), and a multiplet arising from the aromatic protons at δ 7.5–8.9 (4 H). The resonances at δ 14.62 and 9.56 were assigned in analogy with previously observed $=OH^+$ and -CHO resonances in related systems.[7] The proton on the carbonyl oxygen and aldehydic protons, respectively, are coupled to each other, as shown by decoupling experiments. On the basis of coupling constant data from protonated aldehydes[8] the large coupling observed between these protons (J = 15 Hz) indicates that they are trans to each other, as shown in structure **4**. Comparison of the pmr data for protonated salicaldehyde **4** and salicylic acid **3** confirms the assignments in the latter compound of the peaks at δ 14.80 and ~8.5. The remaining signal (δ 11.28) must be the carboxylic proton which is not hydrogen bonded to the phenolic oxygen atom. This resonance is shielded compared with the corresponding resonances in protonated benzoic acid[3g] (δ 12.10) and suggests that little of the positive charge is located on this oxygen atom (as shown in structure **3**). The nmr data, therefore, indicate that salicylic acid and salicylaldehyde are only monoprotonated in Magic Acid solution, and that protonation occurs on the carboxyl and aldehyde groups, respectively. The nonbonded electron pairs of the phenol oxygen atom undergo hydrogen bonding with the protonated acid and aldehyde group, preventing their own protonation, and this results, in the case of salicylic acid, in the nonequivalence of the two acidic OH protons. This contrasts with the situation in diprotonated acetylsalicylic acid and monoprotonated benzoic acid, where the two acidic OH protons are equivalent. Owing to the deactivating effect of the

carboxyl (and protonated carboxyl group) no ring protonation occurs, as is the case with phenol itself.[3f]

We have also obtained the pmr spectra of *m*- and *p*-hydroxybenzoic acids in excess FSO_3H-SbF_5 solution at low temperature. Unlike the ortho isomer (salicylic acid) the meta and para isomers are diprotonated. At −70° the spectrum of protonated *m*-hydroxybenzoic acid consists of singlets at δ 13.36 (2 H, $CO_2H_2^+$) and 12.50 (2 H, OH_2^+) and a complex pattern between δ 8.3 and 9.1 (4 H). The pmr spectrum of the para isomer at −110° consists of broad singlets at δ 13.97 (2 H, $CO_2H_2^+$) and 12.34 (2 H, OH_2^+) and a multiplet between δ 7.8 and 9.1. (Assignments were made based on comparison with data on protonated substituted benzoic acids and phenols.) At comparable acid concentrations, it therefore requires a lower temperature to freeze out the proton-exchange processes of the para isomer. The reason for this is not yet clearly understood. The proton resonances of the phenolic hydroxyls in the *m*- and *p*-hydroxybenzoic acids are considerably deshielded from that of the ortho isomer. This is probably the result of greater positive charge on the phenolic oxygen atom in these isomers, compared with the ortho isomer.

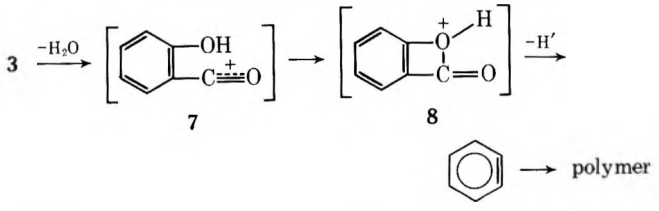
Protonated *m*- and *p*-hydroxybenzoic acids also react differently from the ortho isomer on heating. On warming a solution of *p*-hydroxybenzoic acid in HSO_3F-SbF_5 at 20°, the appearance of a multiplet with the characteristic pattern of an AA′BB′ spin system is observed in the nmr spectrum between δ 8.1 and 9.3. This spectral data and quenching experiments (H_2O), which yield *p*-hydroxybenzoic acid quantitatively, indicate the formation of dication **6**.



6

Similar results are observed for protonated *m*-hydroxybenzoic acid, which cleaves to the meta isomer of ion **6** on warming in FSO_3H-SbF_5 at room temperature. In the nmr spectrum of this dication a multiplet between δ 8.6 and 9.4 is found.

Similar experiments for protonated o-hydroxybenzoic acid gave only polymeric material, most likely *via* intermediates **7** and **8**, leading subsequently to benzyne and its polymeric products. Our studies directed to the generation



of benzyne from salicylic acid derivatives will be reported separately.

Experimental Section

Materials. All compounds were reagent-grade commercial chemicals and were used without further purification.

Nmr Spectra. A Varian A56/60A nmr spectrometer with variable-temperature probe was used for all spectra. Solutions were prepared at −80° using a 1:1 *M* solution of HSO_3F-SbF_5 and SO_2ClF as a diluent according to procedures described previously.[3,4,6] Chemical shifts were referred to external TMS.

Acknowledgment. Support of our work by a grant of the National Institutes of Health is gratefully acknowledged.

Registry No.—**1**, 50-78-2; **2**, 50977-96-3; **3**, 51016-05-8; **4**, 50977-97-4; **6**, 50977-98-5; *m*-**6**, 50977-99-6; Magic Acid, 37204-12-9; salicylic acid, 69-72-7; *m*-hydroxybenzoic acid, 99-06-9; *p*-hydroxybenzoic acid, 99-96-7; protonated *m*-hydroxybenzoic acid, 51016-03-6; protonated *p*-hydroxybenzoic acid, 51016-04-7.

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(1) Part CLXVI: G. A. Olah and G. Liang, *J. Amer. Chem. Soc.*, submitted.
(2) Postdoctoral Research Fellow, 1971–1973.
(3) (a) G. A. Olah and A. M. White, *J. Amer. Chem. Soc.*, **89**, 7072 (1967); (b) G. A. Olah, D. H. O'Brien, and A. M. White, *ibid.*, **89**, 5694 (1967); (c) G. A. Olah and T. E. Kiovsky, *ibid.*, **90**, 6461 (1968); (d) G. A. Olah, A. T. Ku, and J. A. Olah, *J. Org. Chem.*, **35**, 3908, 3925 (1970); (e) N. C. Deno, R. W. Gaugler, and M. J. Wisotsky, *ibid.*, **31**, 1967 (1966); (f) T. Birchall, A. N. Bourns, R. J. Gillespie, and P. J. Smith, *Can. J. Chem.*, **42**, 1433 (1964); (g) T. Birchall and R. J. Gillespie, *ibid.*, **43**, 1045 (1965); (h) M. Brookhart, G. C. Levy, and S. Winstein, *J. Amer. Chem. Soc.*, **89**, 1735 (1967).
(4) (a) G. A. Olah and M. Calin, *J. Amer. Chem. Soc.*, **90**, 4672 (1968); (b) G. A. Olah and Y. K. Mo, *J. Org. Chem.*, **38**, 3221 (1973).
(5) H. O. J. Collier, *Sci. Amer.*, **97** (Nov 1963).
(6) H. Brinkmann and C. Ruchardt, *Tetrahedron Lett.*, 5221 (1972).
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(8) G. A. Olah, D. H. O'Brien, and M. Calin, *J. Amer. Chem. Soc.*, **89**, 3582 (1967).

Photoelectron Spectra of Mesitylene Derivatives. Electronic Interactions Between Arene Ion Groups

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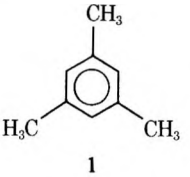
We wish to report the results of our investigation of the He(I) photoelectron spectra of mesitylene (**1**), bimesityl (**2**), 2,7-dimethyl-4,5,9,10-tetrahydropyrene (**3**), *anti*-6,13-dimethyl[2.2]metacyclophane (**4**), and [2.2.2](1,3,5)cyclophane (**5**). These compounds were chosen for study because of their relationship with mesitylene. The symmetry of this parent system dictates a degeneracy among the II ionic states. All of the derivatives (**2**–**5**) are substituted in such a way that this degeneracy should be approximately preserved in the absence of interring interaction. With this approximation the observed splittings, which remove these degeneracies, can be simply interpreted in terms of interring interactions.



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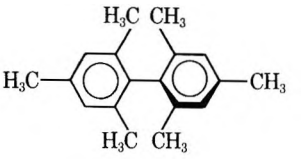

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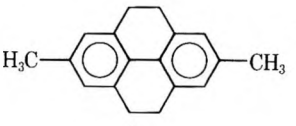

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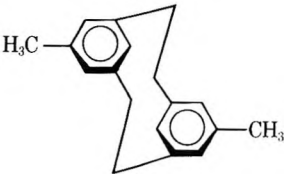

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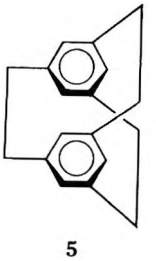

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The spectra are shown as Figures 1 and 2. The first band in the spectrum of mesitylene (IP_{vert} = 8.42 eV)[1]

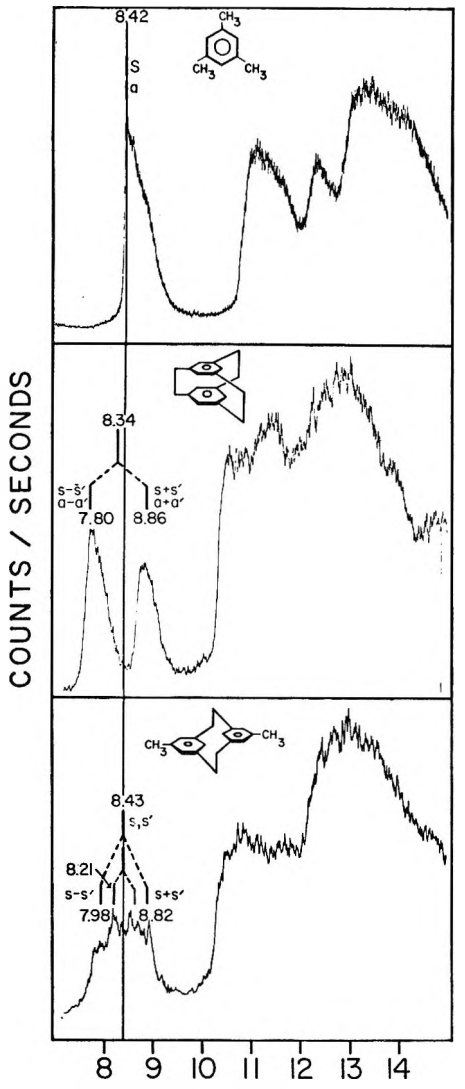


Figure 1. He(I) photoelectron spectra of 1, 5, and 4 (top to bottom).

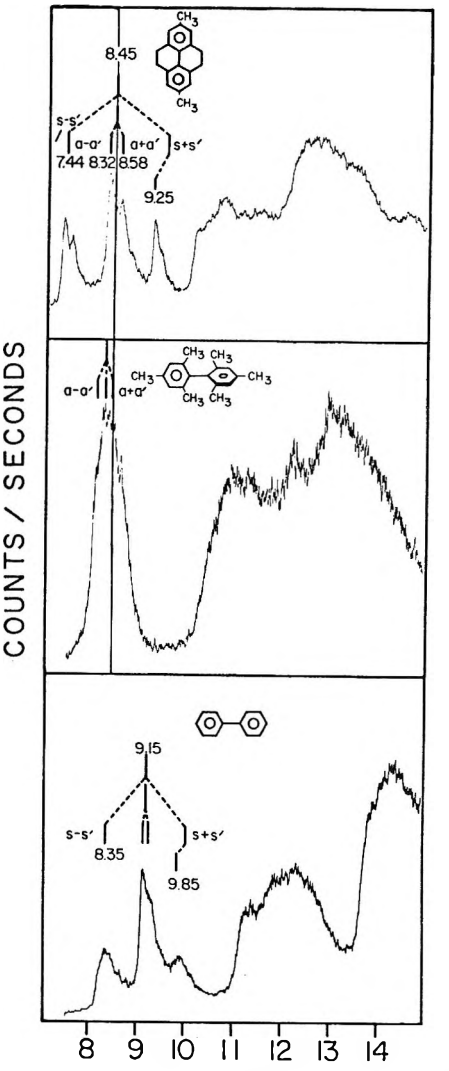
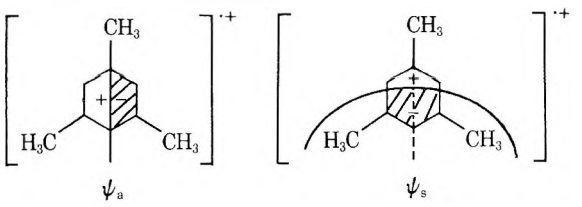


Figure 2. He(I) photoelectron spectra of 3, 2, and biphenyl (top to bottom).

shows the expected shape for degenerate ionic states (Jahn–Teller vibronic coupling as in benzene). The importance of this spectrum is in setting the value about which the corresponding bands in 2–5 should be split. The most striking feature of Figures 1 and 2 is the close adherence of the experimental spectra to this expectation.

Our method of analysis of these spectra is derived from Simpson's[2] structure representation formalism. The observed spectra of 2–5 can be very simply analyzed by considering the basis functions associated with the degenerate lowest π state of 1 to be symmetric (Ψ_s) or antisymmetric (Ψ_a) with respect to a perpendicular plane.



The tris-bridged compound 5[3] and the metacyclophane 4 should show splittings derived from the direct (through space) interaction of the two ionic structures (Ψ_a, Ψ_s) in each of the two rings. Compound 5 shows only two bands for the four possible linear combinations [($\Psi_a + \Psi_{a'}$), ($\Psi_a - \Psi_{a'}$), ($\Psi_s + \Psi_{s'}$), ($\Psi_s - \Psi_{s'}$)] since the interaction constant between Ψ_a, $\Psi_{a'}$ and Ψ_s, $\Psi_{s'}$ (0.52 eV) must be the same. For the metacyclophane 4, the splitting parameter between Ψ_a and $\Psi_{a'}$ will not be the same as that between Ψ_s and $\Psi_{s'}$. Four bands are thus predicted by the model. From simple geometrical consideration, the largest interaction constant is expected from the s, s′, combination and a value of 0.45 eV is derived from the spectrum by inspection. The splitting parameter for the a, a′ interaction is 0.22 eV. These are examples of a lattiresonant[4] interaction.

The tetrahydropyrene derivative 3 was chosen to reveal the strength of the longiresonant (classical conjugation) interaction. The two bridging groups, in this case, bring about near coplanarity of the two rings.[5] Again four bands split about 8.4 eV are predicted from the symmetry and geometrical relationship of the basis structures. The observed spectrum shows a pair of bands with a small coupling (S = 0.14 eV) centered at 8.45 eV which we assign to the a, a′ combinations. The small coupling is expected because of the long distance (*ca.* 3 Å) between nearest charge-bearing atoms involved in the ionization. The first band (maximum at 7.44 eV) is assigned to the antisymmetric combination of s and s′ and this gives the longiresonant splitting parameter the value of +1.01 eV.[6]

In bimesityl the two rings are oriented at 90° to one another.[7] This arrangement produces an orthogonality between the basis functions associated with the two s ionic structures and suggests that the interaction between these structures should be zero. Interaction between the a and a′ basis functions is not so restricted and would constitute

an example of spiroresonant[4] interaction. The magnitude (but not the sign) of this interaction should be similar to that between the same structures in the tetrahydropyrene because the distance between interacting groups is the same. The observed spectrum of bimesityl shows characteristics consistent with this reasoning. The magnitude of the spiroresonance interaction parameter is ≤ 0.2 eV.

The principal variables in this analysis are the interaction parameters. The results are all in qualitative accord with expectations of the structure representation model. However, the small magnitude of the reduction in the interaction between s and s′ on going from the [2.2.2]cyclophane (**5**, $S_{s,s'} = 0.52$ eV) to the metacyclophane (**4**, $S_{s,s'} = 0.44$ eV) deserves comment. The through-bond interactions of the bridging groups were used, in our model, in shifting the s and a basis functions from 9.25 eV (benzene) to 8.42 eV. There is a contribution from the totally symmetric II states for **4** (which is absent in **5**) which we have neglected but this does not appear to be a good explanation of the similarity of the two S values. A more important consideration is the quantitative nature of the atomic density distribution in the Ψ_s basis function. The effect of the three electron-donating substituents in a 1,3,5 relationship is to shift vacancy density toward the 4 position in this structure.[8] The metacyclophane **4** places two such high-density centers (4 and 4′) in close proximity. The third bridge brings the 1 and 1′ centers near to one another but the increment in interaction is not additive since the density in these regions is relatively low in the basis function itself. The magnitude of the interaction parameter is responding to the placement of the nodal surface represented in Ψ_s. Our interpretation of the 0.08-eV displacement of the center of the two first bands in **5** is strain, *i.e.*, the deviation from planarity of the two rings,[3] caused by the three bridging groups though other effects could also give rise to such shifts.

