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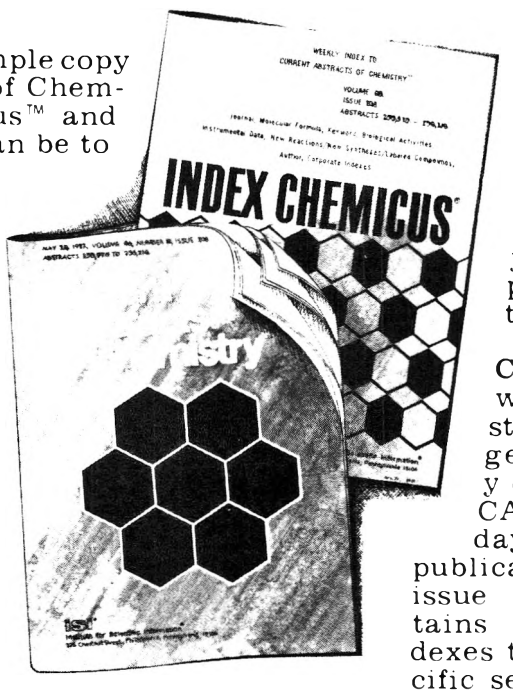

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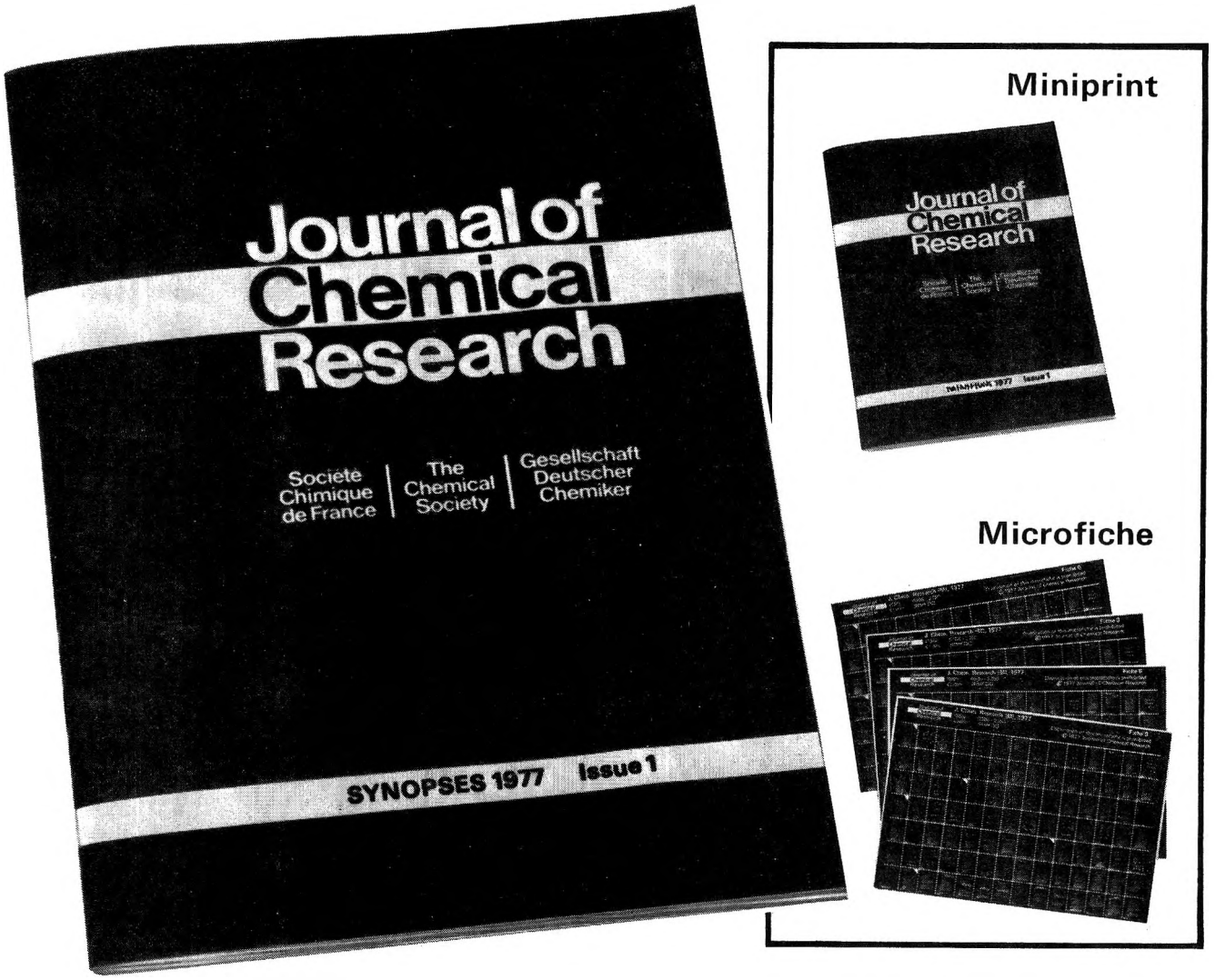

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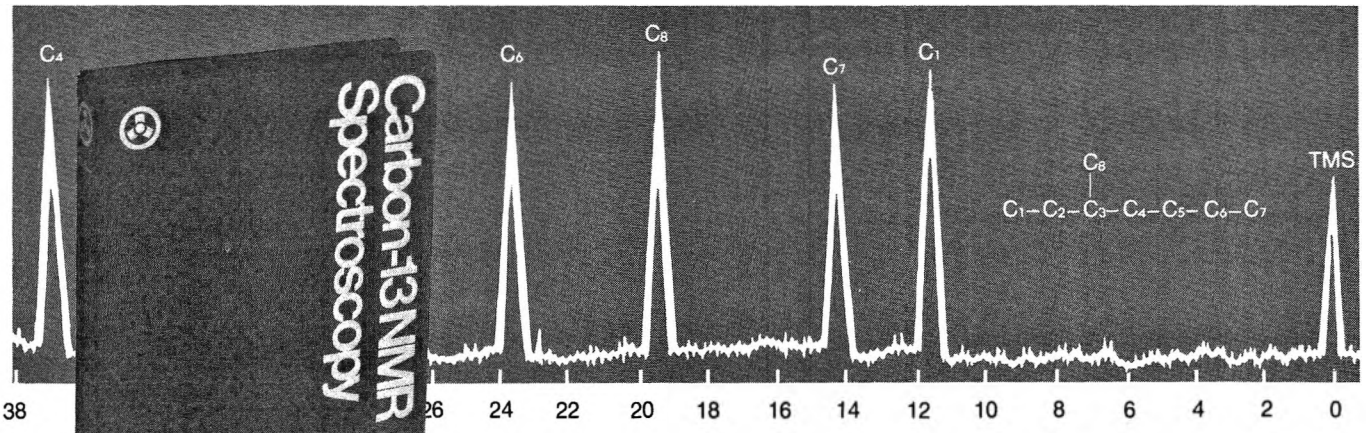

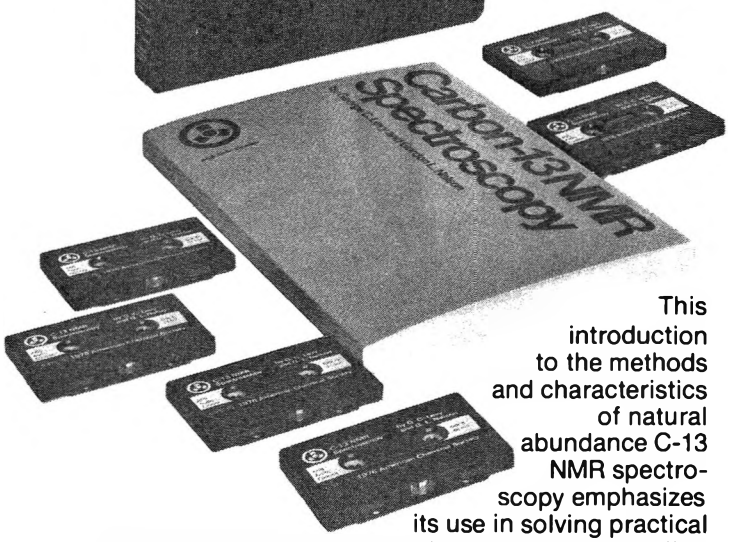

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Reaction of Lithium Dialkylcuprates with Acetoxy Epoxides. Assessment of a Method for Nucleophilic α-Alkylation of Ketones[1]

Richard A. Amos and John A. Katzenellenbogen*

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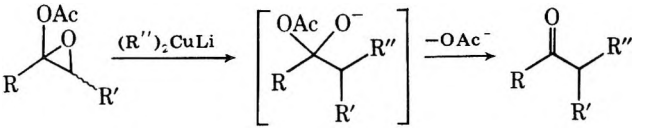
Received December 15, 1976

The reaction between acetoxy oxiranes and lithium dialkylcuprates proceeds at low temperatures (−78 °C) to produce the desired α-alkyl ketones in yields which vary greatly with the cuprate and acetoxy oxirane used (2.3–43%). Lithium dimethylcuprate generally gives the best yields, with lithium di-*n*-butyl- and diphenylcuprate giving more complex product mixtures which contain less of the desired substituted ketone. Formation of the nonalkylated ketone is consistently observed and several potential mechanisms for the reaction are considered in light of its formation. The use of cuprates having a nontransferable ligand and also the use of the epoxides of enol pivalates, benzoates, and mesitoates, as substrates, were explored as a means of controlling formation of the unsubstituted ketone.

The alkylation of carbonyl compounds by reaction of enolates with electrophilic alkylating agents is a reaction of fundamental importance in synthetic organic chemistry. However, there are certain cases where such an electrophilic α-alkylation approach is not favorable. For example, the electrophile may be severely hindered and thus subject to facile elimination reactions, or, in the case of sp^2 or sp hybridized centers, the site may not be subject to direct displacement. In considering alternative methods that would avoid difficulties of this nature, we were intrigued by the possibility of achieving a nucleophilic α-alkylation. In such a process the conventional roles of electrophile (alkylating agent) and nucleophile (enolate) are reversed, and, in this sense, the method represents another example of "umpolung" or "charge affinity inversion".[2] The nucleophilic α-alkylation method is particularly appealing for those cases where the substituent to be introduced is alkenyl or aryl.

Several methods have recently been reported that result in the nucleophilic α-alkylation or arylation of ketones; these utilize as reactants or intermediates α-halo ketones,[3] α,α′-dihalo ketones,[4] hydrazones of α,β-epoxy ketones,[5] vinyl nitro[6] or nitroso compounds,[7] or vinyl azo sulfonates.[8,9] While these approaches operate efficiently in the systems examined, we were particularly intrigued by an approach that appeared to involve a minimum of steps in the preparation of the electrophilic analogue of the enolate and in the regeneration of the ketone after nucleophilic addition.

Lithium dialkylcuprates are known to react with epoxides by displacement at the least-substituted carbon. The cuprates appear superior to alkyllithium reagents in this regard, plus they are unreactive toward ester functions.[10] On the basis of this behavior, we considered it likely that the reaction of a lithium dialkylcuprate with an acetoxy epoxide would proceed as illustrated in the scheme below. The acetoxy function places



one carbon at the oxidation state of a carbonyl group; thus, attack of the cuprate at the other, less hindered center, generates a species that should eliminate acetate ion. The overall reaction would produce the alkylated carbonyl compound by a nucleophilic α-alkylation process in which the electrophile is the acetoxy epoxide (ketone precursor) and the nucleophile is the dialkylcuprate.

We have found that the reaction of organocuprates with acetoxy epoxides does indeed proceed in this manner; however, the yield of the desired alkylation product depends greatly upon the nature of the organocuprate, the structure of the acetoxy epoxide, and the reaction conditions.