The suggested change in the nature of the a, a′ interaction from longiresonant in **3** to spiroresonant in **2** means that the corresponding splitting parameter ($S^{\theta}_{a,a'}$) should have a cos 2θ dihedral angle dependence, where θ is the angle between the planes of the two arene moieties. Using 20° for an estimate of θ in **3** and the observed splitting parameter (0.14 eV, Figure 2), one obtains eq 1.

$$S^{\theta}_{a,a'} = 0.2 \cos 2\theta \quad (1)$$

For the s, s′ interaction a cos θ dependence is suggested and a similar parameterization from the spectrum of **3** gives eq. 2.[5a]

$$S^{\theta}_{s,s'} = 1.08 \cos \theta \quad (2)$$

These equations predict that the splitting of the s, s′ states of bimesityl ($\theta \simeq 90°$) should be zero while that for the a, a′ states should be 0.4 eV ($2S^{90}_{a,a'}$). For biphenyl itself with $\theta \simeq 40°$,[9] the splitting parameter for the s, s′ interaction is estimated at 0.83 eV while that for the a, a′ interaction is 0.03 eV. The observed splittings in the spectrum of biphenyl give $S_{s,s'} = 0.8$ and $S_{a,a'} \leq 0.05$ eV. The observed spectrum of bimesityl is also consistent with these predictions, though the fit is not unambiguous.

This analysis is superficially similar to that given by Maier and Turner[10] for a series of unsymmetrically substituted biphenyls. The principal difference is in the interpretation of spectra of compounds with $90° > \theta > 45°$. The positive intercept of the regression line of that analysis[10] ignores the probable change in the assignment of the lowest ionization potential in this conformation space ($\theta > 45°$) from s, s′ to a, a′ combinations. The recently reported[11] photoelectron spectra of spiroconjugated cations adds weight to the present suggestion.

Experimental Section

The photoelectron spectra were obtained using a Perkin-Elmer PS-18 spectrometer and He(I) source. The peak positions were determined by calibration with an argon (15.76 eV)–xenon (12.13 eV) mixture. (A referee has pointed out that the PS-18 spectra should be calibrated with a low ionization potential calibrant.) Mesitylene was obtained from Matheson Chemical Co. and was purified by distillation. Bimesityl was prepared by the ferric chloride oxidation of mesitylene.[12] The [2.2.2]cyclophane **5** was prepared from the corresponding triene[13] by hydrogenation.

anti-**6,13-Dimethyl[2.2]metacyclophane (4).** This metacyclophane was prepared by photolysis of the corresponding bis(sulfide) in the presence of trimethyl phosphite.[14]

A solution of 3,5-bis(bromomethyl)toluene[15] (33 g, 0.118 mol) in benzene (800 ml) was added by Hershburg dropping funnel at the same rate as $Na_2S \cdot 9H_2O$ (34 g, 0.142 mol) in water (200 ml), and ethanol (600 ml) was added dropwise from a second Hershburg funnel into a 5-l. Morton flask containing 95% ethanol (1 l.) with vigorous stirring, under nitrogen, at room temperature for 29 hr. The solvent was evaporated and the residue was chromatographed on silica gel using hexane to elute the bis(sulfide) 2,11-dithia[3.3]metacyclophane (**4a**). The yield was 8 g (23%), mp 100–101°, nmr ($CDCl_3$, Varian XL-100) singlet, δ 2.17 (6 H); singlet, δ 3.71 (8 H); singlet, δ 6.62 (2 H); singlet, δ 6.72 (4 H).

Anal. Calcd for $C_{18}H_{20}S_2$: C, 71.95; H, 6.71. Found: C, 71.95; H, 6.80.

This bis(sulfide) **4a** (2.0 g, 6.7 mmol) was dissolved in freshly distilled trimethyl phosphite (17 ml) and degassed by freeze–thaw. The solution, in a Vycor reaction tube, was placed in a water-cooled photolysis apparatus under nitrogen and was irradiated with a Hanovia 450-W high-pressure mercury lamp for 40 hr. The bulk of the trimethyl phosphite was removed by evaporation and the residue was chromatographed after preadsorbing on silica gel using hexane eluent. The column chromatography yielded 200 mg of **4**, mp 144–145° (lit.[15] mp 147–149°), along with unreacted bis(sulfide) (major) and the corresponding monosulfide (minor).

The tetrahydropyrene **3** was obtained by the ferric chloride oxidation of the dimethyl metacyclophane, 98% yield, mp 144–145° (lit. mp 146.5–148°).

Acknowledgment. We are grateful to the National Science Foundation and the Du Pont Co. for financial support of this work.

Registry No.—**1**, 108-67-8; **2**, 4482-03-5; **3**, 10549-25-4; **4**, 10549-23-2; **4a**, 42082-65-5; **5**, 27165-88-4; 3,5-bis(bromomethyl)toluene, 19294-043.

References and Notes

(1) (a) A previous report[1b] of the photoelectron spectrum of mesitylene gave the value of the first ionization potential as 8.65 eV. We have rechecked our measurements very carefully and found them to be quite reproducible, giving the first band maximum at 8.43 ± 0.03 eV. This value is near that reported by Watanabe[1c] from photoionization measurements. (b) M. Klessinger, *Angew. Chem., Int. Ed. Engl.*, **11**, 525 (1972). (c) K. Watanabe, *J. Chem. Phys.*, **26**, 542 (1957).

(2) (a) W. T. Simpson, *J. Amer. Chem. Soc.*, **75**, 597 (1953); W. T. Simpson and C. W. Looney, *ibid.*, **76**, 6285, 6293 (1954). This method is mathematically identical with the equivalent orbital method[2b] of Hall which has been used to analyze photoelectron spectra of hydrocarbons.[2c] We prefer the structure representation version becuase it avoids reference to Koopmans' Theorem. (b) C. G. Hall, *Proc. Roy. Soc., Ser. A*, **205**, 541 (1951); J. E. Lennard-Jones and C. G. Hall, *Discuss Faraday Soc.*, **10**, 18 (1951). (c) J. N. Murrell and W. Schmidt, *J. Chem. Soc., Faraday Trans. 2*, **68**, 1709 (1972), and references cited therein.

(3) A more complete discussion of the photoelectron spectrum of this particular compound is given by V. Boekelheide and W. Schmidt, *Chem. Phys. Lett.*, **17**, 410 (1972).

(4) M. J. Goldstein and R. Hoffman, *J. Amer. Chem. Soc.*, **93**, 6193 (1971).

(5) (a) The dihedral angle of 9,10-dihydrophenanthrene has been estimated at 20°. The additional two-carbon bridge in **3** would not be expected to change this value because of its geometrical equivalence with the original bridging unit. (b) A. Unanue and P. Botherel, *Bull. Soc. Chim. Fr.*, 1640 (1966).

(6) The fourth band is at lower energy (9.25 eV) than this predicts (9.46 eV). This is as it should be because of the interaction of the totally symmetric II ion structures which we have neglected here.

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(8) Hückel wave functions give this result.

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Stereoselective Formation of a Pseudo Oxazolone

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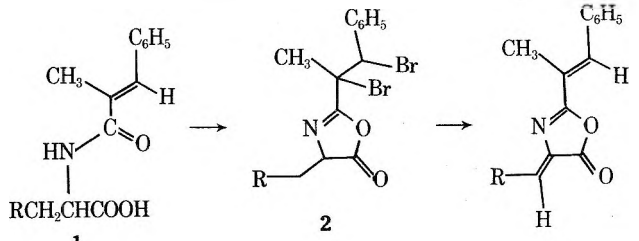
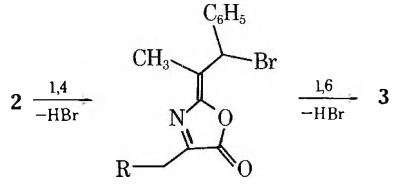
It has recently been shown in our laboratories that unsaturated azlactones (**3**) can be prepared by treatment of *N*-cinnamoyl amino acids (**1**) with a pyridine perbromide–acetic anhydride–pyridine mixture.[1] This reaction most



1 **2** **3**

likely proceeds through a dibromo saturated azlactone (**2**), since we have shown[1] that dibromodihydrocinnamoyl amino acids also afford **3** under these reaction conditions. The halogenated intermediate, **2**, apparently undergoes a 1,4-dehydrobromination, giving a pseudo oxazolone, **4**, which again dehydrobrominates giving **3**. It was shown



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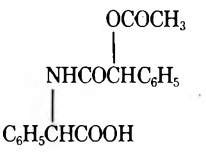
that the configuration of the 1-methylstyryl group was unchanged during the **1** → **3** conversion. If we assume trans bromination to give **2**, then knowledge of the steric course of the 1,4-dehydrobromination step would allow us to infer the stereochemistry of the 1,6-dehydrobromination and, consequently, the configuration of the new double bond at the 4 position. We chose to examine the stereochemistry of the 1,4 elimination by using the two diastereomers of an *N*-mandeloylphenylglycine derivative (**5**), since the required chiral starting materials are readily available. If the reaction occurs stereospecifically, the DD,LL racemate should afford one stereoisomer of the pseudo oxazolone, **6**, while its diastereomer, the DL,LD isomer, should give the other geometric isomer. Formation of the same isomer of **6** from both diastereomers of **5** would indicate that the reaction is stereoselective.

Racemic mandelic acid was O-acetylated and coupled to racemic phenylglycine to give the mandeloyl derivative **5**, which consisted of a diastereomeric mixture. When **5** was treated with an acetic anhydride–pyridine mixture the crystalline pseudo oxazolone **6** was formed. Recrystallization of crude **6** gave the pure compound having physical properties in agreement with those previously reported by Adembri.[2] Liquid chromatography of crude **6** failed to show the presence of a second oxazolone and ^{13}C nmr spectroscopy showed clearly that only one stereoisomer was present. This indicated strongly that the reaction was stereoselective, giving only the more stable product.



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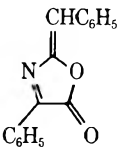

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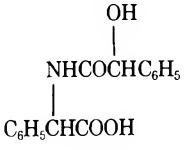
In order to check this result, the optically active mandeloylphenylglycines (**5**) were prepared. *N*-(*O*-Acetyl-D(−)-mandeloyl)-D-(−)-phenylglycine[3] and *N*-(*O*-acetyl-D(−)-mandeloyl)-L(+)-phenylglycine were prepared by the same method used to prepare the racemate. When these isomers were subjected to the acetic anhydride–pyridine treatment, the pseudo oxazolone obtained was identical in all respects with that obtained from the racemate. We were concerned that the results of these experiments might be invalidated by the possibility of racemization of the mandelic acid chiral center during the Schotten–Baumann coupling of the acid chloride with phenylglycine. In order to check this, *N*-(*O*-acetyl)-D(−)-mandelic acid was coupled with each of the enantiomers of phenylglycine methyl ester using carbodiimide, and the ester functions were saponified to give both diastereomers of *N*-mandeloylphenylglycine (**7**). The acetic anhydride–pyridine reagent converted these two compounds into the same pseudo oxazolone **6** in yields almost identical with those obtained before.



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We can conclude from these results that the 1,4 dehydrobromination of intermediate **2** is stereoselective rather than stereospecific. This means that the overall conversion of **1** → **3** is most probably stereoselective. In the six cases that we have investigated[1] so far, the *Z* isomer is formed predominantly when R is aliphatic and exclusively when R is aromatic.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer Model 257 grating infrared spectrophotometer as Nujol mulls with polystyrene as a standard. The proton nuclear magnetic resonance spectra were recorded on a Varian HA-100 spectrometer with tetramethylsilane as the internal or external standard. All chemical shifts are reported in parts per million. The carbon-13 nuclear magnetic resonance spectrum was determined on a JEOL PFT-100 spectrometer. The ultraviolet–visible spectra were obtained on a Perkin-Elmer Model 202 spectrophotometer. Melting points were uncorrected and determined on a Nagle Model Y6 hot stage. Elemental analyses were carried out by Atlantic Microlabs, Atlanta, Ga. Observed rotations were obtained on a Perkin-Elmer Model 141 polarimeter.

O-Acetyl-L(+)-mandelic Acid. A mixture of 7.2 g (0.0475 mol) of L(+)-mandelic acid, $[\alpha]^{27}D$ +158° (c 1.0, H_2O) [lit.[4] $[\alpha]^{26}D$ +157° (c 1.07, H_2O)], and 20 ml (0.278 mol) of acetyl chloride was warmed on a water bath for 2 hr. The excess acetyl chloride was removed *in vacuo*, leaving a colorless oil which crystallized after 2 days. Recrystallization from benzene–*n*-hexane gave 59 g (69%) of the acid: mp 95–97.5° (lit.[5] mp 96.8°); $[\alpha]^{27}D$ +148° (c 1.87, acetone) [lit.[6] $[\alpha]^{25}D$ +153° (c 2.0, acetone)]; nmr ($CDCl_3$) δ 2.10 (s, 3 H, CH_3), 5.95 (s, 1 H, C_6H_5CHO), 7.18–7.48 (m, 5 H, C_6H_5), 11.70 ppm (s, 1 H, COOH); ir (Nujol) 1745 (C=O ester), 1700 cm^{-1} (C=O acid).

O-**Acetyl-D(−)-mandelic Acid.** The method used was similar to that used for the L(+) isomer. Starting with 2.75 g (18 mmol) of D(−)-mandelic acid, $[\alpha]^{27}D$ −147° (c 1.67, 20% HCl) [lit.[4] $[\alpha]^{25}D$ −154° (c 2.06, H_2O)], and 8 ml of acetyl chloride, 2.77 g (79%), mp 80–81°, of the acid was obtained: $[\alpha]^{27}D$ −155° (c 1.34, acetone) [lit.[5] $[\alpha]^{20}D$ −157° (c 2.4, acetone)]; ir (Nujol) 1745 (C=O ester), 1695 cm^{-1} (C=O acid); nmr ($CDCl_3$) δ 2.10 (s, 3 H, CH_3COO), 6.00 (s, 1 H, -OCHCOOH), 7.23–7.60 (m, 5 H, C_6H_5), 11.50 ppm (s, 1 H, COOH).

N-[*O*-**Acetyl-DL-mandeloyl**]-**DL-phenylglycine (5).** To a solution of 31.24 g (0.20 mol) of phenylglycine and 210 ml of 1 *N* sodium hydroxide contained in a 500-ml, three-necked, round-bottomed flask equipped with two dropping funnels and a stirrer and cooled with an ice bath was added dropwise over a 1 hr period 40.47 g (0.193 mol) of *O*-acetyl-DL-mandeloyl chloride[7] and 260 ml of 1 *N* sodium hydroxide. After an additional 30 min of stirring, the mixture was acidified, the combined extracts were dried with anhydrous magnesium sulfate and filtered, and the filtrate was evaporated *in vacuo*, yielding 51.0 g (82%) of the crude product. Recrystallization from ethyl acetate-petroleum ether (bp 30–60°) (6:1) gave 42.6 g (69%) of the acid: mp 172–181°; ir (Nujol) 3375 (NH), 2475–2600 (COOH), 1745 (CH_3COO-), 1718 (COOH), 1625 cm^{-1} (CONH-); nmr (TFA) δ 2.25 (s, 3 H, CH_3), 5.7 (d, 1 H, C_6H_5CHNH), 6.35 (s, 1 H, C_6H_5CHO-), 7.28–7.50 (m, 10 H, 2 C_6H_5), 7.91 ppm (d, 1 H, NH).

Anal. Calcd for $C_{18}H_{17}NO_5$: C, 66.05; H, 5.23; N, 4.28. Found: C, 65.83; H, 5.27; N, 4.19.

N-[*O*-**Acetyl-L(+)-mandeloyl**]-**D(−)-phenylglycine (5).** This compound was prepared by condensation of 16.63 g (0.11 mol) of D(−)-phenylglycine with 25.5 g (0.12 mol) of *O*-acetyl-L(+)-mandeloyl chloride.[8] A 33.0-g (84%) yield of crude product was recrystallized from an ethyl acetate–petroleum ether mixture, giving 22.2 g (57%), mp 193–197°, of pure acid. The analytical sample was recrystallized from an acetic acid–H_2O mixture: mp 199–203°; $[\alpha]^{20}D$ −53.11° (c 3.82, HOAc); ir (Nujol) 3295 (NH), 2490 (COOH), 1720 (CH_3COO), 1600 cm^{-1} (CONH); nmr (TFA) δ 2.18 (s, 3 H, CH_3CO_2), 5.68 (d, 1 H, OCHNH), 6.30 (s, 1 H, OCHOAc), 7.20–7.49 (m, 10 H, 2 C_6H_5), 7.92 ppm (d, 1 H, NHCO).

Anal. Calcd for $C_{18}H_{17}NO_5$: C, 66.05, H, 5.23; N, 4.28. Found: C, 66.02; H, 5.35; N, 4.28.

N-[*O*-**Acetyl-D(−)-mandeloyl**]-**D(−)-phenylglycine (5).** The procedure used was the same used in preparing the racemic **5** and the LD-**5.** A 67% yield, mp 188–198°, of the acid was obtained. The analytical sample was recrystallized from acetic acid–water: mp 202–205°; $[\alpha]^{21}D$ −62.0° (c 1.23, HOAc); ir (Nujol) 3300 (NH), 1748 (CH_3COO-), 1723 (COOH), 1660 cm^{-1} (-CONH-); nmr [$(CD_3)_2CO$] δ 2.09 (s, 3 H, CH_3), 5.55 (d, 1 H, C_6H_5CHNH-), 6.12 (s, 1 H, C_6H_5CHO), 7.18–7.58 (m, 10 H, 2 C_6H_5), 8.0 ppm (d, 1 H, NH).

Anal. Calcd for $C_{18}H_{17}NO_5$: C, 66.05; H, 5.23; N, 4.28. Found: C, 65.80; H, 5.30; N, 4.32.

N-[*O*-**Acetyl-L (+)-mandeloyl**]-**D(−)-phenylglycine Methyl Ester.** To a suspension of 2.09 g (10.4 mmol) of D(−)-phenylglycine methyl ester hydrochloride[9] in 30 ml of methylene chloride was added 1.45 (10.4 mmol) of triethylamine. After 25 min at room temperature 2.0 g (10.4 mmol) of *O*-acetyl-L(+)-mandelic acid was added followed by 2.18 g (10.6 mmol) of *N,N'*-dicyclohexylcarbodiimide (DCC). The light green solution was stirred at room temperature for 2 hr and cooled in an ice bath. Excess DCC was destroyed with trifluoroacetic acid, and the *N,N'*-dicyclohexylurea (2.1 g, 89%) was filtered. The filtrate was washed with 5% sodium bicarbonate and 0.5 *N* hydrochloric acid, dried with anhydrous sodium sulfate, clarified with Norit, and evaporated to dryness *in vacuo*, leaving a solid residue, 3.4 g. The crude product was recrystallized from methylene chloride–hexane, giving 2.38 g (67%), mp 154–157°, of the diester: $[\alpha]^{31}D$ − 24.8° (c 0.56, MeOH); ir (Nujol) 3315 (NH), 1750 ($COOCH_3$), 1725 (CH_3COO), 1695 cm^{-1} (-CONH-); nmr ($CDCl_3$) δ 2.05 (s, 3 H, CH_3COO), 3.55 (s, 3 H, $COOCH_3$), 5.4 (d, 1 H, -CHNH), 5.95 (s, 1 H, -CHOAc), 6.95–7.5 ppm (m, 11 H, 2 C_6H_5, NH).

Anal. Calcd for $C_{19}H_{19}NO_5$: C, 66.85; H, 5.61; N, 4.10. Found: C, 66.64; H, 5.69; N, 4.11.

L(+)-Mandeloyl-D(−)-phenylglycine (7). To a suspension of 1.2 g (3.53 mmol) of the ester in 14 ml of methanol was added 8.0 ml of 1 *N* sodium hydroxide. After standing at room temperature for 19 hr, the solution was cooled and acidified with concentrated hydrochloric acid to pH 2.5. The precipitate was filtered and dried *in vacuo*, giving 0.791 g (79%), mp 190–194°, of the hydroxy acid: $[\alpha]^{22}D$ −120° (c 1.20, EtOH); ir (Nujol) 3410–3430 (OH), 3370 (NH), 1729 (COOH), 1614 cm^{-1} (-CONH-); nmr (DMSO-d_6) δ 2.07 (s, 1 H, OH), 5.07 (s, 1 H, C_6H_5CHOH), 5.38 (d, 1 H, C_6H_5CHNH), 7.18–7.55 (m, 10 H, 2 C_6H_5), 8.36 ppm (d, 1 H, NH).

Anal. Calcd for $C_{16}H_{15}NO_4$: C, 67.36, H, 5.30; N, 4.91. Found: C, 67.11, H, 5.34; N, 4.99.

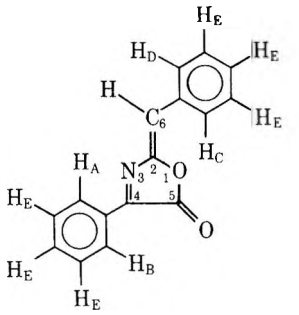
N-[*O*-**Acetyl-D(−)mandeloyl**]-**D(−)-phenylglycine Methyl Ester.** The method used was similar to that used for the L(+) isomer. From 2.09 g (10.4 mmol) of D(−)-phenylglycine methyl ester hydrochloride and 2.0 g (10.4 mmol) of *O*-acetyl-D(−)-mandelic acid was obtained 2.59 g (73%): mp 169–172°; $[\alpha]^{30}D$ −147° (c 0.52, MeOH); ir (Nujol) 3332 (NH), 1741 ($COOCH_3$, CH_3COO), 1665 cm^{-1} (-CONH-); nmr ($CDCl_3$) δ 2.16 (s, 3 H, CH_3COO), 3.68 (s, 3 H, $COOCH_3$), 5.55 (d, 1 H, C_6H_5CHNH-), 6.10 (s, 1 H, C_6H_5CHOAc), 7.18–7.45 ppm (m, 11 H, 2 C_6H_5, NH).

Anal. Calcd for $C_{19}H_{19}NO_5$: C, 66.85; H, 5.61; N, 4.10. Found: C, 66.61; H, 5.72; N, 4.11.

D(−)-Mandeloyl-D(−)-phenylglycine. The procedure used for preparation of L(+)-mandeloyl-D(−)-phenylglycine was used for this isomer also. From 2.5 g (7.34 mmol) of the diester was obtained 1.85 g (88%), mp 148–150°, of the hydroxy acid: $[\alpha]^{25}D$ −112° (c 1.20, EtOH); ir (Nujol) 3400 (OH), 3275 (NH), 1729 (COOH), 1652 cm^{-1} (-CONH-); nmr (DMSO-d_6) δ 2.10 (s, 1 H, OH), 5.09 (s, 1 H, C_6H_5CHOH), 5.40 (d, 1 H, C_6H_5CHNH), 7.2–7.54 (m, 10 H, 2 C_6H_5), 8.40 ppm (d, 1 H, NH).

Anal. Calcd for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91. Found: C, 67.09; H, 5.29; N, 4.94.

2-Benzylidene-4-phenyl-3-oxazolin-5-one (6). To 1.0 g (3.06 mmol) of **5** was added 15 ml of acetic anhydride and 1.0 ml (12.4 mmol) of dry pyridine. The yellow solution was stirred at room temperature for 1 hr and poured into ice water where it was stirred for 1 hr. Filtration gave 0.68 g (89%) of crude pseudo oxazoline, which was recrystallized from isopropyl alcohol to give 0.403 g (53%), mp 137–139° (lit.[2] mp 136–137.5°), of yellow needles: ir (Nujol) 1782 (C=O), 1645 (C=N), 1598 cm^{-1} (C_6H_5); ^1H nmr ($CDCl_3$) δ 6.43 (s, 1 H, H_F), 7.27–7.54 (m, 6 H, H_E), 7.70–7.85 (m, 2 H, H_C, H_D), 8.30–8.45 ppm (m, 2 H, H_A, H_B); ^{13}C nmr ($CDCl_3$, on crude compound) 113.67 (C_6), 128.52–132.66 (aromatic C's), 151.19 (C_2), 152.94 (C_4), 162.69 ppm (C_5); uv (95% EtOH) λ_{max} 249 nm (log ε 3.93), 258 (shoulder, 3.81), 396 (4.45), 413 (4.46).



Registry No.—(±)-**5**, 50859-91-1; L(+),D(−)-**5**, 50859-85-3; D(−),D(−)-**5**, 50859-86-4; L(+),D(−)-**5** methyl ester, 50859-87-5; D(−),D(−)-**5** methyl ester, 50859-88-6; **6**, 14389-69-6; L(+),D(−)-**7**, 50859-89-7; D(−),D(−)-**7**, 50859-90-0; *O*-acetyl-L(+)-mandelic acid, 7322-88-5; *O*-acetyl-D(−)-mandelic acid, 51019-43-3; phenylglycine, 2835-06-5; *O*-acetyl-DL-mandeloyl chloride, 49845-72-9; D(−)-phenylglycine, 875-74-1; *O*-acetyl-L(+)-mandeloyl chloride, 51019-44-4; D(−)-phenylglycine methyl ester hydrochloride, 19883-41-1; DCC, 538-75-0.

References and Notes

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(7) Prepared by treatment of the acid with thionyl chloride, bp 135° (15 mm). The acid was prepared using the procedure described in "Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., 1948, p 12.
(8) Prepared from the acid by treatment with thionyl chloride, bp 140° (22 mm), ir (neat) 1811 (COCl), 1751 cm^{-1} (CH_3COO).
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Intermediates Common to the Reactions of Hydrochlorination of Styrene and Ionization of 1-Phenylethyl Chloride[1]

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Electrophilic addition, nucleophilic substitution, and elimination have long been considered to proceed by similar carbonium intermediates and a considerable amount of definite information regarding the energetics of the various steps in a particular system can be obtained by approaching it from different directions under very similar conditions. These reactions have been tied together in an elegant study reported by Noyce on a system which involves dissociated ions.[2] Thus, the acid-catalyzed hydration–dehydration reactions of the stilbenes are described in great detail where the energy differences for the various ground states and transition states are provided quantitatively. On the other hand, the intermediates invoked in the chlorination[3] and hydrochlorination[4,5a,6a] of olefins in weakly dissociating solvents are ion pairs similar to those produced in solvolysis reactions.[7,8] We felt that it was important to investigate in a similar way a system that involves ion pairs. The phenylethyl–styrene system in acetic acid is particularly attractive since it can be compared to the solvolysis of phenylethyl chloride (RCl), which has been extensively studied in the more nucleophilic aqueous solvents,[5b,6b,d,9,10] and more directly with the data on the hydrochlorination of styrene in AcOH which is available at various temperatures.[4c] We now wish to communicate the results of a comparative study on this system.

Solvolysis of 1-phenylethyl chloride in anhydrous acetic acid containing 0.01 *M* lithium acetate at 75.0° produces 86% 1-phenylethyl acetate and 14% styrene. The rate of acetolysis followed by analysis of inorganic chloride ion[11] provides a value for k_t equal to $3.8 \pm 0.2 \times 10^{-5}$ sec^{-1} at low lithium acetate concentrations. The k_t values listed in Table I show a slight increase by added lithium acetate, where the "*b*" value is *ca.* 0.5. Optically active 1-phenylethyl chloride was prepared from the resolved carbinol[12] with thionyl chloride.[13] The loss of optical activity which accompanies the acetolysis reaction of RCl was measured in an all-glass cell thermostated at 75.0°. The rate of loss of optical activity proceeds substantially faster than acetolysis where the value of k_α is equal to $10.0 \pm 0.2 \times 10^{-5}$ sec^{-1}. The final reaction solutions were >98.5% racemic.[14] The racemization rate constant, k_{rac}, provided by the difference between k_α and k_t, is equal to 6.17×10^{-5} sec^{-1}. Thus, the k_{rac}/k_t ratio of 1.6 indicates that the ionization reaction must proceed *via* ion-pair intermediates which racemize and return to covalent RCl *ca.* 1.6 times faster than they go on to products.

In order to test the intramolecular nature of the racemization process, the rates of chlorine exchange k_e were measured between RCl and radiolabeled lithium chloride. The pseudo-first-order k_e values at 0.013–0.035 *M* LiCl are small compared to the overall reaction and at an average [Cl$^-$] of 0.02 *M*, chlorine exchange is less than 6% of the total return reaction (k_e/k_{rac} = 0.06). Therefore, the return does not occur from dissociated intermediates to any great extent.[7c]

The partitioning of the intermediates to produce covalent RCl and ROAc as based on these measurements differs widely from the hydrochlorination of styrene. The hydrochlorination of styrene[4c] in AcOH containing 0.01 *M* HCl produces a kinetic product mixture containing 93% RCl plus 7% ROAc at 25° and 85% RCl plus 15% ROAc at 75°.[15] Thus the RCl/ROAc formation ratio is 5.6 from the addition reaction and 1.86 from the ionization reaction. In Scheme I is presented a simple mechanistic scheme, with a minimum number of required intermediates, which will fit the results from the two reactions. This scheme is based on the assumption that the two reactions produce the same ion-pair intermediates and that the discrepancy in the results is due to the lack of an adequate measure of k_1.

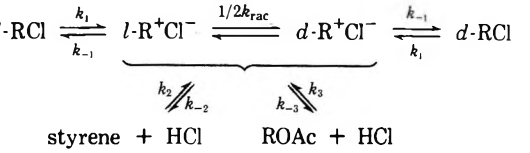
Table I

Summary of *k*'s for 1-Phenylethyl Chloride[a] in Acetic Acid at 75.0°

Salt	$10^5 k$, sec^{-1} k_α	k_t	k_e
0.0569 *M* LiOAc	10.06 ± 0.3		
0.0569 *M* LiOAc	9.92 ± 0.3		
0.0103 *M* LiOAc		3.81 ± 0.23	
0.0257 *M* LiOAc		3.84 ± 0.10	
0.0569 *M* LiOAc		3.88 ± 0.15	
0.0103 *M* LiOAc 0.0130 *M* LiCl			0.26 ± 0.03
0.0128 *M* LiOAc 0.0288 *M* LiCl		3.9	0.46 ± 0.08
0.0103 *M* LiOAc 0.0346 *M* LiCl			0.58 ± 0.08

[a] RCl concentrations are 0.01 *M* for k_t and k_e measurements and 0.07 *M* for k_α measurements.

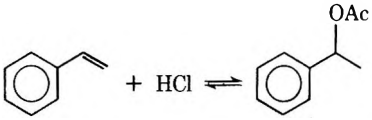
Scheme I



Given the scheme, the k_{-1}/k_{-3} ratio estimated equal to 5.6 from the RCl/ROAc product ratio produced in the hydrochlorination reaction and the k for formation of ROAc equal to 3.3×10^{-5} sec^{-1} provide a better measure of k_1 equal to 18.5×10^{-5} sec^{-1} ($\Delta F^* = 26.30$ kcal). Therefore, total return occurs >98% *via* intimate ion pairs.

The partitioning of the intermediate is such that it returns to RCl (85%) and produces ROAc (15%), providing a $\Delta\Delta F^*$ difference for these processes equal to 1.19 kcal. Of the return reaction, only 33% proceeds with racemization; *i.e.*, the rate of inversion is more endothermic than return by 1.24 kcal. From the ratio of the kinetic products in the acetolysis of RCl one calculates 1.25 kcal as the energy difference for the transition states leading to these products. Finally in order to provide all the energetics corresponding to Scheme I, one could use K_1 equal to *ca.* 180[9] for eq 1 where $\Delta\Delta F_{eq}$ is equal to 3.58 kcal at unit concentrations, and the value of k for the reaction of styrene with 1 *M* HCl in AcOH at 75° of 1.21×10^{-3} sec^{-1},[4c,15] with ΔF^* equal to 25.10 kcal. These energy values are plotted in Figure 1. By difference, the energy associated with the equilibrium in eq 2 provides a value ol K_2 equal to one in AcOH at 75°.

$$\text{ROAc} + \text{HCl} \rightleftharpoons \text{RCl} \qquad K_1 \quad (1)$$



K_2 (2)

Regarding the nature of the transition states for the formation of products, based on the deuterium isotope effects in the solvolysis of RCl, this particular transition

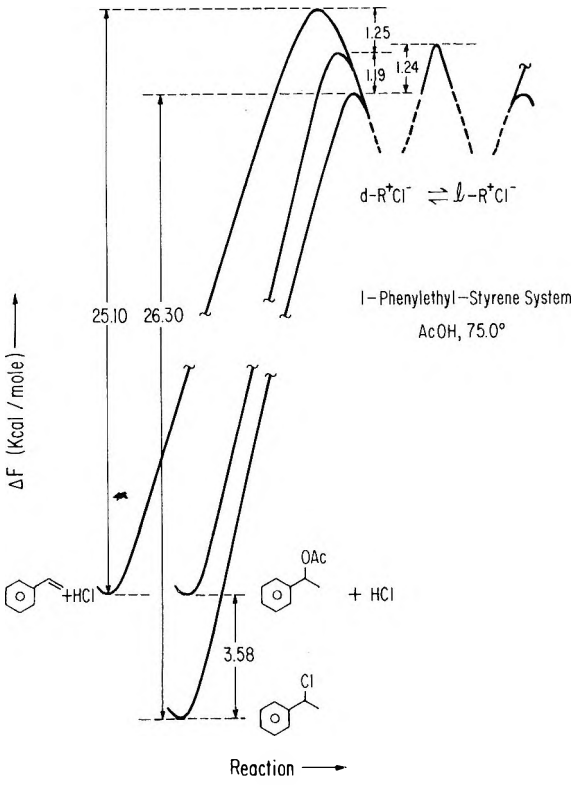


Figure 1.

state must look very much like the intermediate with little covalent bonding of the cation to chloride ion or solvent.[6d]

Considering the nature of the ion-pair intermediates produced in the solvolysis reactions of compounds which produce open carbonium ions, when the counterion is a benzoate[8] or an arylsulfonate[7] anion, racemization does not occur at the "intimate" ion pair but instead occcurs exclusively and efficiently at the "solvent-separated" ion pair. Chemical capture also occurs at this intermediate. However in the solvolysis of the corresponding alkyl halides, racemization and chemical capture is not restricted to the more loose ion pair, but instead racemization can occur at the intimate ion pair stage.[7,16,17] Thus the present results can be fit by the presence of one intimate ion pair common to both reactions which can return to RCl and can racemize. The extent of racemization that accompanies the solvolysis reaction depends on the sensitive balance between the nucleophilicity and dissociating power of the solvent. Because of the difficulty in estimating these properties of solvents, caution must be used in attempting to combine quantitatively those results obtained in different solvents or solvent mixtures with varying per cent composition.