Results

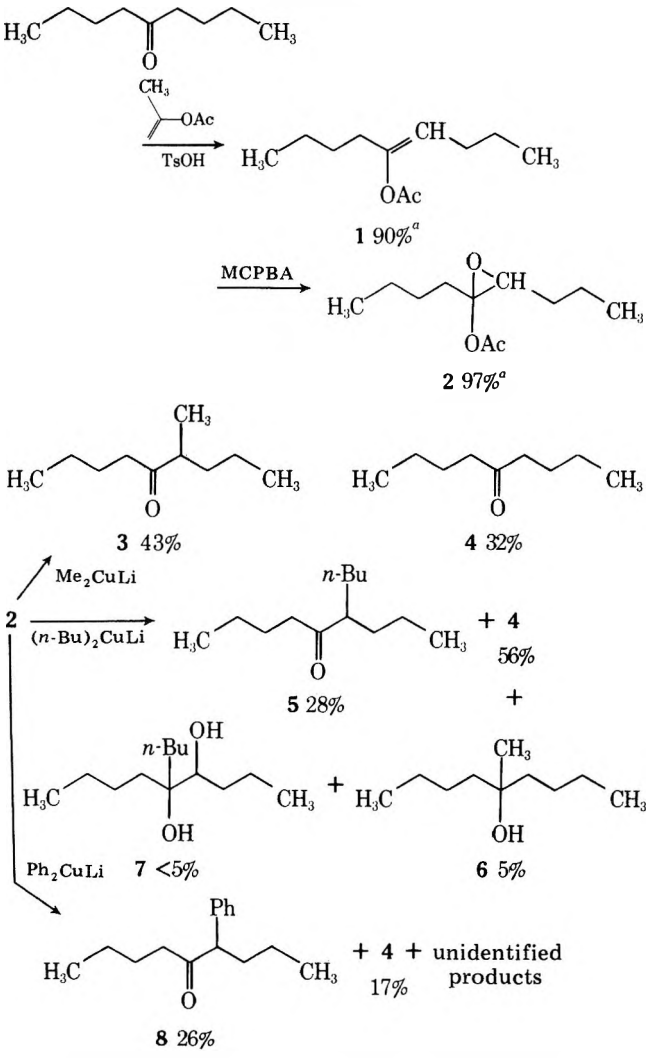
Reaction of Lithium Dialkylcuprates with Acetoxy Epoxides. The enol acetates (1) required for formation of the substituted oxiranes are conveniently prepared from the corresponding ketone and isopropenyl acetate using *p*-toluenesulfonic acid as a catalyst. Epoxidation using *m*-chloroperbenzoic acid yields the desired oxiranes (2) in generally high yields. This class of compounds exhibits a well-known[11] intramolecular thermal or acid-catalyzed isomerization to the corresponding α-acetoxy ketones, but with reasonable care the compounds can be readily prepared. They are stored at

−20 °C and are generally used shortly after their preparation.

5-Acetoxynonane 4,5-oxide (2) reacts with lithium dimethylcuprate (twofold excess in ether at −78 °C) to give the desired 4-methyl-5-nonanone (3) in 43% yield. Unexpectedly, a substantial amount of 5-nonanone (32%) (4) is also produced. The formation of the unsubstituted ketone, a product that results from a formal reduction of the acetoxy epoxide, is observed quite consistently throughout these reactions, and we shall consider its possible sources later.

As shown in Scheme I, compound 2 also reacts with lithium

Scheme I



[a] The olefin and oxirane are a mixture of cis and trans isomers.

di-*n*-butylcuprate to give the desired 4-butyl-5-nonanone (5), as well as the reduction product 5-nonanone (4). In addition, two other products were formed: the tertiary carbinol 6 and the vicinal diol 7, which was characterized by oxidative cleavage using periodic acid and identification of the carbonyl fragments as their 2,4-DNP derivatives. The amounts of these products formed are highly variable, and in an initial study the isolated yields were 13%:34%:30%:26% for 5:4:6:7, respectively.

Alcohol 6 could arise from the addition of two butyl groups to an acetyl group, and diol 7, from the addition of one butyl group to the α-hydroxyl ketone (formed from 2 by acetyl cleavage). Thus, it seemed likely that these alcohols were originating from reactions of free *n*-butyllithium with 2. To confirm this fact, a series of reactions was run with 2 in which the CuI:*n*-BuLi ratio was varied, and the product was ana-

Table I. Dependence of Ketone vs. Alcohol Product Ratio upon Organocopper Composition in Reaction with 5-Acetoxynonane 4,5-Oxide (2)

CuI:*n*-BuLi	Ketones (4 + 5):alcohols (6 + 7)[a]
1:1.0	No reaction
1:1.5	100:0
1:2.0	90:10
1:2.5	25:75
n-BuLi alone	0:100

[a] Approximate molar % based on GLC data.

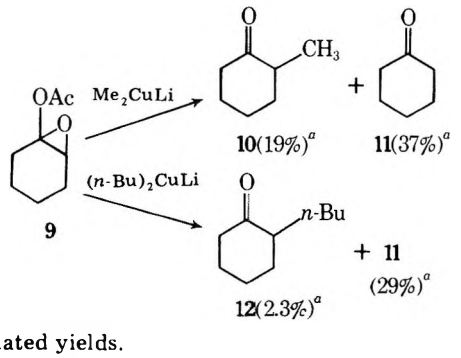
lyzed to determine the relative amounts of ketone and alcohol components.

As shown in Table I, the alkyl copper itself is nonreactive toward the epoxide. In the case of the 1:1.5 ratio, which should contain both butylcopper and di-*n*-butylcuprate, only ketone products were observed (along with some unconsumed starting material). The 1:2.0 ratio frequently shows the formation of some alcohol products, but the amounts produced are highly variable. Apparently, the reaction is very sensitive to slight excesses of *n*-butyllithium, potentially caused by errors in the amount of alkyllithium added, impurities in the cuprous salt, or decomposition of the cuprate during formation.[12,18] The 1:2.5 ratio demonstrates that even a small excess of *n*-butyllithium competes very effectively with the cuprate complex, as the ratio of products is shifted heavily in favor of the alcohols. Finally, the alkyllithium alone shows no formation of ketone products, thus confirming the essential role of copper in directing attack at the oxirane rather than the ester function. In light of these results, we have been able to achieve yields of 28 and 56% for 5 and 4, respectively (Scheme I), with only small amounts of the alcohol products by avoiding excess *n*-butyllithium.

Compound 2 also reacts with lithium diphenylcuprate to give 4-phenyl-5-nonanone (8), but in widely varying yields. The use of commercial phenyllithium for generation of the cuprate reagent gave extremely poor yields, ca. 0.5% isolated. The use of freshly prepared phenyllithium affords better yields of 8 (best 26%), but still shows formation of several as yet unidentified products. One positive aspect to this particular reaction is the formation of somewhat smaller amounts of 4 compared to the other cuprates (best case: 26% of 8, 17% of 4).

The results of dialkylcuprate reactions with 1-acetoxycyclohexane 1,2-oxide (9) were similar to those in the nonane system, but the yields of alkylated ketone were uniformly lower (see Scheme II). Treatment with lithium dimethylcu-

Scheme II



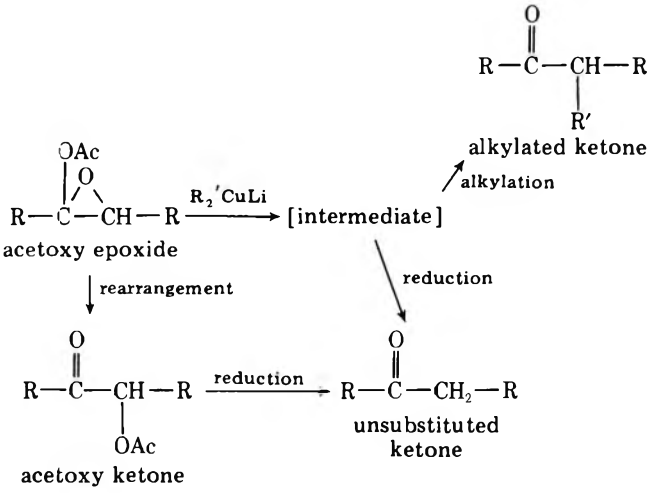
[a] Isolated yields.

prate gave 10 and 11 in yields of 19 and 37%, respectively; reaction of 9 with lithium di-*n*-butylcuprate gave a rather disappointing 2.3% yield of 12, along with considerable amounts (29%) of 11. A substantial portion of the products from the reactions of 9 consisted of material that was polar and rela-

tively nonvolatile (presumed to be condensation products) and was not further characterized. As in the nonane series, the formation of alcohol products can be controlled by avoiding any excess alkyllithium.

Source of Unsubstituted Ketone By-product. As the formation of the unsubstituted ketone is obviously detrimental to the overall yield of the desired product, its possible origins are of considerable interest. Two potential sources that appear likely are shown in Scheme III. The first route would

Scheme III



involve formation of some type of intermediate by reaction of the epoxide with the cuprate reagent (oxidative addition; see Discussion). This intermediate could then undergo further conversion to give either the alkylated ketone or the unsubstituted ketone, in a ratio that might be influenced by a number of factors: leaving group, the R′ group on the cuprate, counterions present, reaction conditions, etc. The second route involves a rearrangement of the acetoxy oxirane to an α-acetoxy ketone followed with attack by the cuprate reagent to give the unsubstituted ketone. The reductive cleavage of some α-acetoxy ketones using lithium dimethylcuprate has been reported and has been further investigated by us.[13]

As mentioned previously, the rearrangements of acetoxy epoxides have been reported to occur under both thermal and acid-catalyzed conditions.[11] However, the temperatures used in the cuprate reactions (−78 to 0 °C) are not sufficient to induce rearrangement, and the solutions certainly are not acidic. Metal cations have been shown[14] to catalyze rearrangements in some epoxides; however, treatment of **9** with a homogeneous mixture of CuI and LiCl in THF at 0 °C and of **2** with a heterogeneous mixture of CuI and LiCl in Et_2O at 0 °C failed to show any evidence of rearrangement. These findings favor the route involving formation of an intermediate (although it is still possible that the rearrangement is catalyzed by some as yet unknown agent).

It is possible in the reactions using lithium di-*n*-butylcuprate that a portion of the unalkylated ketone arises from the reaction of copper hydride (generated by thermal decomposition of the cuprate) with the acetoxy epoxide; however, in most of the butylation reactions, reagent generation, reaction, and quenching were performed below −40 °C, conditions that minimize copper hydride formation. Furthermore, such a copper hydride mechanism cannot be invoked to explain the formation of unalkylated product in the methylation and phenylation reactions.

In an effort to minimize the production of the unsubstituted ketone by-product, we have explored several reaction parameters: the use of mixed cuprates, alteration of the form of the copper salt, and the use of leaving groups other than acetate. The results of these studies are summarized in Tables II and III. The amount of alkylated ketone formed in each case is presented as a mol % of total ketone in the crude reaction product; this permits a direct evaluation of whether the alkylation/reduction ratio is being influenced favorably or not.

Table II. Effect of Organocuprate Composition on Relative Yield of Alkylated Ketone

		Alkylated ketone as mol % of total ketone[a,b]	
Registry no.	Cuprate	System 2	System 9
53128-68-0	*n*-Bu(PhS)CuLi	30	
62197-73-3	*n*-Bu($C_4H_9C{\equiv}C$)CuLi	30	
24406-16-4	*n*-Bu_2CuLi (from CuI)	28[c]	7
	n-Bu_2CuLi (from Me_2S–CuBr)	31	14
15631-48-8	Me_2CuLi (from CuI)	57[c]	46
	Me_2CuLi (from Me_2S–CuBr)	48	41

[a] Percentages are not actual yields but rather the fraction of total ketone content that is the desired alkylation product. [b] Unless otherwise indicated, yield data were determined by GLC analysis. [c] Yield data are based on isolated products.

Table III. Effect of Ester Structure on Relative Yield of Alkylated Ketone

	Alkylated ketone as mol % of total ketone[a,b]					
Cuprate	9[e]	18	19	2	24	25
Me_2CuLi	34[c]	30	32	57[c]	42	39
n-Bu_2CuLi	6[c]	4		28[c]	19	18
Ph_2CuLi[d]					60[c]	

[a] Percentages are not actual yields but the fraction of total ketone content that is desired alkylation product. [b] Unless otherwise indicated, yield data were determined by GLC analysis. [c] Isolated products. [d] Registry no., 23402-69-9. [e] System.