An alternative explanation for greater formation of RCl in the hydrochlorination reaction relative to solvolysis is the possible presence of a concurrent concerted addition pathway which yields RCl exclusively. The decrease in the RCl/ROAc product ratio from 13 to 6 as the solvent changes to the higher ionizing solvent, CF_3CH_2OH,[4a,c] is consistent with this possibility.

Experimental Section

Optically active 1-phenylethyl alcohol was prepared by the method of McKensie and Clough where the 1-phenylethyl acid phthalate brucine salt was recrystallized several times from anhydrous acetone. The carbinol was converted to the alkyl chloride with thionyl chloride. The reaction mixture was dissolved in pentane and the solution was washed carefully with aqueous $NaHCO_3$. The solution was then dried over K_2CO_3 and the pentane was removed under reduced pressure. The alkyl chloride was used as such without further purification, $[\alpha]_{589}$ −38.8°, chloride analysis 99.9% Cl.

The purification of acetic acid solvent and preparation of the salt solutions used in the experiments were performed as previously described.[11] The polarimetric rate measurements were made in a thermostated 1-dm all-glass cell using a Perkin-Elmer polarimeter, Model 141. The titrimetric rate measurements were carried out in sealed ampoules.[11] The k_α and k_t values were calculated using the integrated first-order rate expression.

The exchange rate measurements were carried out using a sealed-ampoule technique as previously described.[11] The separation of organic chloride from inorganic chloride was afforded using pentane and water. Aliquots (2 ml) from each layer were delivered into 10 ml of Bray's solution[18] and the radioactivity level was measured using a Beckman LS100 liquid scintillation counter. The pseudo-first-order exchange rate constants, k_e, were calculated using a modified form of the equation of Swart and Roux[19]

$$k_e t = \frac{2.303[\mathrm{LiCl}]}{([\mathrm{RCl}] + [\mathrm{LiCl}])} \log\left[1 - \gamma e^{k_t t}\,\frac{([\mathrm{RCl}] + [\mathrm{LiCl}])}{[\mathrm{RCl}]}\right]$$

where γ is the fraction of the radioactivity found in the pentane layer.

Product analysis were performed as previously described.[11]

Acknowledgments. The authors wish to acknowledge the Alfred P. Sloan Foundation for their generous financial support and Dr. R. C. Fahey for many interesting discussions.

Registry No.—1-Phenylethyl chloride, 672-65-1.

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Secondary Amines from Trifluoroacetamides

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In connection with some studies of routes to bis(secondary amines) containing multiple ether functions, we investigated the alkylation of trifluoroacetamides followed by removal of the trifluoroacetyl group by basic hydrolysis. To the extent that this method is successful, it has the advantages that trifluoroacetamides are in general easily prepared in high yield from an amine and ethyl trifluoroacetate,[1] and that the trifluoroacetyl group is very readily removed after alkylation. This easy hydrolysis is in contrast to the difficulty of hydrolytic removal of arylsulfonyl groups after a synthesis by alkylation of a sulfonamide.[2] Trifluoromethanesulfonamides are similarly resistant to basic cleavage, but they are readily cleaved by hydride reduction.[3]

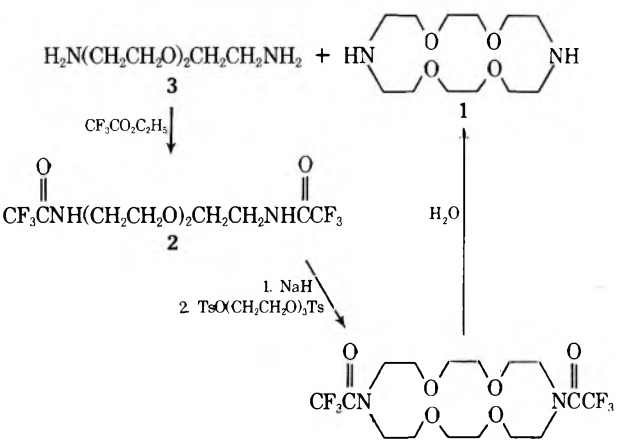
While our work was in progress, a report by Johnstone, *et al.*,[4] appeared on the alkylation of *N*-alkyl- and *N*-aryltrifluoroacetamides. These workers found that methyl and ethyl groups could be introduced in 80–90% yields by reaction of the trifluoroacetamides in acetone with KOH–alkyl halide. However, yields from *n*-propylation were much lower, even when a reactive propylating agent such as *O*-*n*-propyl methylsulfonate was employed.

We find that the utility of the method can be extended to higher *n*-alkyl halides by the use of a dipolar aprotic medium. For example, *N*-butyltrifluoroacetamide was converted to *N,N*-dibutyltrifluoroacetamide in 62% yield by treatment of the sodium salt in dimethylformamide solution with *n*-butyl bromide. Basic hydrolysis to di-*n*-butylamine proceeded readily and in high yield.

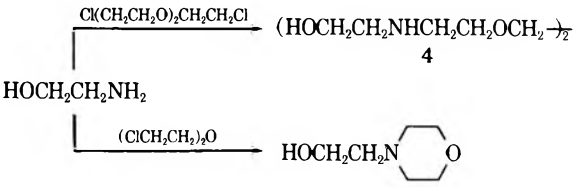
$$CF_3CON(CH_2)_3CH_3 + Br(CH_2)_3CH_3 \xrightarrow{DMF} CF_3CON(CH_2CH_2CH_2CH_3)_2$$
$$Na^+$$

Attempts to adapt this amine synthesis to the case in which cyclic diamine **1** is formed gave at best a 3% yield. One factor responsible for the low yield is probably the reduced ability of nitrogen bearing the negative trifluoroacetyl group to participate in coordination to alkali metal ion, so that no template effect[5] is available to assist ring closure. In any event, reaction of bis(trifluoroacetamide) **2** as the disodium salt with the ditosylate of triethylene glycol in dimethylformamide gave, after basic hydrolysis, 3% of purified diamine **1**, whereas the same reaction with 1,8-dichloro-3,6-dioxaoctane in place of ditosylate gave none of diamine **1**. In contrast, the synthesis employed for the acyclic diamine **3** (given in the Experimental Section) provides **1** directly as a by-product in 4% yield.

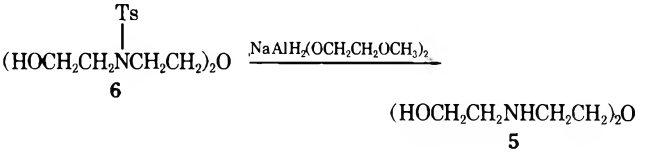
$$Cl(CH_2CH_2O)_2CH_2CH_2Cl + \text{excess } NH_3 \longrightarrow [H_2N(CH_2CH_2O)_2CH_2CH_2]_2NH +$$



The common technique of treating a large excess of primary amine with an alkylating agent to favor formation of secondary amine is effective in the preparation of bis(secondary amine) **4**, but fails in the preparation of **5** because of preferential intramolecular cyclization to *N*-(2-hydroxyethyl)morpholine.[6] Moreover, attempts to alkylate the *N*-trifluoroacetyl derivative of ethanolamine with bis(2-chloroethyl) ether, a relatively unreactive halide, gave none of **5**.



Diamine **5** was finally obtained by alkylation of the *N*-tosyl derivative of ethanolamine with bis(2-chloroethyl) ether to form **6** in 83% yield, followed by reductive removal of tosyl groups[7] to give **5**.



It therefore appears that the synthesis of secondary amines by alkylation of anions derived from trifluoroacetamides is a more generally useful method than previously reported, but that moderately reactive alkylating agents are required, even in aprotic solvents. Side reactions predominated with this method in alkylations involving cyclization to form a large ring or at elevated temperature with an alkylating agent of low reactivity.

Experimental Section[8]

Synthesis of *N*-*n*-Butyltrifluoroacetamide and Conversion to Di-*n*-butylamine. To a cold solution of 71.0 g (0.50 mol) of ethyl trifluoroacetate in 40 ml of anhydrous ether was added dropwise 36.6 g (0.50 mol) of *n*-butylamine. The mixture was stirred for 1 hr, then distilled to give 79.34 g (94%) of *N*-*n*-butyltrifluoroacetamine:[9] bp 50° (1 mm); ir (neat) 3.02 (NH), 3.35, 3.46 (saturated CH), 5.84 (C=O), 6.37 (amide II), 8–9 (CF), 13.9 μ (butyl group); ^{1}H nmr ($CDCl_3$) 7.50 (s, 1, NH), 3.25 (q, 2, NCH_2), 1.9–0.7 ppm (m, 7, $CH_2CH_2CH_3$).

To a suspension of 9.6 g (0.20 mol) of 50% NaH in 100 ml of dimethylformamide was added dropwise a solution of 33.8 g (0.20 mol) of *N*-*n*-butyltrifluoroacetamide in 50 ml of dimethylformamide. After cessation of hydrogen evolution, 27.4 g (0.20 mol) of *n*-butyl bromide was added, resulting in a mildly exothermic reaction. The mixture was stirred overnight, solvent was removed, and the residue was taken up in ether, filtered, and distilled to give 27.82 g (62%) of *N,N*-di-*n*-butyltrifluoroacetamide:[9] bp 44–47° (0.1 mm); ir (neat) 3.37, 3.47 (saturated CH), 5.93 (C=O), 8–9 μ (CF); ^{1}H nmr ($CDCl_3$) 3.7–3.2 (m, 2, NCH_2), 1.9–0.8 ppm (m, 7, $CH_2CH_2CH_3$).

Hydrolysis of *N,N*-di-*n*-butyltrifluoroacetamide to di-*n*-butylamine, bp 36° (15 mm), identified by ir, was accomplished in 95% yield by refluxing for 1 hr with ethanolic sodium hydroxide.

3,6-Dioxaoctane-1,8-diamine (3). Reaction of 524 g (2.80 mol) of 1.8-dichloro-3,6-dioxaoctane in 2.4 l. of absolute ethanol with 2380 g (140 mol) of ammonia was carried out at 125° for 20 hr in a 3-gallon autoclave. After excess ammonia had been vented from

the cooled reaction mixture, the combined liquid and solid was refluxed for 4 hr with 436 g (4.12 mol) of anhydrous sodium carbonate, filtered, and distilled to give three products. Diamine **3**, was an oil; bp 73–79° (0.10 mm); 297 g (71%); ^{1}H nmr ($CDCl_3$) 3.63 (s, 1, OCH_2CH_2O), 3.52 (rough t, J_{HH} = 5 Hz, 1, OCH_2CH_2N), 2.85 (rough t, J_{HH} = Hz, 1, OCH_2CH_2N), and 1.35 ppm (s, 1, NH_2).

Anal. Calcd for $C_6H_{16}N_2O_2$: C, 48.60; H, 10.90; N, 18.90. Found: C, 48.70; H, 10.83; N, 19.06.

A crude sample of **1**, bp 130–170° (~0.5 mm), was recrystallized from ether to give 15.0 g (4%) of pure **1**,[10] mp 112–114°, identified by nmr and mixture melting point with an authentic sample.

A fraction, bp 171–176° (0.2 mm), was 41.7 g (11%) of 3,6,12,15-tetraoxa-9-azaheptadecane-1,17-diamine: ir (neat) 3.00, 3.05, and 6.12 (NH, NH_2), 3.49 (saturated CH), and 9.0 μ (broad COC); ^{1}H nmr ($CDCl_3$) 3.83–3.42 (m, 16, OCH_2), 3.00–2.72 (m, 8, NCH_2), and 1.4 ppm (s, 5, NH_2).

Anal. Calcd for $C_{12}H_{29}N_2O_4$: C, 51.57; H, 10.48; N, 15.04. Found: C, 51.43; H, 10.37; N, 14.80.

1,10-Diaza-4,7,13-16-tetraoxacyclooctadecane (1) from 1,8-Bis(trifluoroacetamido)-3,6-dioxaoctane (2) and 1,8-Ditosyloxy-3,6-dioxaoctane. Addition of 28.8 g (0.60 mol) of diamine **3** to 255.6 g (1.80 mol) of ethyl trifluoroacetate was carried out with external cooling, and the resulting mixture was stirred overnight at 25°. Evaporation of volatiles left 202.4 g (99%) of **2**, mp 42–44°. A sample volatilized onto a cold finger at 120–130° (1 μ) was analyzed.

Anal. Calcd for $C_{10}H_{14}F_6N_2O_4$: C, 35.31; H, 4.16; F, 33.51; N, 8.24. Found: C, 35.49; H, 4.24; F, 33.45; N, 8.23.

A solution of 68.0 g (0.20 mol) of **2** in 200 ml of dry dimethylformamide was added dropwise to a stirred suspension of 19.2 g (0.40 mol) of 50% sodium hydride in 600 ml of dimethylformamide. Then 91.7 g (0.20 mol) of 1,8-ditosyloxy-3,6-dioxaoctane[11] was added, and the mixture was heated at 100° for 16 hr. After removal of dimethylformamide, the crude product was hydrolyzed by refluxing with aqueous NaOH for 3 hr. Concentration, continuous extraction of the residue with ether, and volatilization of the extracted product at 110° (5 μ) gave 1.48 g (3%) of **1**,[10] identified by analysis and by comparison of the nmr spectrum with that of an authentic sample.

Anal. Calcd for $C_{12}H_{26}N_2O_4$: C, 54.93; H, 10.01; N, 10.68. Found: C, 55.40; H, 10.10; N, 10.40.

6,9-Dioxa-3,12-diazatetradecane-1,14-diol (4). Two kilograms (33 mol) of ethanolamine and 374 g (2.0 mol) of 1,8-dichloro-3,6-dioxaoctane were stirred and heated at 130° for 1 day. The mixture was cooled, 163 g (4.0 mol) of NaOH pellets was added, and the mixture was then heated at 100° with stirring for 30 min. Most of the ethanolamine was then stripped off, 500 ml of tetrahydrofuran was added, and the mixture was filtered. Evaporation of the filtrate to 80° (0.5 mm) gave concentrated product **4** which was recrystallized from 1 l. of cold tetrahydrofuran to give 432.3 g (92%) of **4** as an extremely hygroscopic solid, mp 49–55°. An analytical sample was obtained by two recrystallizations from tetrahydrofuran: mp 53.5–55°; nmr [$(CD_3)_2CO$] 3.7–3.4 (m with major peak at 3.59, 3, OCH_2), 3.23 (broad, OH + NH), and 2.85–2.6 ppm (m, 2, NCH_2). Addition of D_2O moved the active H peak to 4.17 ppm (s, 1, OH + NH).

Anal. Calcd for $C_{10}H_{24}N_2O_4$: C, 50.83; H, 10.24; N, 11.86. Found: C, 51.22; H, 10.15; N, 11.67.

6-Oxa-3,9-diazaundecane-1,11-diol (5). To 611 g (10.0 mol) of ethanolamine stirred in an ice bath was added in batches 763 g (4.0 mol) of *p*-toluenesulfonyl chloride at a rate sufficient to maintain a temperature of 25–30°. After addition was complete, the ice bath was removed and an exotherm was allowed to carry the temperature to 80°. The homogeneous mixture was stirred for 1 hr and allowed to stand overnight. The resulting mixture was warmed to dissolve salts and sitrred into 4 l. of water. The oily layer was extracted with a mixture of 2 l. of water and 50 ml of concentrated HCl, the aqueous layer was extracted with 200 ml of ether, and the organic layers were combined, diluted with ether, dried over anhydrous Na_2SO_4, filtered, and evaporated to give 497.9 g (58%) of *N*-(2-hydroxyethyl)-*p*-toluenesulfonamide, mp 55–57°.[12]

A mixture of 107.5 g (0.50 mol) of the above product and 500 ml of purified dimethylformamide was treated with 58 g (0.52 mol) of potassium *tert*-butoxide with stirring and cooling to keep the temperature below 40°. The mixture was stirred overnight and then to it was added 35.8 g (0.25 mol) of bis(chloroethyl) ether. The reaction mixture was stirred and heated at 100–105° for 1 day, cooled, and poured into 2.5 l. of water. The resulting mixture was stirred until the oil crystallized, then triturated thoroughly and filtered. The dried solid **6**, mp 90.5–91.5°, weighed 104.1 g (83%).

A sample was recrystallized twice from tetrahydrofuran–ether for analysis: mp 91.5–92.5°; ir (KBr) 2.95 and 3.00 (OH), 3.26 (unsaturated CH), 3.41 and 3.47 (saturated CH), 6.26, 6.69, and 6.73 (aromatic C=C), 7.46 and 8.61 (NSO_2), and 9 μ (broad, COC, COH); ^{1}H nmr [$(CD_3)_2SO$] main bands of AA'BB' at 470, 461, 450, and 441 Hz (4, aromatic CH) and 4.73 (t, J_{HH} = 5 Hz, 1, OH), 3.7–3.1 (m, 8, OCH_2CH_2N), and 2.40 ppm (s, 3, CH_3).

Anal. Calcd for $C_{22}H_{32}N_2O_7S_2$: C, 52.78; H, 6.44; N, 5.60; S, 12.81. Found: C, 52.55; H, 6.61; N, 5.53; S, 12.92.

The tosyl groups were removed from **6** by a reductive procedure adapted from that reported in ref 7.

Benzene (400 ml) and 50.1 g (0.10 mol) of **6** were stirred under nitrogen while 288 g (~1.0 mol) of 70% sodium bis(2-methoxyethoxy)aluminum hydride in benzene was added dropwise. The mixture was refluxed for 1 day, and 300 ml of water and then 100 ml (1.0 mol) of concentrated HCl were added. The mixture was stirred for 1 hr and filtered through Celite, and the filter cake was washed with 600 ml of water. The combined washings and filtrate were acidified with 25 ml of concentrated HCl and the benzene layer was removed. The aqueous layer was extracted twice with 250 ml of ether, then basified with 12.0 g (0.30 mol) of sodium hydroxide, evaporated to low volume, treated with 25 g of anhydrous Na_2CO_3, and evaporated to 50° (0.5 mm). The residue was stirred well with 300 ml of absolute ethanol and filtered, and the filter cake was extracted with 150 ml of absolute ethanol. The filtrate was evaporated to give 25 g of viscous oil which was distilled in a molecular still to give 12.0 g (62%) of 6-oxa-3,9-diazaundecane-1,11-diol (**5**), bp 127–130° (0.3 μ), n^{25}D 1.4891. On standing, crystals, mp 41.5–43°, formed slowly: ir (neat) 3.03 (broad, OH, NH), 8.7–9.6 μ (COC, COH); ^{1}H nmr [$(CD_3)_2CO$] 3.51, 3.42, and 3.33 (skewed t, 2, OCH_2), 3.11 (s, broad and shifted to lower field by D_2O, 1, OH + NH), and 2.73, 2.64, 2.55, and 2.46 ppm (skewed q, 2, NCH_2).

Anal. Calcd for $C_8H_{20}N_2O_3$: C, 49.98; H, 10.49; N, 14.57. Found: C, 50.56; H, 9.99; N, 14.40.

Registry No.—**1**, 23978-55-4; **2**, 50977-91-8; **3**, 929-59-9; **4**, 50977-92-9; **5**, 50977-93-0; **6**, 50977-94-1; *N*-*n*-butyltrifluoroacetamide, 400-59-9; di-*n*-butylamine, 111-92-2; ethyl trifluoroacetate, 383-63-1; *n*-butylamine, 109-73-9; *N*,*N*-di-*n*-butyltrifluoroacetamide, 313-32-6; 1,8-dichloro-3,6-dioxaoctane, 112-26-5; 3,6,12,15-tetraoxa-9-azaheptadecane-1,17-diamine, 50977-95-2; 1,8-ditosyloxy-3,6-dioxaoctane, 19249-03-7; *p*-toluenesulfonyl chloride, 98-59-9; *N*-(2-hydroxyethyl)-*p*-toluenesulfonamide, 14316-14-4.

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A New Method for Deamination of Naphthylamines[1]

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The Schwechten reaction[3] consists in the heating of a complex of an aromatic diazonium salt and mercuric bromide, **1**, to yield an aryl bromide, **2** (eq 1). These water-insoluble salts are formed by treating solutions of aryldiazonium salts with mercuric bromide. The yields of salts **1** are generally very high but the yields of **2** are not over 70%.[4]

$$\underset{\mathbf{1}}{(ArN_2^+)_2HgBr_4^{2-}} \xrightarrow{\Delta} \underset{\mathbf{2}}{2ArBr} + 2N_2 + HgBr_2 \qquad (1)$$

We sought a solvent for the salts in the hope that the decomposition to aryl bromides might be facilitated by the use of powdered glass. Because of successes in the use of a finely divided solid (powdered glass is only one of many solids that have been used) in the MacFadyen–Stevens reaction[5] and Pesci reaction,[6] we routinely examine the effect of added solids in reactions in which a gas is produced. When a solution of the salt formed from 7-chloro-1-naphthylamine was dissolved in hexamethylphosphoric triamide (HMPA), the evolution of nitrogen commenced at room temperature and was complete in about 20 min. If powdered glass was admixed the decomposition time was about 10 min. Surprisingly, however, the product was not the desired 7-chloro-1-bromonaphthalene but the deaminated product, 2-chloronaphthalene. Accordingly, our study was extended to other solvents and to other salts **1**.

Although the salts **1** were moderately soluble in pyridine, dimethyl sulfoxide (DMSO), and *N*-methylpyrrolidone (NMP) and gas was evolved (but not quantitatively), the products were not produced in as high a yield as in the case of HMPA and the yields of monomeric substances were poor. Accordingly, only the reactions in HMPA were studied further. The results obtained are listed in Table I and the experimental details are discussed in the Experimental Section. In all cases the main compound obtained was the product in which the diazonium grouping had been replaced by hydrogen. Only trace amounts of substituted naphthyl bromides were formed. The only source for the hydrogen which replaces the diazonium grouping is the *N*-methyl group, but no attempts were made to characterize the decomposition products of the solvent, HMPA.

Thus, a new method can be added to other methods which have been used for deamination.[7-11] The new method may be advantageous for the following two reasons: (1) after diazotization in aqueous acid the diazonium compound may easily be isolated as a water-insoluble complex by treatment with mercuric bromide (the complex may be collected rapidly and washed with acetone to yield a readily dried salt), and (2) the reaction with HMPA can be completed in 10–20 min at room temperature. The yields of products were about the same whether powdered glass was used or not. In all of the reported experiments powdered glass was used.

Since the decomposition of arenediazonium hexafluorophosphates in tetramethylurea at 20–65° has been reported to result in deamination,[9] we dissolved *p*-toluenediazonium hexafluorophosphate in HMPA. There was an immediate exothermic reaction with evolution of nitrogen to yield 62% of toluene. Since this yield is greater than that reported when tetramethylurea was used (25–30%)[9,12] we conclude that HMPA is probably preferable to other solvents for deamination of diazonium hexafluorophosphates.

Table I
Formation and Decomposition of Arenediazonium Mercuric Bromide Complexes

1-Aminonaphthalene substituent[a]	Registry no.	Mp[b] of $[ArN_2^+]_2$-$HgBr_4^{2-}$	Registry no.	Naphthalene yield,[c] %
None	134-32-7	104	50986-52-2	70
4-Bromo	2298-07-9	127	50986-53-3	77
5-Bromo	4766-33-0	140	50986-54-4	76
7-Chloro	50987-58-1	117	50986-56-6	93
7-Methyl	6939-34-0	101	50986-58-8	72
2-Aminonaphthalene	91-59-8	103	50986-59-9	94
Ethyl anthranilate	87-25-2	114	50986-60-2	71[d]

[a] The amines were diazotized and treated with mercuric bromide as described.[3] In all cases the yield of dried complex salt, **2**, was 92–99%. [b] The melting point recorded is really a decomposition point and varies with the rate of heating. [c] The yields represent isolated compounds which were at least 95% pure by glpc. The small impurity was the corresponding compound in which bromine had replaced the amino group. [d] The product was diethyl diphenate.

Experimental Section

Preparation of Arenediazonium Bromide–Mercuric Bromide Complexes. These complexes were prepared essentially as described. The precipitated complexes were washed with water and acetone and were air dried. The yields and melting points (decomposition) are listed in Table I.

Decomposition of Arenediazonium Mercuric Bromide Complexes. In a typical experiment 0.01 mol of dried complex **1** was added through a wide rubber tubing to a flask containing 35 ml of HMPA and 2 g of powdered soft glass stirred magnetically at room temperature. The theoretical amount of nitrogen was usually evolved within 10 min and the temperature rose to 40–45°. The reaction mixture was filtered and the filtrate was diluted with water. The ether extract of the reaction products was washed with water, dilute acid, and dilute alkali. After drying by passage through anhydrous $MgSO_4$, the ether was distilled and the residue was vacuum distilled to yield naphthalene or the substituted (deaminated) naphthalene. All products were identified by comparison with authentic samples. In each a purity of greater than 95% was indicated by glpc of the entire distillate before purification. The glpc analyses were performed on an Aerograph Autoprep A-700 model gas chromatograph using a 10 ft × 0.25 in. column packed with 30% silicone gum rubber SE-30 on 45–60 mesh Chromosorb W.

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Synthesis of Spiro[4.6]undecane-1,6-dione

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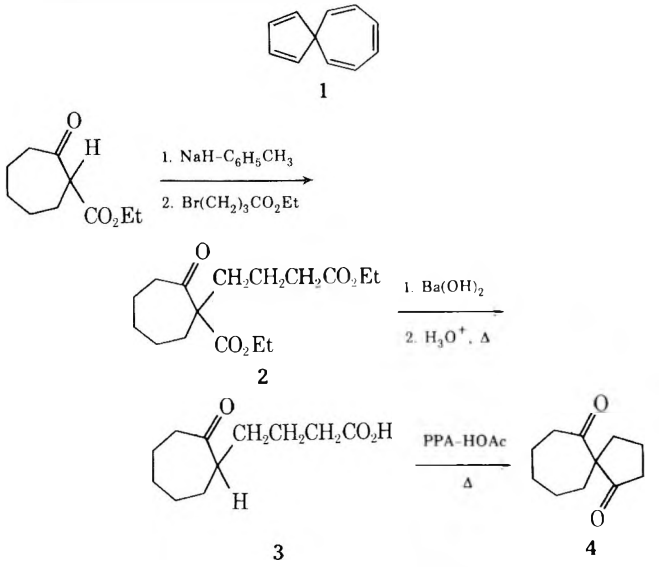
As a part of our long-range objective of exploring the chemistry of spirarenes,[2,3] we have undertaken the synthesis of spiro[4.6]undeca-1,3,6,8,10-pentaene (1). An attractive precursor in the synthesis of 1 is the previously unknown spiro[4.6]undecane-1,6-dione (4). We now wish to report the synthesis of 4, prepared as shown, *via* an acid-catalyzed intramolecular Claisen condensation of 4-(2′-oxocycloheptyl)butyric acid (3).



The acid-catalyzed intramolecular Claisen condensation represents a reaction type which only recently has been exploited as a means of synthesizing in moderate to high yields nonenolizable β-diketones.[4] Our procedure is an extension of the work of Gerlach and Müller, who have reported[5,6] that 4-(2′-oxocyclopentyl)butyric acid undergoes cyclization with polyphosphoric acid–acetic acid solution to give an 85% yield of spiro[4.4]nonane-1,6-dione. The lower yield in the synthesis of 4 (52%) as compared to that of spiro[4.4]nonane-1,6-dione is presumably due to the higher strain energy of the former.

The structure of the spiro ketone 4 was confirmed by physical methods. The infrared spectrum of 4 showed $\bar{\nu}_{max}$ at 1735 and 1695 cm^{-1} due to the carbonyl stretching frequency of cyclopentanone and cycloheptanone rings, respectively. The nmr, uv, mass spectrum, and composition analysis are all consistent with the structure proposed for 4.

The acid-catalyzed intramolecular Claisen condensation described here offers a facile method for the synthesis of spirocyclic 1,3-diketones. Furthermore, this method should be general and provide an alternate synthetic route to spiro molecules in which at least one of the rings is a five- or six-membered ring.

Experimental Section[7]

Preparation of Diethyl 4-(1′-Carbethoxy-2′-oxocycloheptyl)-butyrate (2).[8] The keto diester 2 was prepared by the general procedure of Huisgen and Pawallek.[8] A 56% yield of 2 was obtained as a clear oil: bp 133–137° (0.10 mm) [lit.[8] bp 110–115° (0.01 mm)]; ir (CCl_4) 1730 (ester C=O), 1700 (cycloheptanone C=O), 1175 cm^{-1}; nmr (CCl_4) δ 1.40 (6 H, six lines), 1.40–2.20 (m, 12 H), 2.20–2.90 (m, 4 H), 4.30 (m, 4 H).

Preparation of 4-(2′-Oxocycloheptyl)butyric Acid (3).[9] The keto acid 3 was obtained by the procedure of Kimeki and Bien.[9] An 84% yield of 3 was obtained as a clear oil: bp 142–145° (0.15 mm) [lit.[9] bp 138–140° (0.01 mm)]; ir (CCl_4) 3400–3000 and 2700–2400 (OH), 1700 (C=O), 935 cm^{-1}; nmr ($CDCL_3$) δ 2.1–1.0 (m, 12 H), 2.9–2.1 (m, 3 H), 11.26 (s, 1 H).

Preparation of Spiro[4.6]undecane-1,6-dione (4). To a stirred solution of 34.1 g (0.10 mol) of polyphosphoric acid[10] and 65.0 g (1.08 mol) of purified glacial acetic acid[11] under N_2 was added (dropwise) 10.0 g (0.051 mol) of 3. The reaction mixture was heated for 6 hr at 100° in an oil bath, cooled, poured onto ice, and extracted with benzene (3 × 100 ml). The combined benzene extracts were washed with saturated $NaHCO_3$ (3 × 100 ml) and dried ($MgSO_4$), and the benzene was removed. Vacuum distillation of the residue gave 4.75 g (52%) of 4 as a clear, colorless oil: bp 101–103° (1.25 mm); ir (CCl_4) 1735 (cyclopentanone C=O), 1695 (cycloheptanone C=O), 1145 cm^{-1}; uv (95% ethanol) λ_{max} 303 nm (ε 127); nmr (CCl_4) δ 2.90–1.0 (m); mass spectrum (70 eV) *m/e* (rel intensity) 180 (23, M^+), 152 (16), 135 (16), 125 (25), 124 (17), 123 (25), 110 (17), 97 (24), 96 (31), 95 (22), 81 (38), 79 (18), 69 (15), 68 (15), 67 (37), 57 (28), 55 (88), 54 (17), 53 (17), 43 (100), 39 (39).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.45; H, 8.75.

Acknowledgment. We gratefully acknowledge the support of this work by the donors of the Petroleum Research Fund, administered by the American Chemical Society, and thank Dr. George Hertel of Florida Technological University for providing the mass spectra.

Registry No.—2, 50987-56-9; 3, 33366-38-0; 4, 50987-57-0.

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(7) Ir spectra were recorded with a Perkin-Elmer Model 457 spectrometer. Ultraviolet spectra were determined in 95% ethanol with a Beckman DK-2A spectrometer. Nmr spectra were obtained with a Varian T-60 spectrometer using TMS as an internal standard. The mass spectra were obtained at an ionizing energy of 70 eV on a magnetic sector mass spectrometer with a modified Nier-type source. This mass spectrometer was constructed by Dr. George Hertel of Florida Technological University. Microanalyses were performed by Robertson Laboratory, Florham Park, N. J.
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Utilization of the 1,4-Conjugated Wittig Reaction for the Synthesis of Substituted 1,3-Cyclohexadienes

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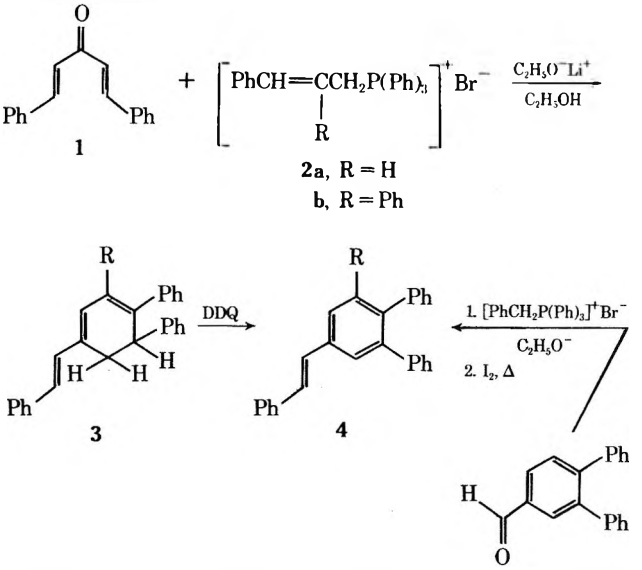
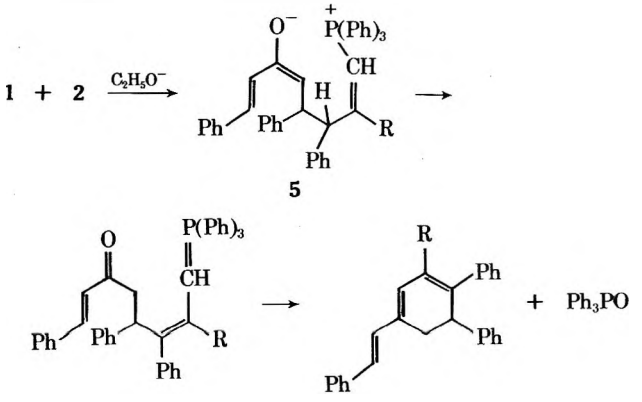
Despite the enormous success of the Wittig reaction for the preparation of olefins,[1-4] this method does have certain limitations. One complication is that the alkylidenephosphorane can function as a proton acceptor and promote enolate condensation reactions.[1] Another side reaction that occasionally occurs in the 1,4 addition of the alkylidenephosphorane to the β-carbon atom of a conjugate ketone.[5] We now report a study which shows that the Michael addition of certain alkylidenephosphoranes with α,β-unsaturated ketones can be advantageously utilized for the synthesis of substituted 1,3-cyclohexadienes.