Alteration in the Nature of the Cuprate Reagent. The use of mixed cuprates in which one of the ligands bound to copper is nontransferable has been finding increasing use because their reaction characteristics are improved and the R group to be donated is conserved, of value particularly when R is difficult to prepare. One such class contains compounds possessing a heteroatom bonded to copper.[15] We chose to study the phenylthio group because its stability is reported to be superior to that of other hetero ligands. Thus, lithium phenylthio(*n*-butyl)cuprate was reacted with **2** to produce both **4** and **5**; however, the product ratio was not significantly different from the lithium di-*n*-butylcuprate (Table II). Acetylenic groups have also been used as nontransferable ligands in cuprates.[16] Formation of the lithium *n*-butyl(*n*-butylethynyl)cuprate by addition of *n*-butyllithium to *n*-butylethynylcopper[17] followed by reaction with **2** again gave **5** as 30% of the total ketone content of the crude product. Thus, it was apparent that use of these mixed cuprates does not produce any significant improvement in the product ratio.

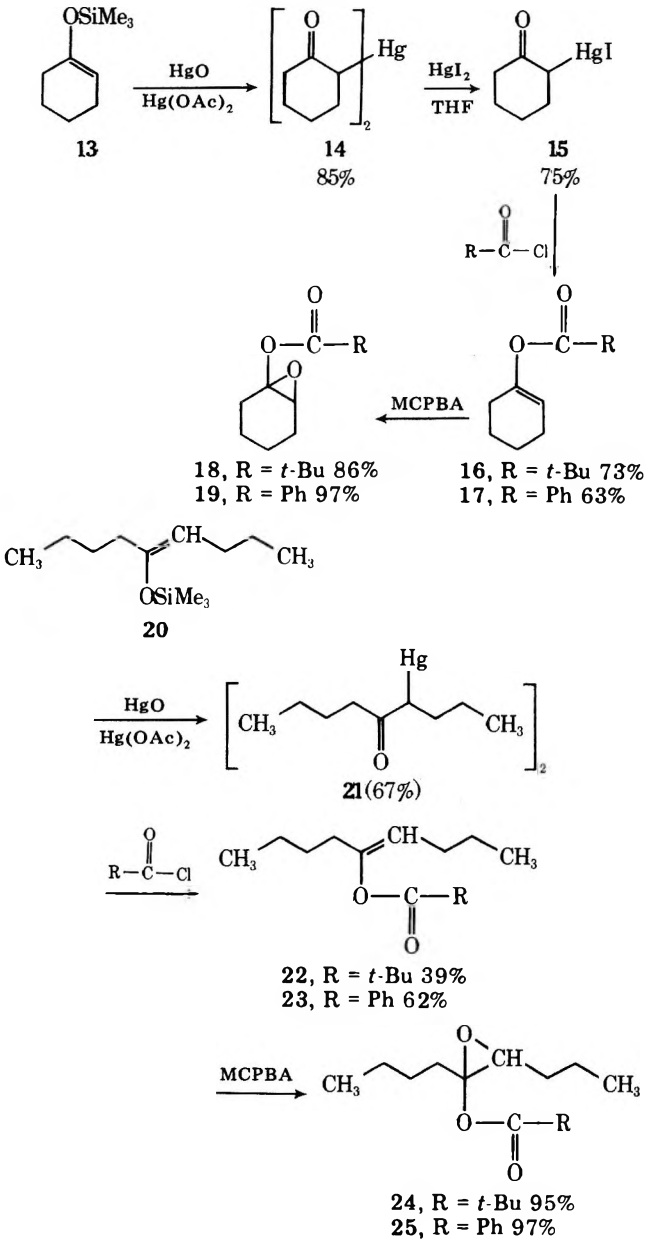
One of the major problems involved in the generation of cuprate reagents is the presence of impurities in the commercially available cuprous salts, and the resulting decomposition of the organocopper that they induce. House has recently described[18] a procedure in which a complex between CuBr or CuCl and dimethyl sulfide is generated, allowing removal of cupric salts as well as other impurities. To investigate

the effect that the nature of the cuprous salt might have on the product ratios, we chose to use the cuprous bromide–dimethyl sulfide complex to purify the salt and to prepare the cuprate reagent.

As indicated in Table II, the methylation reactions with **2** and **9** (using this reagent) showed a small decrease in the amount of alkylated product; the significance of this difference is not clear, since replicate experiments occasionally show variations of this magnitude. In the case of the butylation of **2** and **9**, the trend is in the opposite direction, toward more alkylation product, but again appears to be of marginal significance.

Alteration of the Acyloxy Oxirane. If the alkylation and reduction products originate from a common intermediate (see Scheme III), one might expect that the use of leaving groups other than acetate might have a substantial effect upon the ratio of products. Toward this end, we prepared a number of acyloxy oxiranes that differed in the ester portion, as shown in Scheme IV. We were not able to achieve satisfactory yields

Scheme IV



of the enol esters using classical O-acylation conditions: enolate (formed by either sodium hydride or lithium diisopropylamide) addition to a large excess of acylating agent (benzoyl chloride) in a dipolar aprotic solvent (DMF); however, a method described by House was utilized successfully.[19]

Mercuration of the trimethylsilyl enol ethers **13** and **20** gives the bisketomercurials **14** and **21**. Compound **14** was first converted to the α-iodomercuri ketone derivative **15** and then O-acylated; compound **21** was O-acylated directly, but in somewhat lower yield. The enol esters were epoxidized with *m*-chloroperbenzoic acid and stored at −20 °C to prevent thermal rearrangement.

Treatment of these epoxide derivatives with lithium dimethylcuprate and lithium di-*n*-butylcuprate gave the results shown in Table III. It can be readily seen that both the pivalate and benzoate derivatives gave somewhat lower percentages of the alkylation product compared to the acetates, particularly in the case of the nonane compounds.

In a related study, we also prepared 5-nonanone enol mesitoate (2,4,6-trimethylbenzoate) in the same manner as the pivalates and benzoates. The derivative was then treated with *n*-butyllithium instead of the cuprate in hopes of further defining the role of copper in the reaction. However, this compound was reactive only in the presence of a large excess of the alkyllithium, and attack occurred almost exclusively at the relatively inert ester function, with only traces of the α-alkylation product resulting from attack at the epoxide. These results suggest that the use of the ester function may have only limited use as a potential leaving group in the nucleophilic alkylation of oxygen-substituted epoxides.

Silyl enol ethers would appear to hold promise, since the silyl group would be inert to attack by cuprate reagents, and reacts with alkyllithiums only slowly (at 25 °C), thus allowing more versatility in the organometallic chosen. However, the oxirane formed by reaction of trimethylsilyl enol ethers with *m*-chloroperbenzoic acid rapidly rearranges to the α-trimethylsiloxy ketone, a process that may be catalyzed by the organic acid generated during the epoxidation.[20]

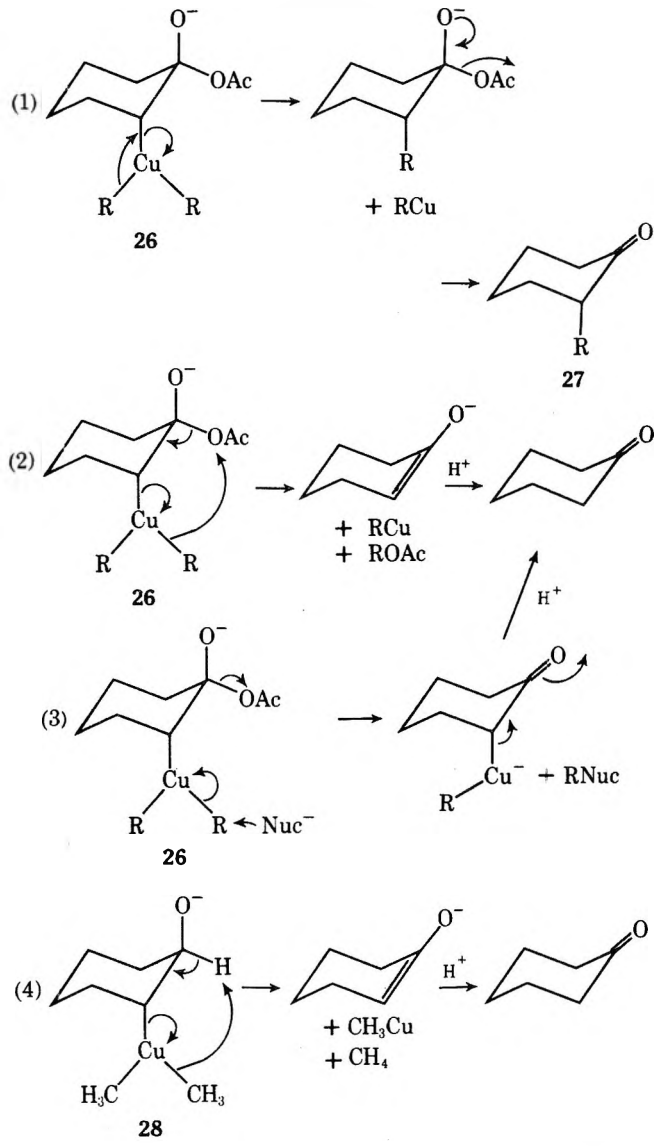
In the hope that steric bulk might retard this rearrangement, we prepared the *tert*-butyldimethylsilyl enol ether of 5-nonanone. However, it too underwent rearrangement upon epoxidation with *m*-chloroperbenzoic acid, despite attempts to remove the benzoic acid during the reaction by extraction into aqueous sodium bicarbonate solution. The rearranged α-siloxy ketone was also formed when epoxidation was attempted with ($Mo(CO)_6$, *t*-BuOOH)[21] or basic benzonitrile–H_2O_2.[22] We were also unable to prepare the epoxide of the triphenylsilyl enol ether[23] of 5-nonanone.

Discussion

The organocoppers differ substantially from alkyllithiums in their reactivity and the sites at which they attack the acyloxy epoxides and related systems. Johnson has proposed[10a] that these differences can be explained by stating that an alkyl carbon is the nucleophile in the case of the alkyllithiums, whereas the copper atom is the nucleophile in the cuprate reagents. The dramatic difference in the sites of attack of the two nucleophiles is readily observed in the reaction of **2** with *n*-butyllithium to give exclusively products (**6** and **7**) resulting from attack at the ester carbonyl, and none of the product (**5**) arising from attack at the oxirane carbon. The cuprate reagent, in contrast, appears to attack exclusively at the latter, since none of the alcohol products (**6** and **7**) are produced when care is taken to exclude any slight excesses of *n*-butyllithium. The fact that metal atoms can act as nucleophiles has been demonstrated by Kochi.[24] He found that lithium dialkylaurates react with alkyl halides to produce a relatively stable gold(III) complex, which, upon thermally induced elimination, gives the coupling product.

If indeed the copper atom is acting as the nucleophile, we could then propose **26** as a possible structure for our postu-

Scheme V



lated intermediate. As shown in the first reaction in Scheme V, alkylated ketone **27** would be produced by a normal type of alkyl donation to the cyclohexane ring with a simultaneous loss of the copper(I) alkyl followed by expulsion of acetate. The copper(I) alkyl is readily observed in the case of the lithium dimethylcuprate as a rapid formation of insoluble yellow polymeric methyl copper. A second alternative (2), which would produce the unsubstituted ketone, would involve a β-elimination of the copper(I) alkyl from **26** with transfer of the remaining R group to acetate. A similar type of mechanism (4) has been proposed by Johnson[10a] to explain the formation of ketones as the major by-products in the addition of cuprates to unsubstituted epoxides: intermediate **28** undergoes the β-elimination to give both the alkyl copper and methane. One other alternative (3) would have an R group from copper undergo a reductive displacement (by acetate or another nucleophile in the reaction medium), to give the enolate.

Mechanisms 2 and 3 would predict the formation of RNuc in amounts equal to the unsubstituted ketone. Thus far we have been unable to demonstrate the presence of any *n*-butyl acetate resulting from attack by acetate in the reaction of **2** with lithium di-*n*-butylcuprate. Work is continuing on isolation of other products due to attack by other potential nucleophiles, namely the alkyl halide or, more likely, the hydrocarbon dimer.