Treatment of an ethanolic solution of *trans,trans*-1,5-diphenylpentadien-3-one (**1**) and *trans*-cinnamylphosphonium bromide (**2a**) with lithium ethoxide for 12 hr at room temperature afforded (*E*)-1-(4,5-diphenyl-1,3-cyclohexadien-1-yl)-2-phenylethylene (**3a**), mp 161–163°, in good yield. The structure assigned to cyclohexadiene **3a** rests on its spectral data and chemical behavior. Oxidation of **3a** with dichlorodicyanoquinone (DDQ) afforded (*E*)-1-(4,5-diphenylbenzen-1-yl)-2-phenylethylene (**4a**). The structure of compound **4a** was unambiguously established by an independent synthesis which utilized the Wittig reaction of 3,4-diphenylbenzaldehyde and triphenylbenzylphosphonium bromide. A similar set of products were obtained when **1** was treated with triphenyl-*trans*-2,3-diphenylallylphosphonium bromide (**2b**) in the presence of lithium ethoxide.



The above reactions can best be described as involving a Michael addition of the organophosphorane derived from **2** with *trans,trans*-1,5-diphenylpentadien-3-one to give intermediate **5**. A subsequent proton transfer, ketonization, and intramolecular Wittig cyclization nicely rationalize the observed products. After the completion of this work, several reports appeared describing a related set of 1,4-conjugated Wittig reactions.[6-9]



Experimental Section

All melting points are corrected and boiling points are uncorrected. Elemental analyses were performed by Scandinavian Microanalytical Laboratory, Herlev, Denmark, and Alfred Bernhardt Laboratories, Hohenweg, Germany. The infrared absorption spectra were determined on a Perkin-Elmer infracord spectrophotometer, Model 137. The ultraviolet absorption spectra were measured with a Cary recording spectrophotometer, using 1-cm matched cells. The nuclear magnetic resonance spectra at 60 MHz were determined with the Varian Associates high-resolution spectrometer and at 100 MHz using a Jeolco MH-100 spectrometer.

(*E*)-1-(4,5-Diphenyl-1,3-cyclohexadien-1-yl)-2-phenylethylene (**3a**). A solution of lithium ethoxide (prepared by dissolving 0.4 g of lithium wire in 25 ml of absolute ethanol) was added to a stirred slurry of *trans,trans*-1,5-diphenylpentadien-3-one (5 g) and *trans*-cinnamylphosphonium bromide (9.8 g). The resulting mixture was allowed to stir at room temperature overnight. The precipitate that formed was collected by filtration and recrystallized from ethanol to give 3.6 g (45%) of (*E*)-1-(4,5-diphenyl-1,3-cyclohexadien-1-yl)-2-phenylethylene (**3a**): mp 161–163°; ir (KBr) 6.23, 6.7, 6.9, 9.28, 9.70, 10.48, 11.68, 12.18, 12.95, 13.3, 13.9, 14.25, and 14.5 μ; uv (cyclohexane) 372 nm (ϵ 34,280), 266 (4850). and 233 (9860); nmr ($CDCl_3$) τ 7.01 (m, 2 H), 5.85 (dd, 1 H, J = 8.0 and 4.0 Hz), 3.6 (broad d, 1 H, J = 7.0 Hz), 3.28 (d, 1 H, J = 16.0 Hz), 3.02 (d, 1 H, J = 6 Hz), 2.98 (d, 1 H, J = 16.0 Hz), and 2.2–2.8 (m, 15 H); m/e 334 (M^+).

Anal. Calcd for $C_{26}H_{22}$: C, 93.37; H, 6.63. Found: C, 93.02; H, 6.59.

The structure of the above product was verified by oxidation to (*E*)-1-(4,5-diphenylbenzen-1-yl)-2-phenylethylene (**4a**).

Oxidation of (*E*)-1-(4,5-Diphenyl-1,3-cyclohexadien-1-yl)-2-phenylethylene. A solution containing 300 mg of cyclohexadiene **3a** and 250 mg of dichlorodicyanoquinone in 50 ml of toluene was heated at reflux for 30 hr. The solution was evaporated to dryness and the brown residue was chromatographed through a Florisil column using benzene as the eluent. The benzene fractions were concentrated under reduced pressure to afford (*E*)-1-(4,5-diphenylbenzen-1-yl)-2-phenylethylene (**4a**, 203 mg, 66%): mp 121–123°; ir (KBr) 6.2, 6.75, 6.9, 9.25, 10.25, 10.95, 12.05, 12.8, 13.0, 13.2, 13.55, and 14.45 μ; nmr ($CDCl_3$) τ 2.0–3.0 (m, aromatic and vinyl); uv (cyclohexane) 315 and 230 nm (ϵ 38,980 and 21,930); m/e (parent) 332.

Anal. Calcd for $C_{26}H_{20}$: C, 93.94; H, 6.06. Found: C, 93.82; H, 6.09.

(*E*)-1-(4,5-Diphenylbenzen-1-yl)-2-phenylethylene was also independently synthesized by treating 3,4-diphenylbenzaldhyde with triphenylbenzylphosphonium bromide. The desired 3,4-diphenylbenzaldehyde was prepared from 1-carbomethoxy-4,5-diphenylcyclohexa-1,4-diene.[10]

(*E*)-1-(3,4,5-Triphenyl-1,3-cyclohexadien-1-yl)-2-phenylethylene (3b). A solution of lithium ethoxide (prepared by dissolving 0.4 g of lithium wire in 25 ml of absolute ethanol) was added to a stirred slurry of benzalacetone (4.4 g) and triphenyl-*cis*-2,3-diphenylallylphosphonium bromide (10.1 g). The resulting mixture was allowed to stir at room temperature for 12 hr. The precipitate that formed was collected by filtration and recrystallized from ethanol to give 3.7 g (51%) of (*E*)-1-(3,4,5-triphenyl-1,3-cyclohexadien-1-yl)-2-phenylethylene (**3b**): mp 151–153°; ir (KBr) 6.23, 6.7, 6.92, 9.33, 9.68, 10.41, 11.36, 11.92, 12.25, 13.0, 13.3, 13.9, 14.3, and 14.5 μ; nmr ($CDCl_3$) τ 6.8–7.1 (ddd, 2 H, J = 4.0, 8.0, and 18.0 Hz), 5.9 (dd, 1 H, J = 4.0 and 8.0 Hz), 3.1–3.6 (m, 3 H, vinyl), and 2.4–3.0 (m, 20 H, aromatic); uv (cyclohexane) 371, 283 and 238 nm (ϵ 36,850, 18,200, and 19,860); m/e (parent) 4.10.

Anal. Calcd for $C_{32}H_{26}$: C, 93.62; H, 6.58. Found: C, 93.21; H, 6.51.

A mixture containing 300 mg of compound **3b** and 300 mg of dichlorodicyanoquinone was heated in 50 ml of toluene for 29 hr. The solvent was evaporated under reduced pressure and the residue was chromatographed through a Florisil column using benzene as the eluent. The combined benzene fractions were evaporated under reduced pressure and the residue was taken up in hot ethanol. Upon standing at room temperature, 170 mg (60%) of (*E*)-1-(3,4,5-triphenylbenzen-1-yl)-2-phenylethylene (**4b**) precipitated: mp 201–203°; ir (KBr) 6.2, 6.68, 6.9, 7.08, 9.25, 10.37, 11.17, 12,88, 13.05, 13.25, and 13.4 μ; nmr ($CDCl_3$) τ 2.3–3.1 (m, vinyl and aromatic); uv (cyclohexane) 316 and 258 nm (ϵ 39,450 and 29,900); m/e (parent) 408.

Anal. Calcd for $C_{32}H_{24}$: C, 94.08; H, 5.92. Found: C, 93.99; H, 6.08.

Acknowledgment. We are grateful to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for financial support. The National Science Foundation provided financial assistance in the purchase of the nmr spectrometer used in this research.

Registry No.—**1**, 35225-79-7; **2a**, 38633-40-8; **2b**, 51003-89-5; **3a**, 51003-12-4; **3b**, 51003-13-5; **4a**, 51003-14-6; **4b**, 51002-94-9; benzalacetone, 122-57-6.

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Reductions of Benzyl and Cyclohexyl Chloroformates with Tri-*n*-butyltin Hydride

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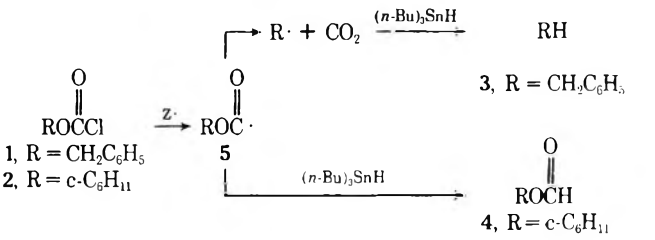
The lowering of transition-state energy provided by the generation of carbon dioxide in conjunction with the formation of carbonium ions and silver chloride in the reactions of chloroformates with silver ion[1] suggests that the same driving force might be available to promote the conversion of chloroformates to a formal chlorine atom, carbon dioxide, and a carbon radical. If the carbon radical could be reduced by a hydrogen-atom donor, such a process would be of synthetic value as part of a route for the deoxidation of alcohols alternative to other procedures.[2] In fact, Kuivila and Walsh have reported that benzyl chloroformate is reduced by tri-*n*-butyltin hydride to a 4:6 ratio of toluene and benzyl formate and that ethyl chloroformate gives solely ethyl formate under similar conditions.[3] It has been noted by a number of workers that the alkoxycarbonyl radical, an intermediate in the tri-*n*-butyltin hydride reduction,[4] while thermodynamically disposed to fragment to carbon dioxide and a carbon radical,[5] does have an appreciable activation energy toward such decomposition.

When the reaction of benzyl chloroformate (**1**) with tri-*n*-butyltin hydride and azobisisobutyronitrile (AIBN) as initiator is carried out for 22 hr in hexane at 36° at concentrations of less than 0.3 *M* in each reactant, the sole product is toleune (**3**) in 22% yield and less than 1% benzyl formate. Increase in the concentration of the hydride, however, leads to increasing amounts of benzyl formate at the expense of toluene. Reduction of benzyl chloride to toluene under the same conditions is *ca.* 1.6 times faster than the reduction of **1**. However, no significant conversion of benzyl chloroformate to benzyl chloride occurs in the absence of the other reactants, and a methanol quench of a partial reaction showed an upper limit of 4% benzyl chloride present after a reaction of 13 hr.

Reaction of cyclohexyl chloroformate (**2**) under conditions similar to those which gave toluene from benzyl chloroformate produced only cyclohexyl formate (**4**) and less than 1% cyclohexane. Greater dilutions did not produce cyclohexane.

Rationalization of these results in terms of the alkoxycarbonyl radical **5** is consistent with previous studies which suggest that the rate of fragmentation of **5** is dependent on the stability of the radical formed.[3-6] The reciprocal relationship of toluene and benzyl formate as a function of hydride concentration suggests that fragmentation and reduction of the benzyloxycarbonyl radical can be competitive under these conditions. Apparently the stability of the benzyl radical is sufficiently influential to foster fragmentation, whereas a stabilized radical would not be produced by loss of carbon dioxide from cyclohexyloxycarbonyl radical, and it survives to be reduced. A related result and similar rationale have been reported for the conversions of benzyl and *n*-octyl formate to toluene and *n*-octyl alcohol, respectively, with palladium.[7] Con-



version of the chloroformate function to a hydrocarbon may be of some specialized synthetic value for cases in which the intermediate radical is stabilized, although the present procedure would involve product isolation by gas chromatography. The formation of cyclohexyl formate from cyclohexyl chloroformate does suggest, however, that unless a stabilized radical is possible the present procedure does not offer an attractive general route for the deoxidation of alcohols by the reduction of chloroformates.

Numerous attempts were made to convert cyclohexyl chloroformate to cyclohexane by reduction with lithium aluminum hydride–aluminum chloride or triethylsilane and by photolysis with tri-*n*-butyltin hydride, triphenylsilane, and triethylsilane. In no case was a glpc peak corresponding to more than 5% cyclohexane observed. Attempted reductions of cyclohexyl chlorosulfite and cyclohexyl chloroglyoxylate with tri-*n*-butyltin hydride were also unsuccessful and gave destruction of starting material in exothermic reactions, but cyclohexane could not be detected.

Experimental Section

All reactions were run in a dry nitrogen atmosphere. Gas chromatography was performed on an Aerograph A90-P3, with a 3- or 10-ft column packed with 20% XF 1150 on 60/80 acid-washed, DMCS-treated Chromosorb P. Benzyl[8] and cyclohexyl[9] chloroformates and cyclohexyl chloroglyoxalate[10] were prepared by reaction of the purified alcohols with phosgene or oxalyl chloride and gave satisfactory C, H, and Cl microanalyses. Cyclohexyl chlorosulfinate[11] was prepared by reaction of cyclohexanol with thionyl chloride and by reaction of dicyclohexyl sulfite with thionyl chloride[12] and was characterized by ir and nmr spectroscopy. Tri-*n*-butyltin hydride was prepared by lithium aluminum hydride reduction of the chloride[13] and its purity was determined as >96% by refractive index, reduction of benzyl chloride, and titration.[14]

Reaction of Benzyl Chloroformate with Tri-*n*-butyltin Hydride. Reaction of benzyl chloroformate (52.6 mg, 0.308 mmol), tri-*n*-butyltin hydride (83.9 mg, 0.88 mmol), and azobisisobutyronitrile (AIBN, 1.5 mg, 0.01 mmol) in hexane (1.00 ml) with stirring for 22 hr at 36° showed 22% yield of toluene and less than 1% benzyl formate. AIBN initiator increased the rate of reaction. Increase in metal hydride or decrease in solvent quantity increased the percentage of benzyl formate formed at the expense of toluene; a reaction twice as concentrated as that described above gave a toluene:benzyl formate ratio of 24:1, while a reaction six times as concentrated produced the same products in a ratio of 2.3:1. Benzene or ether solvent did not appreciably change the rate of reaction but gave somewhat lower toluene yields. In no instance was a significant amount of benzyl alcohol formed. Toluene and benzyl formate were identified by collection from the gas chromatograph and comparison of infrared spectra with those of authentic samples.

Since benzyl chloride was found to reduce to toluene under conditions similar to those under which benzyl chloroformate is reduced, a control experiment was carried out by quenching the reaction with methanol after 13 hr. Benzyl chloroformate reacts

with methanol to give benzyl methyl carbonate; benzyl chloride does not react with methanol under these reaction conditions. The carbonate/(carbonate + chloride) ratio exceeded 96%.

Acknowledgment. We wish to thank the National Institutes of Health (General Medicine) for support of this work and the National Science Foundation for fellowship support.

Registry No.—**1**, 1885-14-9; **2**, 13248-54-9; **3**, 108-88-3; **4**, 4351-54-6; $(n\text{-Bu})_3SnH$, 688-73-3.

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Carbon-13 Nuclear Magnetic Resonance Spectral Analysis Using Spin-Lattice Relaxation Data and Specific Deuteration. Thiamine Hydrochloride

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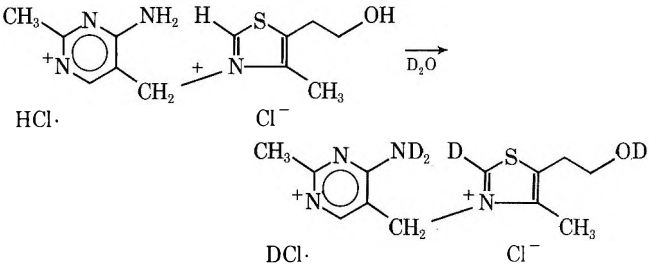
Carbon-13 spin-lattice relaxation data (the spin-lattice relaxation time, T_1, and nuclear Overhauser effect, NOE) can be useful parameters for organic spectral analysis.[2] In particular, ^{13}C–^{1}H dipolar T_1's (which account for ^{13}C relaxation in large organic molecules) can indicate the degree of proton substitution for each carbon in the molecule.[1b] ^{13}C T_1's for nonprotonated carbons in these molecules may also facilitate spectral assignments, since the efficiency of the dipolar relaxation mechanism for a given carbon depends strongly on the intermolecular distances between the carbon and nearby protons.[2c,d]

The sensitivity of T_1^{DD} (the dipolar T_1) to internuclear distances can be exploited in another way. When a carbon bearing protons is selectively deuterated, the ^{13}C T_1 for that carbon increases because the deuterium nucleus has a smaller magnetic moment than the proton. If all attached protons are replaced by deuterium nuclei, then T_1^{DD} for that carbon will increase by *ca.* tenfold (combining much less efficient ^{13}C–^{2}H dipolar relaxation with ^{13}C–^{1}H dipolar relaxation from nearby nonbonded protons). The effect of deuteration can also be seen on T_1^{DD} for nearby *nonprotonated carbons,* which depend on nonbonded protons for their relaxation.

The ^{13}C nmr spectrum of vitamin B_1, thiamine hydrochloride, has been published[3] but many of the assignments were listed as tentative. We report here a ^{13}C nmr spectral study of this compound. Most of the present resonance assignments were made by use of model compounds and standard chemical shift correlations.[4] However several lines could not be assigned on that basis.

^{13}C chemical shift and spin-lattice relaxation data for thiamine hydrochloride are given in Table I. Also in Table I are T_1 data for the partially deuterated compound separately prepared and redissolved in CD_3OD–D_2O. The exchange reaction results in pentadeuteration of the ion pair

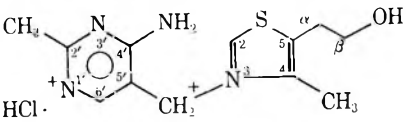


complex as shown (the "unusual" deuteration at C-2 is well known[5]).

A methanol–water solvent system was used in this work because a small solvent effect resulted in better separation of the closely spaced peaks corresponding to C-2′ and C-4′. Assignment of these closely spaced nonprotonated carbon resonances by conventional methods is not possible. Even the C-2′ and C-4′ T_1's (in the nondeuterated compound) do not distinguish between the two signals based on distances to nearby protons. Deuteration of the amino group in the exchange reaction affords definitive assignments, however. T_1^{DD} for the C-4′ carbon (α to the ND_2 group) increases by *ca.* 300% (see Table I) while the increase in T_1 for C-2′ is three times smaller. For the remaining carbons in the partially deuterated compound, smaller changes in T_1^{DD} can be noted (however, note that ΔT_1 is subject to considerable error since it is a difference between two derived quantities.).

The significant positive ΔT_1 value for C-4 is interesting, but as yet we have no certain explanation for this. We also have no explanation for the substantial negative ΔT_1 values observed for the two CH_3 carbons. Possibilities for the former effect include conformational considerations such as molecular stacking; the latter effect might indicate a reduced rate of CH_3 group rotation in the deuterated medium. Other, more easily interpreted molecular dynamics effects are indicated from the data in Table I. For example, T_1's for the 2′-CH_3 and 4-CH_3 carbons indicate that both CH_3 groups are spinning rapidly. The 5-α and 5-β CH_2 carbons and also the ring-bridging CH_2 group undergo some group segmental motion.[2c]

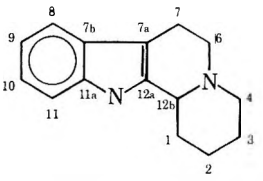
Table I
^{13}C Nmr Data for Thiamine Hydrochloride[a]



	Chemical shift[b]	CH_3OH–H_2O[c] T_1	NOE	T_1^{DD}[e]	CD_3OD–D_2O[c] T_1	NOE	T_1^{DD}[e]	ΔT_1^{DD}, %[d]
			Pyrimidine Ring					
C-2′	163.78	4.7	1.7	5.5	7.1	1.3	10.9	+98
C-4′	164.18	4.2	1.7	4.9	9.8	1.0	19.6	+300
C-5′	106.50	4.7	1.8	5.2	4.5	1.9	4.7	−10
C-6′	146.44	0.37	2.0	0.37	0.31	2.1	0.31	−16
2′-CH_3	21.93	1.2	2.1	1.2	0.8	1.9	0.8	−33
			Thiazole Ring					
C-2	155.28	0.30	2.0	0.30	*f*	*f*		
C-4	143.62	6.2	1.8	6.9	6.9	1.6	8.6	+25
C-5	137.30	6.4	1.9	6.7	6.4	1.9	6.7	0
5-α-CH_2	30.34	0.37	2.2	0.37	0.32	2.0	0.32	−14
5-β-CH_2	61.04	0.34	2.1	0.34	0.34	1.9	0.36	+6
4-CH_3	12.20	1.2	2.1	1.2	0.85	2.0	0.85	−29
			Bridging CH_2					
	50.96	0.28	2.0	0.28	0.24	2.0	0.24	−14

[a] 1.2 *M* in stated solvent systems, 25.2 MHz, 38 ± 3°. [b] In parts per million downfield from TMS (internal dioxane δ 67.40). [c] 1:1 methanol–water solvent (see text). Estimated errors: T_1 (sec) ±5–10%, NOE (η) ±0.1–0.2, T_1^{DD} (sec) ±10–20%. [d] $\Delta T_1^{DD} = [T_1^{DD}$ (partially deuterated) $- T_1^{DD}$ (protio)$]/T_1^{DD}$ (protio) × 100. [e] T_1^{DD} calculated from $(T_1)(1.99)/$NOE observed. Experimental NOE's are given but (physically impossible) NOE's larger than 2.0 were not used in calculations of T_1^{DD}; instead 2.0 was used in those cases. [f] Not measured.

We are using this technique to confirm ^{13}C nmr spectral assignments for other natural products. For example, in the alkaloid below, spectral assignments for the nonprotonated olefinic carbons were confirmed by deuteration at carbons 7 and 12b.[6]



Dideuteration at C-7 increased T_1 for the resonance assigned to carbon 7a by *ca.* 100% while the other nonprotonated carbon T_1's were increased by only 30–40%. Deuterium substitution at 12b lengthened the 12a carbon T_1 by 45% while not appreciably affecting the other carbons (all T_1's were predominantly dipolar).

Experimental Section

The T_1 values in Table I were obtained with an inversion-recovery pulse sequence. Both direct and indirect NOE's were obtained; the values reported in Table I are averages of several runs. Direct NOE's were measured on ^1H decoupled spectra using pulse-modulated decoupling. NOE's of 1.7–1.8 indicate minor but probably significant contributions from other relaxation mechanisms.

In the pulse-modulated $\{^1H\}$ experiments, ^{13}C pulse intervals > $\sim 4T_1$ for all carbons were used. Wideband $\{^1H\}$ decoupling (*ca.* 15 W) was gated on *only* during tha data acquisition periods (typically 0.8 sec). The nuclear Overhauser effect does not grow in during an individual free induction decay acquisition, even if T_1 is much less than 1 sec (*e.g.*, for the protonated CH and CH_2 carbons); the long delays between pulses eliminate previously generated NOE through ^{13}C–^1H relaxation processes.

Registry No.—Thiamine hydrochloride, 67-03-8.

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The Specific Introduction of an Isopropylidene Group in the Synthesis of the Monoterpene Terpinolene and the Sesquiterpene (±)-α-Curcumene

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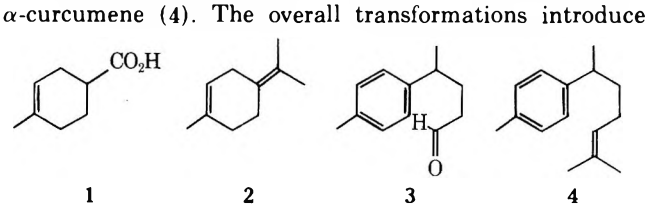
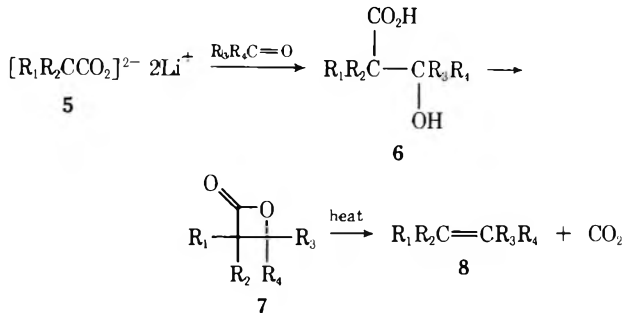
The isopropylidene group is a commonly occurring structural feature found in naturally occurring products.[2] In order to demonstrate the application of a simple procedure for the introduction of this grouping in synthetic routes to natural products, we wish to report the conversions of the carboxylic acid **1** into the monoterpene terpinolene (**2**) and the aldehyde **3** into the sesquiterpene (±)-α-curcumene (**4**). The overall transformations introduce



1 **2** **3** **4**

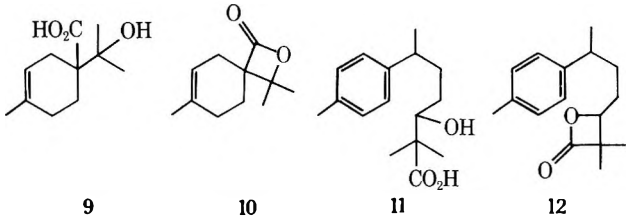
Scheme I



an isopropylidene group either (1) at a position bearing a carboxyl group or (2) at a position bearing a carbonyl group.

The steps involved in these transformations are outlined in Scheme I. Treatment of lithium salts of α-lithio carboxylic acids **5** with carbonyl substrates yields β-hydroxy acids **6**.[3] These β-hydroxy acids can be cyclized to β-lactones **7**, which on thermolysis readily lose CO_2 to yield olefins **8** with introduction of a double bond at a specific position.[4]

Terpinolene. Terpinolene (**2**) has been previously synthesized *via* a [4 + 2] cycloaddition of isoprene and dimethylallene.[5] In our synthetic route the desired carboxylic acid **1** was prepared by a Diels–Alder cycloaddition of isoprene and acrylic acid. The lithium α-lithio carboxylate salt of **1** was prepared by treatment of **1** with 2 equiv of lithium diisopropylamide in THF and this α anion was treated with acetone to yield the β-hydroxy acid **9** (65%). This acid **9** was converted to β-lactone **10** (82%) by treatment at 0° with benzenesulfonyl chloride in pyridine. Thermolysis of β-lactone **10** at 140° (3 hr) led to terpinolene (**2**, 93%).



9 **10** **11** **12**

(±)-α-Curcumene. The synthesis of (±)-α-curcumene has previously been accomplished by treatment of aldehyde **3** with isopropylidenetriphenylphosphorane.[6] Other routes to this sesquiterpene have also been reported.[7] Aldehyde **3**[8] was the starting material for the present synthesis. The lithium α-lithio carboxylate salt of isobutyric acid was generated by treatment of isobutyric acid with 2 equiv of lithium diisopropylamide. Aldehyde **3** was added to this α anion to produce the β-hydroxy acid **11** (73%). This acid was converted to β-lactone **12** (77%) by treatment with benzenesulfonyl chloride in pyridine. The β-lactone was thermally decarboxylated at 140° (3 hr) to yield the racemic sesquiterpene (±)-α-curcumene (90%).

It appears that this method should find general use for the specific introduction of double bonds in natural product syntheses. It should prove a good alternative to the Wittig reaction or some more complicated procedure for introducing an isopropylidene group.[9]

Experimental Section

All melting points are uncorrected. The ir spectra were recorded using a Perkin-Elmer 237B spectrophotometer. The nmr spectra were recorded on a JEOL MH-100 using TMS as an internal standard. Microanalyses were performed by Robertson Laboratory, Florham Park, N. J. 07932.

4-Methyl-3-cyclohexenecarboxylic Acid (1). Isoprene (2.7 g, 40 mmol) and acrylic acid (2.8 g, 40 mmol) were heated in a sealed tube at 100–110° for 24 hr. After cooling, the solid was recrystallized from hexane–chloroform to yield a white solid: mp 96–97° (lit.[10] mp 99°); ir ($CHCl_3$) 3100 and 1700 cm^{-1}; nmr ($CDCl_3$) δ 1.7 (s, 3 H, $-CH_3$), 1.8–2.4 (m, 6 H, $-CH_2-$), 2.4–2.7 (m, 1 H, $-CHCO_2H$), 5.5 (broad, 1 H, =CH–), and 11.9 ppm (s, 1 H, $-CO_2H$).

β-Hydroxy Acid 9. Lithium diisopropylamide was prepared by dissolving 2.02 g (20 mmol) of diisopropylamine in 50 ml of THF under nitrogen and adding 10.5 ml (20 mmol) of 1.9 *M* *n*-butyllithium in hexane at −40°. The mixture was stirred for 20 min below 0° and recooled to −40°, and 1.42 g (10 mmol) of **1** was added while keeping the temperature below −20°. The reaction was heated at 50° for 2 hr and again cooled to −40°, and 0.58 g (10 mmol) of acetone was added. The reaction was stirred for an additional 2 hr, poured over 100 g of ice, and extracted with 4 × 25 ml of ether. The aqueous phase was acidified with 3 *N* HCl, extracted with 4 × 25 ml of ether, and dried over $MgSO_4$, and the solvent was removed at reduced pressure. This yielded 1.3 g (65%) of a solid, fractionally recrystallized from pentane: mp 67–69°; ir ($CHCl_3$) 3450, 3100, and 1700 cm^{-1}; nmr ($CDCl_3$) δ 1.3 [s, 6 H, $(CH_3)_2COH$], 1.7 (s, 3 H, $CH_3C=$), 1.6–2.8 (m, 6 H, $-CH_2-$), 5.5 (m, 1 H, HC=C), and 8.6 ppm (broad, 2 H, –OH and $-CO_2H$). This material was not purified further.

β-Lactone 10. The crude β-hydroxy acid **9** (0.80 g, 4.0 mmol) was dissolved in 40 ml of anhydrous pyridine and cooled to −5°. To the stirred mixture 2.15 g (12.0 mmol) of $PhSO_2Cl$ was added, and the mixture was held at 0° for 18 hr, poured over 100 g of ice, and extracted with 5 × 25 ml of ether. The organic phase was washed with 2 × 50 ml of saturated $NaHCO_3$, dried over $MgSO_4$, and stripped at reduced pressure (0.5 mm to remove pyridine). This yielded 0.59 g (82%) of a solid which was recrystallized from pentane: mp 36–37°; ir (neat) 1810 cm^{-1}; nmr ($CDCl_3$) δ 1.50 and 1.53 [s, each 3 H, $(CH_3)_2CO$], 1.7 (s, 3 H, $CH_3C=$), 1.8–2.4 (m, 6 H, $-CH_2-$), and 5.4 ppm (broad, 1 H, HC=C).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.27; H, 8.78.

Terpinolene (2). The β-lactone **10** (0.4 g, 2.2 mmol) was heated at 140° for 3 hr. The resulting liquid was distilled at 100° (18 mm) to yield 0.28 g (93%) of **2**: $n^{25}D$ 1.4891; ir (neat) 2980, 2920, 1440, and 1370 cm^{-1}; nmr ($CDCl_3$) δ 1.68 (broad, 9 H, $CH_3C=$), 2.0 (m, 2 H, $-CH_2C=$), 2.3 (m, 2 H, $-CH_2C=$), 2.8 (m, 2 H, $=CCH_2C=$), and 5.45 ppm (m, 1 H, HC=).[11]

Anal. Calcd for $C_{10}H_{16}$: C, 88.16; H, 11.84. Found: C, 88.55; H, 11.69.

β-Hydroxy Acid 11. The identical procedure used for the formation of the β-hydroxy acid **9** was performed on 0.5 g (5.7 mmol) of isobutyric acid using 1.0 g (5.7 mmol) of aldehyde **3** as the electrophile. This yielded 1.1 g (73%) of an oil which was used without further purification: ir (neat) 3420, 3150, and 1700 cm^{-1}; nmr ($CDCl_3$) δ 1.1–1.4 (m, 9 H, CH_3-), 1.5–2.8 (m, 5 H, $-CH_2-$ and CH_3CH-), 2.4 (s, 3 H, CH_3Ar), 3.7 (m, 1 H, HCOH), and 7.2 ppm (s, 4 H, ArH).

β-Lactone 12. The same procedure used to make β-lactone **10** was run on 0.7 g (2.7 mmol) of **11** using 1.4 g (8.0 mmol) of $PhSO_2Cl$. This yielded an oil which was decolorized in pentane with carbon to yield 0.49 g (77%) of a clear liquid **12**: ir (neat) 1820 cm^{-1}; nmr ($CDCl_3$) δ 1.05–1.4 (m, 9 H, CH_3-), 1.4–2.8 (m, 5 H, $-CH_2-$ and CH_3CH-), 2.36 (s, 3 H, CH_3Ar), 4.2 (m, 1 H, HCO–), and 7.2 ppm (s, 4 H, ArH).

Anal. Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 77.85; H, 8.77.

(±)-α-Curcumene (4). In a microdistillation apparatus, 0.3 g (1.2 mmol) of the β-lactone **12** was heated to 140° (760 mm) for 3 hr. The bath temperature was raised to 160° and the oil **4** was molecularly distilled, giving 0.22 g (90%) of a clear liquid: uv ($CHCl_3$) 261, 267, and 274 nm; ir (neat) 3100, 3060, 3030, 2970, 2930, 2880, 1510, 1450, 1375, and 810 cm^{-1}; nmr ($CDCl_3$) δ 1.2 (d, 3 H, J = 7 Hz, CH_3CH-), 1.54 (s, 3 H, $CH_3C=$), 1.68 (s, 3 H, $CH_3C=$), 1.4–2.1 (m, 4 H, $-CH_2-$), 2.36 (s, 3 H, CH_3Ar), 2.7 (m, 1 H, CH_3CH-), 5.18 (t, 1 H, HC=C), and 7.2 ppm (s, 4 H, ArH); $n^{25}D$ 1.4993. The physical and spectral data are consistent with those in the literature.[12]

Registry No.—**1**, 4342-60-3; **2**, 586-62-9; **3**, 3241-74-5; **4**, 3649-81-8; **9**, 50987-52-5; **10**, 50987-53-6; **11**, 50987-54-7; **12**, 50987-55-8; isoprene, 78-79-5; acrylic acid, 79-10-7.