It would appear that the fate of the proposed intermediate **26** could be influenced by changing either the R group on the cuprate or the leaving group on the epoxide. In fact, the influence of the R group is quite significant, with *n*-butyl usually giving the least favorable ratios of alkylated to nonalkylated product, and phenyl the most favorable. Of course, in this case we are limited by the R group we desire to add to the ketone. The other alternative, the use of groups other than acetate, would not be placed under such a restriction. Unfortunately, in the two cases examined thus far, the enol pivalates and benzoates, the ratio of ketone products was shifted away from the desired alkylation product.

While alteration of the steric bulk of the leaving group did not have a favorable effect on the extent of ketone alkylation, it is possible that changes in the electronic nature of the group (i.e., leaving groups other than esters) might have a more desired effect. Two points should be raised in this regard: the derivative should be relatively easy to prepare from the carbonyl compound, since the desired net effect is a nucleophilic α-alkylation of a ketone, and, secondly, the epoxide derivative must be stable. We were fortunate in that the ester epoxides are relatively stable compared to other functionalized epoxides. For example, chloro olefins can be epoxidized using peracids, but the intermediate chloro epoxides are frequently unstable and undergo a facile rearrangement to the corresponding α-chloro ketones.[25] Although some enol ethers can be epoxidized without rearrangement, others, including the silyl ether that we investigated, undergo further reaction rapidly.[26]

While the reaction of an organocuprate with an acyloxy-epoxide produces substituted ketone in which the substituent group is derived from a nucleophile, the relatively modest yields and the concomitant production of the unsubstituted ketone mar this approach to nucleophilic ketone alkylation. We are currently in the process of examining other systems that may enable this process to be carried out more efficiently.

Experimental Section

Melting points were determined on a Fisher-Johns hot-stage apparatus and are corrected. ^{1}H NMR spectra were recorded on Varian T-60 or A-60 spectrometers; chemical shifts are reported in ppm downfield from a tetramethylsilane internal standard (δ scale). Infrared spectra were recorded on a Perkin-Elmer Model 137 spectrometer. Mass spectra were obtained from either a Varian MAT CH-5 or SM-112 spectrometer and were at 70 eV, unless otherwise noted. Elemental analyses were provided by the microanalytical service lab of the University of Illinois.

Analytical gas-chromatographic work utilized a Hewlett-Packard 5750 instrument equipped with flame-ionization detectors. Columns used were either a 10 ft × 0.125 in. SE-30, 5% on Gas-Chrom Q, 80/100; or a 5 ft × 0.125 in. OV-17, 3% on Supelcoport, 100/120. Preparative gas chromatography was performed using a Varian 90-P instrument with a 10 ft × 0.375 in. SE-30, 5% on Chromosorb W, 60/80 column.

Glassware for reactions involving organometallic reagents was dried for a minimum of 2 h at 120 °C, and such reactions were run under a N_2 atmosphere. THF and DME were dried by distillation from sodium naphthalide; anhydrous diethyl ether (Mallinckrodt) was used as received. All other reagents were used as commercially available unless otherwise noted. The organolithium reagents (ventron) were titrated before use, utilizing either the double-titration method[27] or the single-titration method using 1,10-phenanthroline as an indicator.[28]

The phenyllithium,[29] the silyl enol ethers **13** and **20**,[30] *n*-butylethynylcopper,[17] and the cuprous bromide–dimethyl sulfide complex[18] were all prepared by literature methods.

Cyclohexanone Enol Acetate. Cyclohexanone, 24.5 g (0.25 mol), was mixed with 50 mL of benzene and 60 mL (0.55 mol) of isopropenyl acetate, followed by 2.0 g of *p*-toluenesulfonic acid as a catalyst. The mixture was heated on an oil bath so as to maintain a slow distillation of acetone through a 12-in. glass-helices column. When GLPC analysis showed the reaction to be complete (ca. 6 h), the reaction mixture was diluted with ether, washed several times with saturated $NaHCO_3$, and

dried over $MgSO_4$. Distillation afforded 21.1 g (60%) of a colorless liquid: bp 87–90 °C at 28 mm Hg, lit.[31a] 180–182 °C at 760 mmHg; ^1H NMR (CCl_4) δ 5.20 (m, 1 H), 2.00 (s, 3 H), 1.95–2.25 (m, 4 H), 1.50–1.80 (m, 4 H).

5-Nonanone Enol Acetate (1). The above procedure was followed using 21.3 g (0.15 mol) of 5-nonanone, 50 mL (0.45 mol) of isopropenyl acetate, and 25 mL of benzene. An additional 25 mL of isopropenyl acetate was added later when GLC analysis showed the reaction to be incomplete. Work-up as before afforded 24.7 g (90%) of a colorless liquid; bp 41–42 °C at 2.0 mmHg; ^1H NMR (CCl_4) δ 4.98, 4.87 (t, J = 7 Hz, 1 H, cis and trans isomers), 2.05, 2.00 (s, 3 H, cis and trans isomers), 1.60–2.30 (m, 4 H), 1.10–1.60 (m, 6 H), 0.75–1.10 (m, 6 H).

Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94. Found: C, 71.71; H, 10.85.

Cyclopentanone Enol Acetate. The above procedure was followed using 21.0 g (0.25 mol) of cyclopentanone, 60 mL (0.55 mol) of isopropenyl acetate, and 0.6 g of p-toluenesulfonic acid. No benzene was used as a cosolvent. Work-up as before gave 19.8 g (63%) of a colorless liquid; bp 153–156 °C, lit.[31b] 156–158 °C; ^1H NMR (CCl_4) δ 5.20–5.35 (m, 1 H), 2.15–2.60 (m, 4 H), 2.05 (s, 3 H), 1.60–2.15 (m, 2 H).

1-Acetoxycyclohexane 1,2-Oxide (9). A mixture of cyclohexanone enol acetate, 5.6 g (40 mmol), in 75 mL of CH_2Cl_2 was cooled on an ice bath. m-Chloroperbenzoic acid, 9.70 g (48 mmol at 85% purity), was dissolved in 200 mL of CH_2Cl_2 and added to the above solution over a 2-h period. The mixture was stirred for 2–6 h at 0 °C and then gradually allowed to warm to room temperature while following the reaction progress by GLC. Care should be taken to avoid excessive reaction times at the higher temperatures. When the starting material was consumed, the excess peracid was removed by washing with saturated Na_2SO_3. Extracts were washed with saturated $NaHCO_3$ and dried over $MgSO_4$. The solvent was removed under reduced pressure to give 5.97 g (96%) of a colorless liquid. The purity of the product was usually high, and further purification was generally avoided due to the lability of the compound. The neat liquid was stored at −20 °C at all times. ^1H NMR (CCl_4) δ 3.08 (t, J = 2 Hz, 1 H), 1.70–2.25 (m, 4 H), 1.97 (s, 3 H), 1.25–1.70 (m, 4 H).

Anal. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: C, 61.54; H, 7.90.

5-Acetoxynonane 4,5-Oxide (2). The above procedure was followed using 9.2 g (50 mmol) of 5-nonanone enol acetate (1) in 50 mL of CH_2Cl_2 and 12.2 g (60 mmol at 85% purity) of m-chloroperbenzoic acid in 200 mL of CH_2Cl_2. Work-up as before yielded 9.65 g (97%) of a colorless liquid purified by silica gel chromatography (5% ether/hexane). ^1H NMR (CCl_4) δ 2.65–2.90 (m, 1 H), 2.00 (s, 3 H), 1.15–1.70 (m, 10 H), 0.70–1.15 (m, 6 H).

Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 66.09; H, 10.22.

1-Acetoxycyclopentane 1,2-Oxide. The above procedure was followed using 9.45 g (75 mmol) of cyclopentanone enol acetate and 15.3 g (115 mmol at 85% purity) of m-chloroperbenzoic acid. Work-up as before afforded a colorless liquid which could be distilled (without apparent rearrangement) to give 8.95 g (84%) of the product; bp 39–42 °C at 0.7 mm Hg; ^1H NMR (CCl_4) δ 3.46 (broad s, 1 H), 2.01 (s, 3 H), 1.35–2.40 (m, 6 H).

Anal. Calcd for $C_7H_{10}O_3$: C, 59.14; H, 7.09. Found: C, 59.03; H, 6.89.

Reactions with 5-Acetoxynonane 4,5-Oxide (2). (A) Lithium Dimethylcuprate. Cuprous iodide, 7.62 g (40.0 mmol), was slurried with 50 mL of anhydrous ether and cooled to −20 °C. Methyllithium, 48.5 mL of a 1.65 M solution in ether (80.0 mmol), was added to give a nearly colorless solution. Further cooling to −78 °C was followed by the addition of 4.0 g (20.0 mmol) of 2 in 15 mL of ether over a 10-min period. The yellow solution was stirred for 2.5 h at −78 °C and then gradually warmed to 0 °C for an additional 1 h. The mixture was quenched with 5 mL of saturated NH_4Cl, filtered, and dried over $MgSO_4$. GLC analysis showed only two major components. Silica gel chromatography (solvent gradient 3–80% ether/hexane) gave the pure compounds along with some mixed fractions. Small amounts of polar products were also isolated but not characterized.

(1) 5-Nonanone (4): 0.91 g (32%); ^1H NMR (CCl_4) δ 2.15–2.50 (broad t, J = 6.5 Hz, 4 H), 1.05–1.80 (m, 8 H), 0.70–1.05 (m, 6 H); 2,4-DNP derivative mp 39–39.5 °C, lit. 41 °C;[32] mass spectrum (2,4-DNP) m/e (rel intensity) 322 (M^+, 49).

(2) 4-Methyl-5-nonanone (3): 1.35 g (43%); ^1H NMR (CCl_4) δ 2.20–2.65 (m, 3 H), 1.02 (d, J = 7 Hz, 3 H), 0.70–1.80 (m, 14 H); mass spectrum m/e (rel intensity) 156 (M^+, 5), 114 (29), 99 (12), 85 (95), 72 (45), 71 (69), 57 (100). n^{20}_D 1.4219.

Anal. Calcd for $C_{10}H_{20}O$: C, 76.86; H, 12.90. Found: C, 76.88; H, 12.73.

(B) Lithium Di-n-butylcuprate. Cuprous iodide, 7.62 g (40 mmol), was slurried with 60 mL of anhydrous ether and cooled to −45 °C. n-Butyllithium, 39.0 mL of a 2.05 M solution in hexane (80 mmol), was added to give a dark solution. Cooling to −78 °C was followed by the addition of 4.0 g (20 mmol) of 2 in 10 mL of ether over a 10-min period. After stirring for an additional 3 h at −78 °C, the mixture was quenched with 5 mL of saturated NH_4Cl, filtered, and dried over $MgSO_4$. GLC analysis showed four major components which were separated by silica gel chromatography using an ether/hexane solvent gradient (5–80%).

(1) 5-Nonanone (4): 0.96 g (34%); ^1H NMR (CCl_4) δ 2.15–2.50 (broad t, J = 6.5 Hz, 4 H), 1.05–1.80 (m, 8 H), 0.70–1.05 (m, 6 H); mass spectrum m/e (rel intensity) 142 (M^+, 13), 85 (88), 58 (70), 57 (100).

Anal. Calcd for $C_9H_{18}O$: C, 76.00; H, 12.76. Found: 76.06; H, 12.72.

(2) 5-Methyl-5-nonanol (6): 0.96 g (30%); ^1H NMR (CCl_4) δ 2.02 (s, 1 H, exchangeable with D_2O), 1.15–1.60 (m, 12 H), 1.08 (s, 3 H), 0.70–1.15 (m, 6 H). An authentic sample was prepared by reaction of 5-nonanone with methyllithium. This product showed identical GLC retention time and mass spectrum with the isolated reaction product. Mass spectrum m/e (rel intensity) 143 (10), 101 (10), 83 (17), 57 (17). n^{20}_D 1.4314.

(3) 4-Butyl-5-nonanone (5): 0.53 g (13%); ^1H NMR (CCl_4) δ 2.10–2.50 (m, 3 H), 1.05–1.80 (m, 14 H), 0.70–1.05 (m, 9 H); mass spectrum m/e (rel intensity) 198 (M^+, 1), 142 (20), 141 (4), 113 (22), 100 (27), 85 (59), 57 (100); n^{20}_D 1.4320.

Anal. Calcd for $C_{13}H_{26}O$: C, 78.72; H, 13.21. Found: C, 78.60; H, 13.12.

(4) 5-Butyl-4,5-nonanediol (7): 1.14 g (26%); mp 74–75 °C; ^1H NMR (CCl_4) δ 3.20–3.50 (m, 1 H), 2.21 (s, 2 H, exchangeable with D_2O), 1.10–1.70 (m, 16 H), 0.70–1.10 (m, 9 H); IR (Nujol) 3380, 1470, 1380 cm^{-1}; mass spectrum (10 eV) m/e (rel intensity) 199 (0.2), 159 (19), 144 (10), 143 (100), 85 (8).

Anal. Calcd for $C_{13}H_{28}O_2$: C, 72.17; H, 13.04. Found: C, 72.08; H, 13.11.

A later run, using the above procedure but with care to avoid any excess of n-butyllithium, gave GLC yields of 56 and 28% for 4 and 5, respectively, with only very small amounts of 6 and 7.

(C) Lithium Diphenylcuprate. Cuprous iodide, 0.95 g (5 mmol), was slurried with 25 mL of anhydrous ether and cooled to −45 °C. Phenyllithium, 8.85 mL of a 0.96 M solution in ether (8.5 mmol), was then added to give a dark solution. Further cooling to −78 °C was followed by a rapid addition of 0.5 g (2.5 mmol) of 2 in 5 mL of ether. The mixture was stirred at −78 °C for 4 h and an additional 18 h at −25 °C. Following addition of 2 mL of saturated NH_4Cl, the product was filtered and dried over $MgSO_4$. GLC analysis revealed a complex mixture of products and only the ketone components were isolated using silica gel chromatography (3% ether/hexane).

(1) 4-Phenyl-5-nonanone (8): 0.14 g (26%); ^1H NMR (CCl_4) δ 7.21 (s, 5 H), 3.56 (t, J = 7 Hz, 1 H), 2.28 (t, J = 6.5 Hz, 2 H), 0.60–2.10 (m, 14 H); IR (neat) 1720, 755, 700 cm^{-1}; mass spectrum m/e (rel intensity) 218 (M^+, 2), 176 (13), 133 (16), 91 (100), 85 (83), 57 (53); n^{20}_D 1.4738.

Anal. Calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 82.53; H, 10.09.

(2) 5-Nonanone (4): 0.06 g (17%); product was identical in all respects to previously isolated samples.

Oxidative Cleavage of 7. To verify the structure of diol 7, a periodate oxidation was performed. The diol, 0.11 g (0.5 mmol), was dissolved in 10 mL of ether, and the mixture was added slowly to a solution of 0.14 g (0.6 mmol) of H_5IO_6 in 40 mL of ether. The mixture was stirred for 2 h at 0 °C, during which time a white precipitate of HIO_3 formed. The mixture was then neutralized with saturated $NaHCO_3$ and the organic layer was separated and dried over $MgSO_4$. The product was diluted with 10 mL of absolute ethanol and the two carbonyl fragments were separated by distillation (the lighter one distilling with the ethanol) and derivatized.

(1) 5-Nonanone: 2,4-DNP mp 41–42 °C, lit.[32] 41 °C; mass spectrum (2,4-DNP) m/e (rel intensity) 322 (M^+, 36).

(2) Butanal: 2,4-DNP mp 122–123 °C, lit.[33] 123 °C; mass spectrum (2,4-DNP) m/e (rel intensity) 252 (M^+, 100).

Reaction with 1-Acetoxycyclohexane 1,2-Oxide (9). (A) Lithium Dimethylcuprate. Cuprous iodide, 3.81 g (20 mmol), was slurried with 25 mL of anhydrous ether and cooled to −10 °C. Methyllithium, 24.2 mL of a 1.65 M solution in ether (40 mmol), was added to give a colorless solution. Further cooling to −78 °C was followed by the addition of 1.56 g (10 mmol) of 9 in 10 mL of ether. The mixture was stirred for 3 h at −78 °C and then gradually warmed to 0 °C. After quenching with 5 mL of saturated NH_4Cl, the product was filtered and dried over $MgSO_4$. GLC analysis showed only two major

products. These ketone components were separated from the polar residues by silica gel chromatography (3–10% ether/hexane solvent gradient). Since the chromatography failed to give a clean separation of the two ketones, the yields were determined by GLC, and pure samples for derivative preparation were obtained by preparative GLC.

(1) Cyclohexanone (11): 0.36 g (37%); 2,4-DNP mp 158–161 °C, lit.[33] 162 °C; mass spectrum (2,4-DNP) *m/e* (rel intensity) 278 (M^+, 92).

(2) 2-Methylcyclohexanone (10): 0.21 g (19%); 2,4-DNP mp 137–138 °C, lit.[33] 137 °C; mass spectrum (2,4-DNP) *m/e* (rel intensity) 292 (M^+, 78).

(B) Lithium Di-*n*-butylcuprate. Cuprous iodide, 11.43 g (60 mmol), was slurried with 50 mL of anhydrous ether and cooled to −45 °C. *n*-Butyllithium, 50.0 mL of a 2.40 M solution in hexane (120 mmol), was added to give a dark solution. Further cooling to −78 °C was followed by the addition of 4.68 g (30 mmol) of **9** in 20 mL of ether. The mixture was stirred for 3.5 h at −78 °C and then quenched with 5 mL of saturated NH_4Cl. Separation of the products was achieved by silica gel chromatography (3–80% ether/hexane solvent gradient). Some difficulty was encountered in separating **6** and **11** cleanly, so their yield was determined by GLC.

(1) Cyclohexanone (11): 0.84 g (29%); 2,4-DNP mp 158–161 °C, lit.[33] 162 °C; mass spectrum (2,4-DNP) *m/e* (rel intensity) 278 (M^+, 58).

(2) 5-Methyl-5-nonanol (**6**): 1.35 g (29%); identified by coinjection with an authentic sample on GLC.

(3) 2-Butylcyclohexanone (**12**): 0.09 g (2%); 2,4-DNP mp 107–109 °C, lit.[34] 109–110 °C; semicarbazone mp 146–148 °C, lit.[35] 150 °C; mass spectrum (2,4-DNP) *m/e* (rel intensity) 334 (M^+, 24).

A substantial amount of polar material remained (1.55 g) but no attempt was made to characterize each component present.

α-Mercuricyclohexanone Derivatives 14 and 15. Using the procedure described by House,[19] 7.58 g (35 mmol) of HgO and 0.27 g (0.84 mmol) of $Hg(OAc)_2$ were slurried with 1.5 mL of water and 5.5 mL of ethanol. Compound **13**, 11.91 g (70 mmol), was added over a 10-min period with evolution of heat and disappearance of the red coloration. An additional 25 mL of ethanol was added to keep the solution fluid during the addition. After stirring for 1 h at 25 °C, the mixture was diluted with 150 mL of warm $CHCl_3$, dried over $MgSO_4$, and filtered while still warm. The chloroform was reduced to ca. 30 mL and dilution with hexane gave 11.67 g (85%) of white crystals of **14**, collected by suction filtration.

Without further purification, 11.06 g (28 mmol) of **14** was added to a solution of 12.74 g (28 mmol) of HgI_2 in 100 mL of THF to produce a cloudy white solution. After stirring for 1 h, the mixture was diluted with 50 mL of hexane and 50 mL of $CHCl_3$. Cooling on ice afforded white crystals, which were filtered and recrystallized from $CHCl_3$/hexane to give 17.5 g (75%) of **15**, mp 117–119 °C, lit.[19] 115–117 °C.

Bisketomercurial Derivative 21. The procedure for the preparation of **14** was followed using 14.99 g (70 mmol) of **20**. Work-up followed by recrystallization from hexane gave 11.17 g (67%) of **21**, mp 151–152 °C. ^1H NMR ($CDCl_3$) δ 3.01 (t, J = 7 Hz, 2 H), 1.85–2.50 (m, 4 H), 0.70–1.85 (m, 28 H).

Anal. Calcd for $C_{18}H_{34}O_2Hg$: C, 44.75; H, 7.09. Found: C, 44.43; H, 6.98.

Cyclohexanone Enol Pivalate (16). Compound **15**, 8.31 g (20 mmol), was suspended in 30 mL of DME, followed by the addition at 25 °C of 4.82 g (40 mmol) of pivaloyl chloride in 12 mL of DME. The solution became homogeneous within 5–10 min and was stirred for an additional 2 h. Saturated $NaHCO_3$ (5 mL) was added and the DME was removed under reduced pressure. The product was extracted with ether and washed several times with $NaHCO_3$ to remove the excess acid chloride. After drying briefly over $MgSO_4$, silica gel chromatography (5% ether/hexane) gave 2.65 g (73%) of a colorless liquid. ^1H NMR (CCl_4) δ 5.05–5.20 (m, 1 H), 1.85–2.20 (m, 4 H), 1.50–1.80 (m, 4 H), 1.17 (s, 9 H); mass spectrum *m/e* (rel intensity) 182 (M^+, 7), 98 (72), 97 (13), 85 (18), 83 (17), 70 (25), 57 (100); n^{20}_D 1.4517.

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.69; H, 9.90.

Cyclohexanone Enol Benzoate (17). Compound **15**, 6.63 g (16 mmol), was slurried with 30 mL of DME, followed by the addition at 25 °C of 4.50 g (32 mmol) of benzoyl chloride in 15 mL of DME. The solution became homogeneous within 30 min and was stirred an additional 4 h. Work-up as above followed by silica gel chromatography (15% ether/hexane) gave 2.03 g (63%) of a colorless liquid. ^1H NMR (CCl_4) δ 7.75–8.05 (m, 2 H), 7.10–7.45 (m, 3 H), 5.25–5.45 (m, 1 H), 1.95–2.40 (m, 4 H), 1.50–1.95 (m, 4 H); mass spectrum *m/e* (rel intensity) 202 (M^+, 4), 105 (100), 77 (38); n^{20}_D 1.5403.

Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 76.94; H, 6.93.

5-Nonanone Enol Pivalate (22). Compound **21**, 4.83 g (10 mmol), was slurried with 30 mL of DME, followed by the addition at 25 °C of pivaloyl chloride, 4.82 g (40 mmol), in 15 mL of DME. The solution was homogeneous after 15 min and was stirred for an additional 2 h. Work-up as above followed by silica gel chromatography (4% ether/hexane) gave 1.78 g (39%) of a colorless liquid. ^1H NMR (CCl_4) δ 4.86, 4.80 (t, J = 7 Hz, 1 H, cis and trans isomers), 1.10–2.30 (m, 10 H), 1.22 and 1.18 (s, 9 H, cis and trans isomers), 0.70–1.10 (m, 6 H); mass spectrum *m/e* (rel intensity) 226 (M^+, 3), 142 (8), 113 (18), 101 (1), 100 (18), 85 (21), 57 (100); n^{20}_D 1.4330.

Anal. Calcd for $C_{14}H_{26}O_2$: C, 74.29; H, 11.58. Found: C, 74.58; H, 11.36.

5-Nonanone Enol Benzoate (23). Compound **21**, 4.83 g (10 mmol), was slurried with 30 mL of DME, followed by the addition at 25 °C of 5.62 g (40 mmol) of benzoyl chloride in 15 mL of DME. When the reaction failed to become homogeneous within 0.5 h, the mixture was warmed to 50 °C and stirred at that temperature for 16 h. Work-up as above followed by silica gel chromatography (10% ether/hexane) afforded 3.05 g (62%) of a colorless liquid. ^1H NMR (CCl_4) δ 7.75–8.05 (m, 2 H), 7.10–7.45 (m, 3 H), 5.08, 4.90 (t, J = 7 Hz, 1 H, cis and trans isomers), 1.65–2.45 (m, 4 H), 1.10–1.65 (m, 6 H), 0.70–1.10 (m, 6 H); mass spectrum *m/e* (rel intensity) 246 (M^+, 5), 105 (100), 77 (24); n^{20}_D 1.4980.

Anal. Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 78.01; H, 9.12.