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Communications

Facile Reaction of Potassium Hydride with Ketones. Rapid Quantitative Formation of Potassium Enolates from Ketones *via* Kaliation[1]

Summary: In contrast to lighter saline hydrides, KH in tetrahydrofuran vigorously metalates a wide range of ketones with little or no self-condensation or reduction; solutions of highly reactive potassium enolates are formed quantitatively in minutes at 20°.

Sir: Potassium hydride in ethereal solvents exhibits exceptional reactivity toward weak carbon acids such as fluorene (pK_A = 23), methyl *tert*-butyl ketone (pK_A = 20.8), and indene (pK_A = 19), in marked contrast to the sluggishness or inertness of lighter saline hydrides (NaH and LiH). Of particular interest is the metalation of ketones; quantitative formation of highly reactive potassium enolates requires only minutes at room temperature even with relatively hindered structures. Pure solutions of the enolates—free of ketone by ir—are obtained by decantation.

Ketone enolates are versatile reactive intermediates of interest as probes of cation solvation and ion pairing in ambient ions,[2] in formation of carbon–carbon bonds in synthesis,[3] and as ligands of transition metals.[4] Formation of enolates from ketones has been accomplished recently by a variety of methods[5-12] with lithium as the cation in the great majority of cases. Only occasionally have saline hydrides been employed[13,14] despite their attractive simplicity: they are insoluble in nonreacting organic solvents and are readily separated; the sole by-product of metalation is hydrogen gas; and hydrides are both readily available and indefinitely stable. Unfortunately, reaction of LiH and NaH with unactivated ketones has proven exceptionally sluggish. Even a relatively acidic ketone—butyrophenone—has been reported to require several days at 35° (ether solvent) for complete metalation by NaH.[13a] Metalation by NaH is also complicated by considerable self-condensation of the ketone.[14]

KH[16a] is far more reactive than LiH[16a] or NaH[16a] toward ketones in tetrahydrofuran (THF), as illustrated in Figure 1 in metalation of methyl *tert*-butyl ketone (pinacolone). This enhanced reactivity is *not* an artifact of the degree of dispersion of solid KH; even particularly finely divided NaH (sedimentation rate in pentane <0.1 times that of KH) reacts much more sluggishly.

Metalation is readily accomplished by addition of the ketone to a vigorously stirred suspension of KH in anhydrous THF at 20°; hydrogen evolution commences immediately and is very vigorous. In a typical example 25 mmol of pinacolone was metalated in 5 min by 28 mmol of KH suspended in 40 ml of THF, the bulk of the hydrogen being evolved in <2 min. The clear supernatant solution showed 0–1% ketone in several runs by ir analysis.[17] The 1710-cm^{-1} absorption (C=O stretch) disappears upon metalation and is replaced by a strong absorption at 1568 cm^{-1}. Glpc analysis of a sample quenched in a mixture of ether and 1.0 *M* HCl showed 100% recovery of ketone. Addition of excess triethylamine and trimethylchlorosilane[5] to the reaction mixture at −78° yielded >98% trimethylsilyl enol ether.

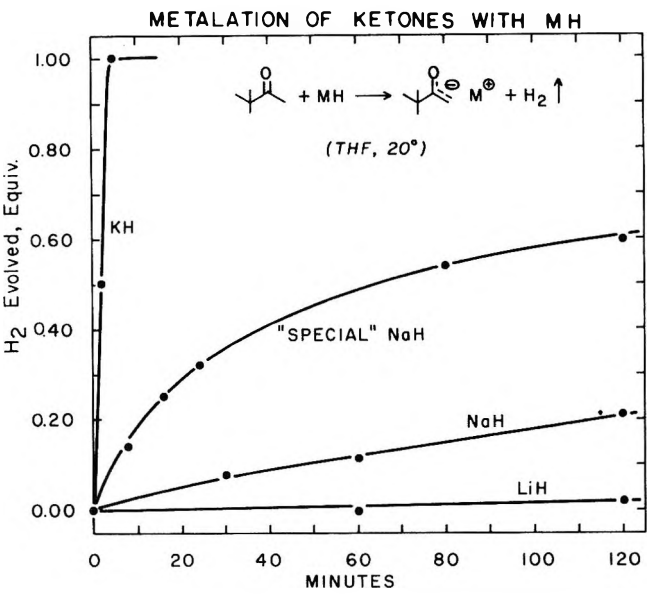

Figure 1. Metalation of pinacolone in tetrahydrofuran (0.5 *M*) with excess saline hydrides. "Special NaH" was a sample of particularly finely divided NaH obtained from Ventron Corp.[16b] Other hydrides are standard commercial products of Alfa Products Div. of Ventron Corp.

Similar results were obtained with a variety of ketones including those labile toward self-condensation, as shown in Table I. No reduction of the carbonyl group by KH was observed.[18] Unsymmetrically substituted ketones yield directly equilibrium mixtures of enolates.

Potassium enolates are highly reactive. Thus the enolate of 2,4-dimethyl-3-pentanone reacts with excess methyl iodide in 5 min at −78°; a 50:1 ratio of mono to dialkylated products is formed.[19]

In the absence of excess ketone, potassium enolates do not equilibrate; however, the highly reactive enolates may be equilibrated readily in the presence of small amounts of free ketone even at −78° to yield enolate mixtures enriched in the more stable component. Thus 3-methyl-2-butanone is metalated to yield an equilibrium mixture of enolates containing 88% *less* substituted isomer at 20°; no

Table I: Kaliation of Ketones at 20° [a]

Compd	Time (min) 50%[b]	Time (min) 100%[b]	Enolate yield, %[c]	Enolate (less:more substd)[d]
Acetone	0.5	1.5	90	
2-Heptanone	0.5	1.5	100	46:54
3-Me-2-butanone	0.5	1	101	88:12
3,3-DiMe-2-butanone	2.0	5	97	
2,4-DiMe-3 pentanone	2.5	10	100	
Isobutyrophenone	3.5	12	93	
Cyclohexanone	0.5	1.5	88	
2-Methylcyclohexanone	2.0	6	95	33:67

[a] 25.0 mmol of ketone, 28–32 mmol of KH in ~50 ml of THF. Glyme solvents are also satisfactory. No evidence of reduction was observed. [b] Per cent reaction was determined by gas evolution. [c] Determined by quenching samples containing hydrocarbon standards in water followed by glpc analysis. Ketone was absent in enolate solutions by ir. [d] By silylation at −78°. Silyl ethers isolated had spectra consistent with structures.

change in the composition is observed in 1 hr at −78°. However, if the enolate solution (0.4 *M*) is stirred at −78° for 0.75–1.0 hr with 0.08 equiv of free ketone, the enolates are reequilibrated to a mixture containing >98.5% less substituted isomer.

Alkylation and silylation may be carried out without difficulties *in situ* in the presence of excess KH.

The solutions of potassium enolates may be transformed into lithium enolates by metathesis with lithium bromide in THF; KBr precipitates immediately upon mixing. In the case of pinacolone, the cation exchange was accompanied by a shift in the enolate ir absorption from 1568 to 1604 cm^{-1}, consistent with tighter association of the lithium ion with the more electronegative end of the anion. The preparation of enolates of di- and trivalent cations is in progress.

Current preparations of enolates are often based upon lithium amides.[10,11] However, varying amounts of addition to the carbonyl group appear to occur even with the highly hindered lithium diisopropylamide. Moreover, lithium enolates are far less reactive (10^{-3}–10^{-4}) than potassium enolates,[13a] and lithium halides do not precipitate from ethereal solvents to assist metathesis reactions.

The exceptionally high reactivity of KH toward ketones provides a novel direct route to highly reactive potassium enolates. The facile formation of these intermediates provides new possibilities for investigation of enolate chemistry.

Acknowledgment. Assistance from Research Corporation and Esso Research and Engineering Company is gratefully acknowledged.

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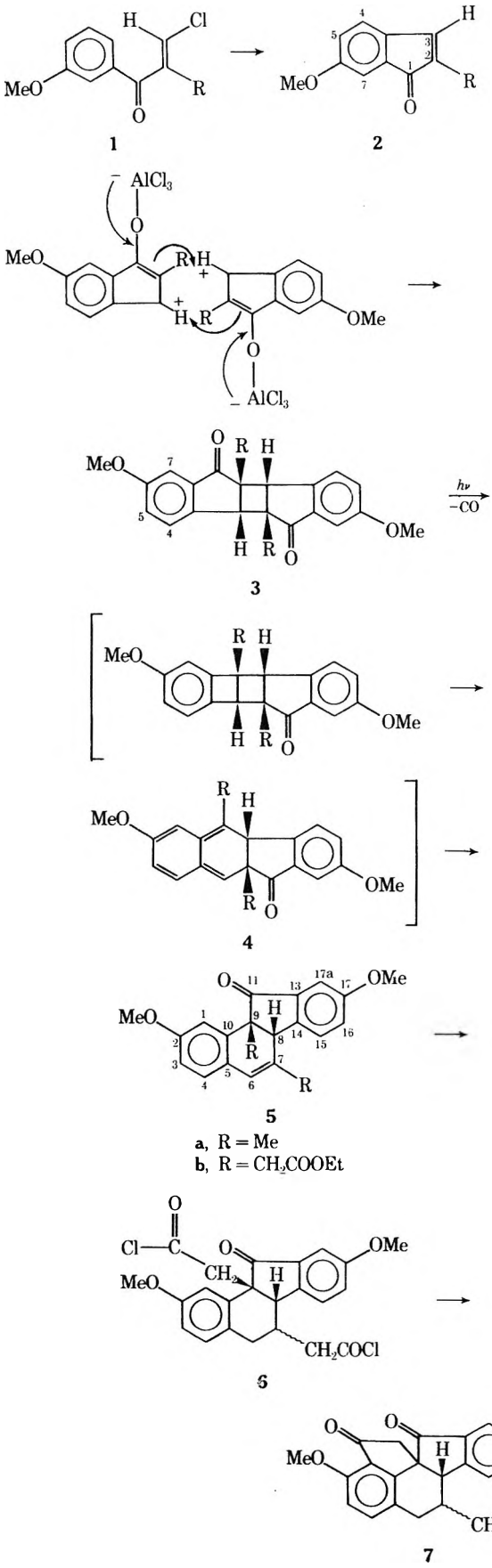
Photochemical Transformation of Truxones to C-Nor-D-homo Steroid Systems

Summary: Photodecarbonylation of truxones leads to benzobicyclohexene systems which undergo a rearrangement to products with a C-nor-D-homo steroid skeleton.

Sir: In the synthesis of 6-methoxyindenones **2** through the $AlCl_3$-catalyzed internal ketovinylation of the corresponding β-chlorovinyl ketones **1**,[1] we observed the formation of small to large amounts of truxones, which were identified as endo head-to-tail dimers **3**.[2] The ability of the 6-methoxy group to stabilize a positive charge on the C_3 is probably responsible for this easy $AlCl_3$-catalyzed dimerization, which does not occur with 2-ethyl-5-methoxyindenone, even at much higher temperatures.[3] In an attempt to obtain the indenone **2a** through a photocycloreversion from the dimer **3a**, a new product was obtained, which, according to the mass spectral analysis, should correspond to a decarbonylated dimer. A 16-hr irradiation of the endo dimer **3a** with a high pressure mercury lamp afforded 54% of the decarbonylated product and 46% indenone **2a**. This decarbonylated product was identified as **5a**, a product with a C-nor-D-homo steroid skeleton. An alternative structure **4a** was rejected as the product showed no long-wavelength absorption (400 nm) as is observed in comparable o-quinodimethanes.[4] The decarbonylated product did not show any Diels–Alder activity with tetracyanoethylene, as was expected for **4a**.

The nmr spectrum of the decarbonylated product shows a coupling constant of 1.5 Hz between one of the methyl groups and the vinylic proton. This is in good agreement with structure **5a**, but not with structure **4a**, where a coupling across six bonds is required. In C_6D_6 1-H undergoes a large downfield shift (0.54 ppm) which is expected for structure **5a** but not for the corresponding proton in structure **4a**. The dimer **3b** gives analogous results. According to the mass spectral data of the rearranged product **5b**, the most important fragmentation is loss of CH_3COOEt from the molecular ion (M − 88). This indicates that the 8-H and the 9-CH_2COOEt are located at



the same side of the five-membered C ring. This is also proved by the following conversions. The styrene double bond of the product **5b** has been hydrogenated and the resulting diester converted into the corresponding bis acid chloride **6**. Friedel–Crafts internal acylation afforded the product **7**. The fact that this internal acylation was possible proves the cis junction between the B and C ring in the starting steroid. In the case of a trans junction such a cyclization would not be possible, according to molecular models. The orientation of the 7-carboethoxymethyl is not clear and more experiments are needed to clarify this point.[5] The product **5** could be formed by a photochemical disrotatory ring opening of the benzobicyclohexene system, followed by a thermal 1,5-sigmatropic shift of the remaining benzoyl group. Since no product resulting from migration of the benzylic hydrogen in **4** was observed and since the migratory aptitude of an hydrogen is greater than for an acyl group in similar rearrangements,[6] this mechanism is less likely. An alternative mechanism[7] consists of a photochemical "type I" cleavage of the cyclobutyl–carbonyl bond in the benzobicyclohexene intermediate. This cleavage, followed by benzoyl migration and ring opening, could lead to compound **5**. Stereospecificity can be accounted for by the rigidity of the cyclobutyl ring.

Studies about the mechanism are under investigation together with the synthesis of mixed dimers of different methoxyindenones, with respect to the synthesis of new C-nor-D-homo steroid systems, which are interesting intermediates in the synthesis of C-nor-D-homo analogs of natural steroids[8] and of some natural steroidal alkaloids.[9]

Acknowledgment. The authors wish to thank Professor Dr. J. Verhulst for his constant interest and encouragement. They thank the "Nationaal Fonds voor Wetenschappelijk Onderzoek" for financial support and for a postdoctoral fellowship to one of them (H. M.). The authors are also indebted to Dr. F. Compernolle and Dr. S. Toppet for mass spectral and nmr analysis and to P. Valvekens for elemental analyses.

Supplementary Material Available. Some experimental details will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy of $2.00 for microfiche, referring to code number JOC-74-1325.

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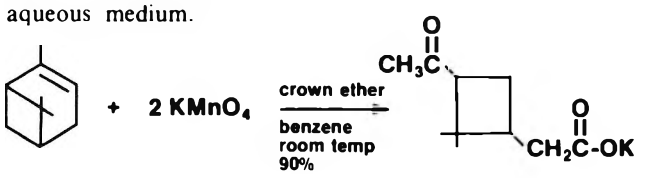
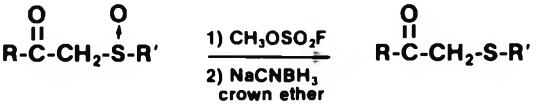
A Royal Method for Improving Reactions that Utilize Potassium Salts:

Crown Ethers

Since the discovery of their remarkable ability to solubilize alkali metal salts in non-polar solvents, crown ethers,[1] a class of macrocyclic polyethers, have found novel application in synthesis. For instance, potassium permanganate readily dissolves in benzene in the presence of dicyclohexyl-18-crown-6 to form a purple solution ("Purple Benzene") which oxidizes alcohols, olefins, aldehydes and aralkyl hydrocarbons in excellent yield under neutral conditions.[2] α-Pinene is oxidized in 90% yield[2] in contrast to only 40-60% yield in an aqueous medium.

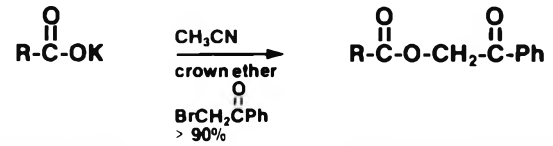


Reduction of alkoxysulfonium salts formed by alkylation of sulfoxides with Magic Methyl® (methyl fluorosulfonate) proceeds readily with sodium cyanoborohydride in the presence of crown ethers[3] to give the sulfides in excellent yield. β-Ketosulfoxides are reduced to β-ketosulfides[3] whereas extensive decomposition occurs in the absence of the crown ether:



Also, sodium borohydride reduces ketones in aromatic hydrocarbon solvents in the presence of dibenzo-18-crown-6.[4]

Phenacyl esters which are difficult to obtain in good yield using classical procedures are easily formed[3] by refluxing a benzene or acetonitrile suspension of the aryl salt, crown ether and the β-bromoacetophenone:



The alkylation of acetoacetic ester enolates gives less *O*-alkylated product in the presence of a crown ether[5] especially in weakly polar solvents. Dicyclohexyl-18-crown-6 also markedly changes the rates and stereochemical course[6] of alkoxide-catalyzed carbanion-generating reactions. Moreover, the reaction of 5-decyl tosylate with potassium alkoxides[7] produces more *trans* olefin in the presence of dicyclohexyl-18-crown-6. In a similar fashion the stereochemical course of the reaction of potassium *tert*-butoxide with *trans*-2-phenylcyclopentyl tosylate[8] is markedly changed by the addition of dicyclohexyl-18-crown-6.

Crown ethers also find application in the resolution of α-amino acids,[9] in the manufacture of an ion-selective electrode,[10] and in studies of ion-transport mechanisms.[1]

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