Epoxidation of the Enol Pivalate and Benzoate Derivatives. (A) 1-Pivaloyloxycyclohexane 1,2-Oxide (18). The *m*-chloroperbenzoic acid, 1.22 g (6.0 mmol at 85% purity), was dissolved in 25 mL of CH_2Cl_2 and then added slowly (1 h) at 0 °C to a solution of 0.91 g (5 mmol) of **16** in 25 mL of CH_2Cl_2. The solution was stirred for 6 h at 0 °C and then stored overnight at −20 °C. If necessary to complete the reaction, the mixture can be warmed to room temperature and monitored by GLC, taking care to avoid excessive time at the higher temperatures. The product was washed with 2 × 25 mL of saturated Na_2SO_3, and with 3 × 25 mL of saturated $NaHCO_3$. After drying over $MgSO_4$, the solvent was stripped at low temperature, <25 °C, and the last traces were removed under vacuum, <1 mm Hg. A colorless liquid (0.85 g; 86%) was isolated and used without further purification. ^1H NMR (CCl_4) δ 3.02 (t, J = 2 Hz, 1 H), 1.70–2.20 (m, 4 H), 1.20–1.60 (m, 4 H), 1.15 (s, 9 H); mass spectrum *m/e* (rel intensity) 198 (M^+, 6), 114 (7), 113 (29), 85 (31), 57 (100).

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.89; H, 8.92.

(B) 1-Benzoyloxycyclohexane 1,2-Oxide (19). The above procedure was followed using 1.01 g (5 mmol) of **17**. Product (1.06 g; 97%) was isolated and purified by silica gel chromatography (10% ether/hexane). ^1H NMR (CCl_4) δ 7.90–8.20 (m, 2 H), 7.25–7.65 (m, 3 H), 3.26 (t, J = 2 Hz, 1 H), 1.80–2.40 (m, 4 H), 1.25–1.80 (m, 4 H); mass spectrum (10 eV) *m/e* (rel intensity) 218 (M^+, 2), 113 (17), 105 (100), 97 (1), 96 (4), 77 (1).

Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.62; H, 6.46.

(C) 5-Pivaloyloxynonane 4,5-Oxide (24). The above procedure was followed using 1.13 g (5 mmol) of **22**. A colorless liquid (1.15 g; 95%) was isolated and used without further purification. ^1H NMR (CCl_4) δ 2.73 (t, J = 6 Hz, 1 H), 0.70–2.20 (m, 16 H), 1.15 and 1.17 (s, 9 H, derived from cis and trans enol pivalates); mass spectrum (10 eV) *m/e* (rel intensity) 242 (M^+, 0.4), 226 (3), 170 (2), 157 (2), 142 (4), 141 (3), 85 (100), 57 (56).

Anal. Calcd for $C_{14}H_{26}O_3$: C, 69.38; H, 10.81. Found: C, 69.51; H, 10.61.

(D) 5-Benzoyloxynonane 4,5-Oxide (25). The above procedure was followed using 1.23 g (5 mmol) of **23**. A colorless liquid (1.27 g; 97%) was isolated and purified by silica gel chromatography (3% ether/hexane). ^1H NMR (CCl_4) δ 7.90–8.20 (m, 2 H), 7.25–7.65 (m, 3 H), 2.85–3.15 (m, 1 H), 1.20–2.40 (m, 10 H), 0.70–1.20 (m, 6 H); mass spectrum *m/e* (rel intensity) 105 (100), 85 (37), 77 (20), 57 (28).

Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.37; H, 8.51.

Compound **18** showed a substantial amount of rearrangement after 11 days at room temperature, whereas **19** and **25** showed no evidence (^1H NMR) of such a reaction after 14 days. As a precaution, however, the epoxides were stored at −20 °C.

Reactions of Enol Pivalate and Benzoate Epoxides. (A) With Lithium Dimethylcuprate. Cuprous iodide, 0.38 g (2 mmol), was suspended in 20 mL of ether and cooled to −20 °C. Methyllithium was then added until the yellow precipitate initially formed disappeared to give a colorless and homogeneous solution. Following further cooling to −78 °C, 1 mmol of the appropriate epoxide (0.20 g of **18**, 0.22 g of **19**, 0.24 g of **24**, and 0.26 g of **25**) in 5 mL of ether was added. After stirring the resulting yellow solution for 3 h at −78 °C, it was

then quenched with 1–2 mL of saturated NH_4Cl. The product was filtered and dried over $MgSO_4$. The ratio of alkylated to nonalkylated ketone was then determined by GLC analysis and the results are summarized in Table III.

(B) With Lithium Di-*n*-butylcuprate. Cuprous iodide, 0.38 g (2 mmol), was suspended in 20 mL of ether and cooled to −45 °C. *n*-Butyllithium, 1.69 mL of a 2.13 M solution in hexane (3.6 mmol to avoid any excess of alkyllithium), was then added to give a dark solution. After further cooling to −78 °C, 1 mmol of the appropriate epoxide (0.20 g of **18**, 0.24 g of **24**, and 0.26 g of **25**) in 5 mL of ether was added. After stirring the dark solution for 3 h at −78 °C, it was quenched with 1–2 mL of saturated NH_4Cl, filtered, and dried over $MgSO_4$. The ratio of alkylated to nonalkylated ketone was determined by GLC analysis and the results are summarized in Table III.

Reaction of 2 with the Mixed Alkynyl Cuprate. The *n*-butylethynylcopper, 0.72 g (5 mmol), was suspended in 20 mL of anhydrous ether and cooled to −50 °C. *n*-Butyllithium, 2.30 mL of a 2.13 M solution in hexane (4.9 mmol), was added with no apparent change in color or solubility of the yellow suspension. After stirring for an additional 30 min, the mixture was cooled to −78 °C and 0.5 g (2.5 mmol) of **2** in 5 mL of ether was added. After 2.5 h at −78 °C, the dark-green solution was quenched with saturated NH_4Cl, filtered, extracted, and dried over $MgSO_4$. Although the reaction was only ca. 60% complete, it was possible to determine by GLC the amount of alkylation product relative to the total ketone content, and it was not found to be significantly different from the di-*n*-butylcuprate reaction (30 and 28%, respectively).

Lithium Phenylthio(*n*-butyl)cuprate. Preparation and Reaction with 2. Following a previously described procedure,[15] thiophenol, 0.41 g (3.75 mmol), was added to 15 mL of anhydrous ether and cooled to 0 °C. *n*-Butyllithium, 2.26 mL of a 1.66 M solution in hexane (3.75 mmol), was added to generate the thiophenoxide anion. Cuprous iodide, 0.71 g (3.75 mmol), was slurried with 10 mL of ether, and the above solution was added at 25 °C to give a dark solution. After cooling to −78 °C, 2.26 mL of 1.66 M *n*-butyllithium (3.75 mmol) was added, followed by 0.5 g (2.5 mmol) of **2** in 5 mL of ether. After stirring for 1 h at −78 °C, the mixture was allowed to warm slowly to 0 °C. The reaction was quenched with saturated NH_4Cl after 3-h total time, and was washed with 2 × 30 mL of 3 N NaOH to remove the thiophenol. The extracts were dried over $MgSO_4$. The amount of alkylated product relative to total ketone was determined by GLC and was not found to be significantly different from the di-*n*-butylcuprate reaction (30 and 28%, respectively).

Reaction of 2 and 9 with Cuprous Bromide–Dimethyl Sulfide Derived Cuprates. (A) Lithium Dimethylcuprate. The cuprous bromide–dimethyl sulfide complex, 1.03 g (5 mmol), was dissolved in 10 mL of Me_2S and 10 mL of anhydrous ether. After cooling to 0 °C, methyllithium was added until the initially formed yellow precipitate just disappeared. The mixture was cooled to −78 °C and 2.5 mmol of the appropriate epoxide (0.39 g of **9** and 0.5 g of **2**) in 5 mL of ether was added rapidly. The resulting yellow solution was stirred for 3 h at −78 °C and then quenched with 1–2 mL of saturated NH_4Cl. The product was filtered, washed with dilute NH_4OH to remove the Cu complex, and dried over $MgSO_4$. Although the reactions were not complete under these conditions, it was possible to get the alkylated to nonalkylated ketone ratios by GLC and the results are summarized in Table II. Reactions can be forced to completion by a gradual warming to 0 °C.

(B) Lithium Di-*n*-butylcuprate. The cuprous bromide–dimethyl sulfide complex, 1.03 g (5 mmol), was dissolved in 10 mL of Me_2S and 10 mL of anhydrous ether. After cooling to −45 °C, 4.17 mL of 2.28 M *n*-butyllithium (9.5 mmol) was added to give a dark solution. The mixture was cooled further to −78 °C and 2.5 mmol of the appropriate epoxide (0.39 g of **9** and 0.5 g of **2**) in 5 mL of ether was added rapidly. After stirring for 4 h at −78 °C, the reactions were worked up as described above. The product ratios are indicated in Table II.

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Registry No.—*cis*-**1**, 62183-26-0; *trans*-**1**, 62183-39-5; *trans*-**2**, 62183-27-1; *cis*-**2**, 62183-40-8; **3**, 35900-26-6; **4**, 502-56-7; **4**, DNP, 3657-08-7; **5**, 40239-44-9; **6**, 33933-78-7; **7**, 62183-28-2; **8**, 41718-52-9; **9**, 14161-46-7; **10** DNP, 5138-30-7; **11**, 108-94-1; **11** DNP, 1589-62-4; **12** DNP, 1166-09-2; **15**, 37160-47-7; **16**, 62183-29-3; **17**, 13163-64-9; **18**, 62183-30-6; **19**, 62183-31-7; **20**, 62183-32-8; **21**, 62183-33-9; **22**, 62183-34-0; **23**, 62183-35-1; **24**, 62183-36-2; **25**, 62183-37-3; isopropenyl acetate, 108-22-5; cyclohexanone enol acetate, 1424-22-2; cyclopentanone enol acetate, 933-06-2; cyclopentanone, 120-92-3; 1-acetoxycyclopentane 1,2-oxide, 62183-38-4; butanal 2,4-DNP, 1527-98-6; pivaloyl chloride, 3282-30-2; benzoyl chloride, 98-88-4.

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2-Methoxyallyl Bromide. A Superior Acetonyl Alkylating Agent

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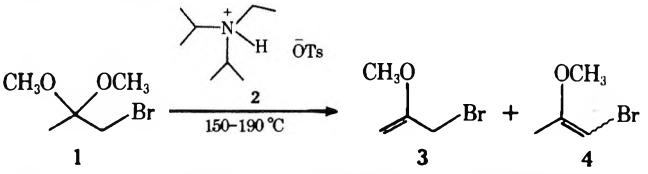
Heating 1-bromo-2,2-dimethoxypropane (**1**) in the presence of a catalytic amount of diisopropylethylammonium *p*-toluenesulfonate (**2**) gives 3-bromo-2-methoxy-1-propene (**3**) in greatly improved yield. Bromide **3** is a good alkylating agent monoalkylating acids, nitriles, esters, ketones, dialkylamides, enamines, and imines in yields of 44–96%. Alkylation of the lithium salt of imines with **3** followed by hydrolysis leads to α-acetonyl ketones which can be cyclized to 3,4-disubstituted cyclopentenones.

In our attempts to extend the Robinson annelation[1] to the formation of cyclopentenones via a three-carbon annelating agent, we desired an effective method of adding an acetonyl side chain to the α carbon of ketones or their equivalents. Several possible reagents for addition of this side chain have been described previously; however, each has problems in its use. The direct alkylation with haloacetones is useful only with the most acidic carbons due to the predominance of side reactions.[2,3] Alkylations with 2,3-dichloro-1-propene have been successful, but difficulties occur in that the vigorous conditions necessary for the unmasking of the vinyl chloride usually lead to the isolation of furans.[4] Lansbury has developed a nongeneral method of electrophilic cyclization to cyclopentanones from these alkylated intermediates, requiring solvolytic conditions.[5] Alkylations with propargyl bromide are troubled by allene formation.[6] Better results have been obtained with the use of the protected 3-bromo-1-trimethylsilyl-1-propyne,[6] but, again, rather stringent conditions are required for conversion of the silylated alkyne to the acetonyl group. The use of methallyl halides as alkylating agents has also been described, but conditions for the subsequent conversion to the acetonyl side chain, ozonolysis or treatment with osmium tetroxide/periodate, are undesirable in many cases.[7] Yoshikoshi and co-workers have recently described the successful addition of an acetonyl side chain synthon to trimethylsilyl enol ethers via a $SnCl_4$-catalyzed Michael addition to 2-nitropropene.[8] Jung has reported the use of 2-trimethylsilyl-3-iodo-1-propene as an acetonyl synthon but unmasking of the ketone requires epoxidation followed by strong acid again limiting the applicability of the reagent.[9] Ketals such as 1-bromo-2,2-dimethoxypropane (**1**) are, of course, extremely poor alkylating agents.

Results and Discussion

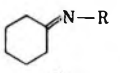
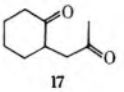
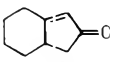
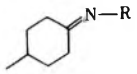
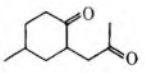
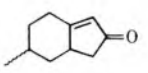
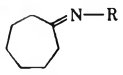
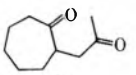
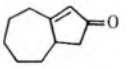
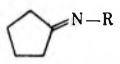
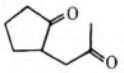
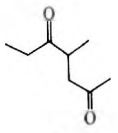
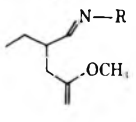
Our solution to the problem of alkylating with a masked acetonyl side chain was found in the use of 2-methoxyallyl bromide (**3**). The 2-methoxyallyl halides have been synthesized by three groups.[10-12] The alkylation chemistry of 2-methoxyallyl bromide and the analogous 2-tetrahydropyranyloxyallyl bromide have been briefly studied by Bruce and Ban[10] and by Horning et al.[11] We felt that a further investigation of their alkylation chemistry was in order.

Access to the 2-methoxyallyl halides previously has been obtained by the reaction of *N*-halosuccinimides with 2-methoxypropene, or by the pyrolysis of 1-halo-2,2-dimethoxypropanes.[10,12] The former method resulted in a carbon tetrachloride solution of the 2-methoxyallyl halide contaminated with products resulting from the addition of succinimide to the enol ether double bond. The latter method resulted in only 10–20% conversion to the desired 2-methoxyallyl halide. We have found that pyrolytic cracking of 1-bromo-2,2-dimethoxypropane[12] (**1**) in the presence of diisopropylethylammonium tosylate (**2**) leads to a mixture, **5**, of 2-methoxyallyl bromide (**3**), 1-bromo-2-methoxy-1-propene (**4**), and starting material **1** (in an average ratio of 65:21:14).[13] Attempts to separate this mixture by distillation, even through spinning band columns, failed due to decomposition, but direct use of the product mixture in alkylation reactions was found to be satisfactory. The cracking is best accomplished by heating the 1-bromo-2,2-dimethoxypropane (**1**) and 0.016 equiv of the ammonium salt **2** to 150–190 °C while distilling off the methanol formed through a 12-in. fractionating column. After all of the methanol has been removed, quick distillation of the remaining liquid through a short-path distillation apparatus yields the product mixture, crude **3** ≡ **5**. Best results are obtained if the cracking time is kept to less than 90 min, i.e., retaining a small amount of starting material, as 2-methoxyallyl bromide (**3**) will polymerize slowly under these conditions. The product mixture, which contains less than 1% protic impurities, is stable for long periods of time if stored below 0 °C; samples stored at 25 °C darken after a month or so. Mass recoveries via this method are in the range of 85–90%. This procedure works well on a scale of 30 g but scaling up of the reaction size much beyond this point results in a decrease in the yield, probably due to polymerization of the 2-methoxyallyl bromide. This polymerization results from the increased time necessary for conversion to products if the size of the reaction is increased.



Several tertiary alkylammonium salts were investigated for use as cracking catalysts, including the *p*-toluenesulfonate salts of dicyclohexylethylamine, diisopropylethylamine, benzyldiisopropylamine, tributylamine, and quinaldine.[12] Other acidic catalysts included H_2SO_4, *p*-toluenesulfonic acid,

Table I. Imine Alkylations

Starting material (R = C_6H_{11})	Product	Yield, %	Cyclopentenone	% yield from alkn product
 11	 17	84	 23	68
 12	 18	81	 24	70
 13	 19	75	 25	74
 14	 20	43	*a*	
 15	 21	65		
 16	 22	76	*b*	

[a] Cyclization resulted in a mixture of several products. [b] Hydrolysis in oxalic acid resulted in the formation of tars.

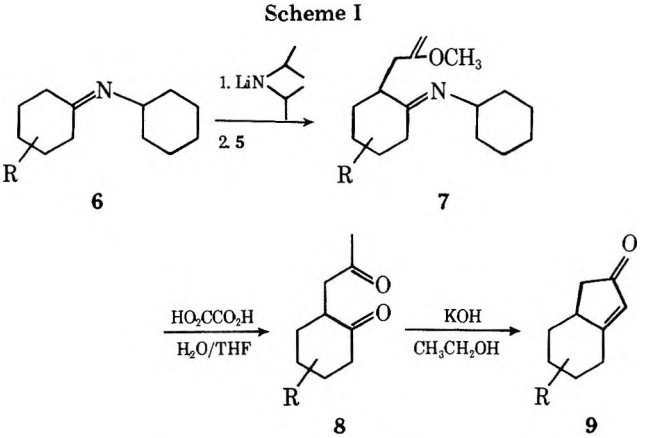
KSO_4H, and Rexyn 101. Of all these tested, diisopropylethylammonium *p*-toluenesulfonate (**2**) was found to be vastly superior. Use of the other salts listed above as catalysts resulted in less favorable ratios of 2-methoxyallyl bromide to 1-bromo-2-methoxypropene and/or a lower total conversion of the starting ketal **1** to product.

A similar but alternate method of cracking bromo ketal **1** was also investigated. A cracking column was prepared from about 12 in. of 15-mm glass tubing. This column was packed with 3-mm glass beads coated with the cracking catalyst desired. The column was heated to 260 °C with a flow of argon through it, and the bromo ketal **1** was dropwise added to the top of the column. The effluent gases were collected in a trap cooled to −78 °C. Subsequent distillation of the mixture, first to remove the methanol and then to purify the product, resulted in a product of the same average composition as that obtained previously. However, mass recoveries were in the 40–50% range and the catalyst decomposed on the column beads after two or three runs, rendering the method less practical than the simple cracking.

We also investigated the preparation of 2-methoxyallyl chloride[12] and iodide[12] via the same procedure used to prepare the bromide. Attempted cracking of 1-chloro-2,2-dimethoxypropane[12] resulted in a very low conversion to products, while the attempted cracking of 1-iodo-2,2-dimethoxypropane[12] resulted in explosive decomposition. Preparation of 2-methoxyallyl iodide (**10**) by reaction of 2-methoxyallyl bromide (**3**) with sodium iodide in methyl formate resulted in a solution of 2-methoxyallyl iodide (**10**) that, when concentrated in vacuo at 25 °C, underwent a vigorous exothermic decomposition liberating iodine. Subsequently, 2-methoxyallyl iodide (**10**) was prepared in situ from bromide **3** by addition of 1 equiv of a solution of anhydrous lithium iodide in THF. For direct preparation, therefore, the bromide **3** is the preferred reagent.

Having acquired an easy access to 2-methoxyallyl bromide, uncontaminated by protic impurities, its alkylation chemistry was investigated. Alkylation of metalloenamines, derived from imines and lithium diisopropylamide,[14] resulted in excellent yields (85–98%) of the monomethoxyallylated imines **7**, which could be hydrolyzed in good to excellent yields to 2-acetonyl ketones[15] **8**. The 2-acetonyl ketones **8** could then easily be cyclized to the corresponding cyclopentenones **9** with potassium hydroxide in refluxing ethanol;[16] of course, the resulting 1,4-diketones can be made to undergo any of their other characteristic reactions. Scheme I represents the reactions studied.

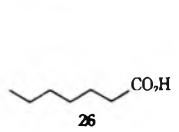
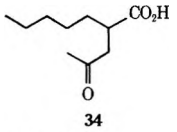
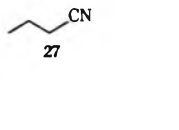
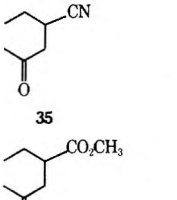
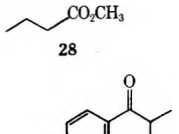
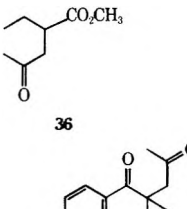
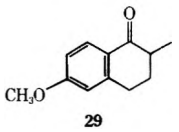
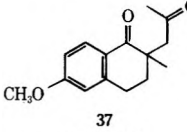
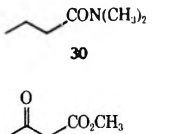
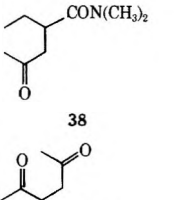
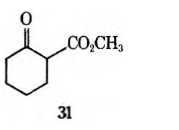
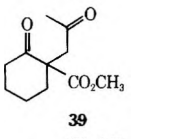
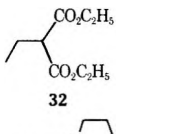
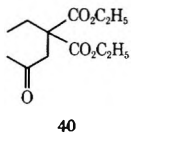
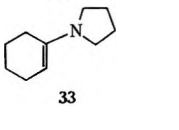
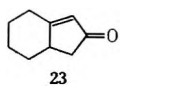
Scheme I



The procedure represents a general and convenient access to substituted cyclopentenones in about 60% overall yield from readily available starting materials. Alkylation of other activated methylene compounds with 2-methoxyallyl bromide (**3**) also proved successful. Acids, esters, amides, nitriles, and β-keto esters will readily monoalkylate with this reagent at −78 °C giving good to excellent yields of methoxyallylated product. Hydrolysis of the enol ether obtained was easily accomplished in dilute aqueous acid.

All alkylated compounds had satisfactory spectral data and were determined to be greater than 95% pure on the basis of

Table II. Other Alkylations

Starting material	Product	Yield, %
 26	 34	85
 27	 35	96
 28	 36	74
 29	 37	81
 30	 38	44
 31	 39	80
 32	 40	94
 33	 23	45

GC analysis. Alkylation results are summarized in Tables I and II.

The mildness of the conditions required to unmask the acetonyl group, water at pH 3 if desired, compared to the severe conditions required for previously available acetonyl synthons, and the effectiveness of the monoalkylation of a variety of functional groups should prove 2-methoxyallyl bromide (3) to be the reagent of choice for adding an acetonyl group to an active methylene compound. Thus, a highly efficient method for introducing the acetonyl side chain, useful for ultimate transformation to substituted cyclopentenones where applicable, has been realized via the use of 2-methoxyallyl bromide.

Experimental Section

All boiling points given are uncorrected. ^{1}H NMR spectra were obtained on a Varian EM-360 (60 MHz) spectrometer using tetramethylsilane as an internal standard. Infrared spectra were obtained from a Perkin-Elmer 467 grating infrared spectrometer. Mass spectra were obtained from a Varian-MAT CH-7 mass spectrometer. All starting materials were distilled before use. Tetrahydrofuran was dried over potassium benzophenone dianion and was freshly distilled under argon prior to use.

Diisopropylethylammonium *p*-Toluenesulfonate (2). To 3.80 g (20 mmol) of *p*-toluenesulfonic acid monohydrate in 10 mL of anhydrous methanol was added 2.80 g (22 mmol) of diisopropylethylamine. The resulting solution was concentrated in vacuo, yielding an oil which on standing crystallized. The solid was crushed and the last traces of solvent were removed by drying at 0.05 Torr: yield 6.00 g (100%); mp 87–88.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.37 (m, 15 H), 2.35 (s, 3 H), 2.8–3.3 (m, 2 H), 3.3–3.9 (m, 2 H), 7.17 (d, 2 H), 7.82 (d, 2 H), 9.18 (br s, 1 H).

1-Bromo-2,2-dimethoxypropane(1).[12] To 42 mL ($\leq$0.50 mol) of bromoacetone prepared according to the method of Levene[17] and containing 5–15% 1,1-dibromoacetone were added 60 mL (0.55 mol) of trimethyl orthoformate, 25 mL of CH_3OH, and 10 drops of H_2SO_4. After stirring for 2 h, all the bromoacetone had been converted to the ketal. The mixture was basified with 2 mL of triethylamine and concentrated in vacuo to remove most of the methyl formate. The resulting reaction mixture was added to an ice-cold solution of 20 g of sodium hydroxide in 200 mL of methanol, destroying the unketalized 1,1-dibromoacetone.

The resulting reaction mixture was partitioned between 300 mL of pentane and 200 mL of H_2O. The aqueous layer was extracted with 100 mL of pentane and the combined pentane layers were washed with 50 mL of water and dried over potassium carbonate. Concentration in vacuo and distillation gave 73 g (0.40 mol, $\geq$80%) of 1-bromo-2,2-dimethoxypropane (1): bp (80 Torr) 83–87 °C, (760 Torr) 156 °C; ^{1}H NMR (CCl_4) δ 1.36 (s, 3 H), 3.16 (s, 6 H), 3.26 (s, 2 H); IR (neat) 1219 (CH_2Br), 1110, 1077, 1049 cm^{-1} (C—O); mass spectrum (70 eV) 182 (M^+) (absent), 153 (43), 151 (44), 89 (100), 57 (69), 43 (83), 29 (34).

Cracking of Bromo Ketal 1. Preparation of 3-Bromo-2-methoxypropene (2-Methoxyallyl Bromide) (3 and 5). A mixture of 25 g of 1-bromo-2,2-dimethoxypropane (1) and 0.4 g of diisopropylethylammonium *p*-toluenesulfonate (2) was heated at 150–190 °C (bath temperature) while distilling off the methanol through a 12-in. Vigreaux fractionating column about 15 mm in diameter. The temperature of the heating bath was never allowed to exceed 200 °C, and the rate of methanol distillation was kept at a moderate rate (~1 drop/s) so as to be complete in less than 1.5 h. After removal of the methanol was complete, as shown by a rise of the head temperature to >130 °C, the distilling column was removed and the product mixture was rapidly distilled through a short-path distillation head, resulting in collection of 17.9 g (87% mass recovery) of the product mixture, **5**, i.e., crude **3**: bp (760 Torr) 134–137 °C, *d* 1.16; ^{1}H NMR 3-bromo-2-methoxy-1-propene (**3**) (CCl_4) δ 3.55 (s, 3 H), 3.79 (s, 2 H), 4.03 (d, 1 H, J = 2.6 Hz), 4.23 (d, 1 H, J = 2.6 Hz); 1-bromo-2-methoxy-1-propene (**4**) (CCl_4) δ 1.92 (br s, 3 H), 3.51 (s, 3 H), 5.11 (br s, 1 H). The mixture was found to contain ~65% 2-methoxyallyl bromide (**3**), ~21% 1-bromo-2-methoxypropene (**4**), and ~14% of the starting bromoketal (**1**) by gas chromatography at 150 °C on a 2 m × 6 mm ID column containing 15% OV17 on Chromosorb W AWDMCS: retention time 3.1 min, **4**; 3.6 min, **3**; 5.5 min, **1**. This mixture, **5**, was used as such in subsequent alkylations, and was stored at −20 °C when not in use.

Preparation of Imines. The procedure of Stork and Benaim was used to prepare the starting imines.[14] The following imines were prepared.

***N*-Cyclohexylidenecyclohexylamine**[18] **(11):** 95%; bp (10 Torr) 121–123.4 °C; ^{1}H NMR (CCl_4) δ 0.95–1.90 (m, 16 H), 19.5–2.40 (m, 4 H), 3.0–3.4 (m, 1 H); IR (neat) 1658 cm^{-1} (C=N); mass spectrum (70 eV) 179 (M^+) (31), 136 (49), 98 (100), 56 (37), 55 (85), 41 (50).

***N*-(4-Methylcyclohexylidene)cyclohexylamine**[19] **(12):** 83%; bp (7 Torr) 119–121 °C; ^{1}H NMR (CCl_4) δ 0.97 (d, 3 H), 1.2–3.0 (m, 19 H), 3.0–3.4 (m, 1 H); IR (neat) 1652 cm^{-1} (C=N); mass spectrum (70 eV) 193 (M^+) (20), 136 (43), 112 (48), 83 (38), 56 (67), 55 (78), 54 (35), 43 (100), 41 (50).

***N*-Cycloheptylidenecyclohexylamine**[20] **(13):** 70%; bp (0.05 Torr) 102–105 °C; ^{1}H NMR (CCl_4) δ 1.0–2.0 (m, 18 H), 2.1–2.8 (m, 4 H), 3.0–3.4 (m, 1 H); IR (neat) 1640 cm^{-1} (C=N); mass spectrum (70 eV) 193 (M^+) (19), 112 (65), 83 (50), 68 (35), 56 (54), 55 (100), 41 (71).

***N*-Cyclopentylidenecyclohexylamine**[21] **(14):** 83%; bp (0.05 Torr) 64–67 °C; ^{1}H NMR (CCl_4) δ 1.0–1.9 (m, 14 H), 1.95–2.4 (m, 4 H), 2.8–3.3 (m, 1 H); IR (neat) 1680 cm^{-1} (C=N); mass spectrum (70 eV) 165 (M^+) (28), 136 (45), 84 (100), 83 (34), 55 (66), 54 (41), 41 (41).

***N*-(3-Pentylidene)cyclohexylamine**[20] **(15):** 81%; bp (0.02 Torr) 60–63 °C; ^{1}H NMR (CCl_4) δ 1.0 (t, 6 H), 1.2–1.9 (m, 10 H), 2.2 (q, 4 H), 3.0–3.5 (m, 1 H); IR (neat) 1660 cm^{-1} (C=N); mass spectrum (70 eV) 167 (M^+) (24), 138 (42), 86 (35), 83 (85), 56 (100), 55 (63), 41 (35).

***N*-Butylidenecyclohexylamine**[22] **(16):** 78%; bp (80 Torr) 118–119 °C; ^{1}H NMR (CCl_4) = 0.8–1.1 (m, 3 H), 1.2–2.3 (m, 14 H), 2.7–3.2 (m, 1 H), 7.69 (d, 1 H); IR (neat) 1666 cm^{-1} (C=N); mass spectrum (70 eV) 153 (M^+) (2), 125 (70), 110 (100), 83 (30), 82 (34), 55 (69), 44 (64), 43 (33), 41 (48).

General Procedure for Alkylation of Imines. Alkylations were run using a variation of the procedure of Stork and Benaim.[14] To a solution of 1.3 mmol of lithium diisopropylamide (generated in situ from diisopropylamine and butyllithium) in 5 mL of anhydrous THF

at 0 °C containing two crystals of 1,10-phenanthroline as an indicator was added 1 mmol of the imine. The rust-colored solution was stirred at 0 °C for 0.5 h and then 0.3 mL (1.5 mmol) of **5** was added, followed by stirring an additional 15 min at 0 °C. The solution was slowly warmed to room temperature and stirred for 4–6 h. The solvent was removed in vacuo, and the residue was dissolved in 9 mL of THF. To this solution was added 1.5 mL of 1 M aqueous oxalic acid, and the solution was stirred at room temperature for 2 h. The solvent was again removed in vacuo and the residue was dissolved in ether and washed twice with water. The ether layer was separated, dried over $MgSO_4$, and filtered. The ether was removed in vacuo, leaving the crude alkylated product which was purified by bulb to bulb distillation. The following compounds were prepared from their respective imines via the above procedure.

2-Acetonylcyclohexanone[16] **(17):** 84%; bp (0.02 Torr) 105–107 °C; ^1H NMR (CCl_4) δ 2.1 (s, 3 H), 1.0–3.2 (m, 11 H); IR (neat) 1710 cm^{-1} (C=O); mass spectrum (70 eV) 154 (M^+) (21), 97 (38), 55 (40), 43 (100), 18 (35).

2-Acetonyl-4-methylcyclohexanone (18): 81%; bp (0.02 Torr) 109–111 °C; ^1H NMR (CCl_4) δ 1.0 (d, 3 H, trans), 1.31 (d, 3 H, cis), 2.09 (s, 3 H), 1.5–3.5 (m, 10 H); IR (neat) 1710 cm^{-1} (C=O); mass spectrum (70 eV) 168 (M^+) (12), 111 (36), 55 (41), 43 (100), 41 (28), 18 (57). Ratio c/t = 3/1.

2-Acetonylcycloheptanone[23] **(19):** 75%; bp (0.02 Torr) 116–119 °C; ^1H NMR (CCl_4) δ 0.8–3.3 (m, 13 H), 2.07 (s, 3H); IR (neat) 1710 cm^{-1} (C=O); mass spectrum (70 eV) 168 (M^+) (7), 111 (25), 98 (25), 55 (48), 43 (100).

2-Acetonylcyclopentanone[24] **(20):** 43%; bp (0.02 Torr) 108–111 °C; ^1H NMR (CCl_4) δ 2.07 (s, 3 H), 0.8–3.1 (m, 9 H); IR (neat) 1738 (C=O); 1719 cm^{-1} (C=O); mass spectrum (70 eV) 140 (M^+) (14), 97 (38), 83 (40), 43 (100).

4-Methyl-2,5-heptanedione (21): 65%; bp (0.02 Torr) 92–95 °C; ^1H NMR (CCl_4) δ 0.85–1.35 (m, 6 H), 2.06 (s, 3 H), 1.8–3.2 (M, 5 H); IR (neat) 1712 cm^{-1} (C=O); mass spectrum (70 eV) 142 (M^+) (2), 113 (42), 57 (78), 43 (100), 29 (38).

2-(2-Methoxy-2-propenyl)butylidenecyclohexylamine (22): 76%; bp (0.02 Torr) 116–119 °C; ^1H NMR (CCl_4) δ 0.89 (t, 3 H), 0.95–2.0 (m, 14 H), 2.0–2.6 (m, 2 H), 3.47 (s, 3 H), 3.78 (s, 2 H), 7.46 (d, 1 H); IR (neat) 1660 (C=N), 1625 cm^{-1} (C=C); mass spectrum (70 eV) 223 (M^+) (2), 208 (83), 192 (34), 126 (35), 110 (49), 83 (66), 55 (100), 43 (30), 41 (91), 29 (33).

Preparation of Cyclopentenones from 2-Acetonyl Ketones. The 2-acetonyl ketones were cyclized with KOH in refluxing ethanol by the procedure of Islam and Raphael.[16] The following compounds were obtained in this manner.

Bicyclo[4.3.0]non-6-en-8-one[16] **(23):** 68%; bp (0.05 Torr) 59–62 °C; ^1H NMR (CCl_4) δ 0.8–3.1 (m, 11 H), 5.73 (s, 1 H); IR (neat) 1705 (C–O), 1620 cm^{-1} (C=C); mass spectrum (70 eV) 136 (M^+) (100), 121 (31), 108 (58), 107 (39), 95 (48), 94 (25), 93 (35), 80 (27), 79 (64), 77 (28), 39 (42).

3-Methylbicyclo[4.3.0]non-6-en-8-one[25] **(24):** 70%; bp (0.025 Torr) 109–111 °C; ^1H NMR (CCl_4) δ 0.99 (m, 3 H), 0.8–3.0 (m, 10 H), 5.74 (s, 1 H); IR (neat) 1708 (C=O), 1623 cm^{-1} (C=C); mass spectrum (70 eV), 150 (M^+) (100), 135 (32), 122 (41), 108 (52), 107 (67), 95 (65), 94 (36), 93 (66), 91 (31), 82 (35), 80 (41), 79 (76), 77 (38), 55 (31), 41 (39), 39 (56).

Bicyclo[5.3.0]dec-7-en-9-one[23] **(25):** 75%; bp (0.025 Torr) 117–119 °C; ^1H NMR (CCl_4) δ 1.0–2.0 (m, 10 H), 2.3–3.0 (m, 3 H), 5.75 (s, 1 H); IR (neat) 1700 (C=O), 1608 cm^{-1} (C=C); mass spectrum (70 eV) 150 (M^+) (100), 122 (31), 108 (38), 107 (84), 95 (72), 94 (46), 93 (46), 82 (41), 79 (75), 77 (37), 41 (31), 38 (38).

Alkylation of Other Activated Methylene Compounds with 2-Methoxyallyl Bromide (3). The following compounds were alkylated via the published procedure: *n*-heptanoic acid[26] **(26)**, methyl butyrate[27] **(28)**, and *N,N*-dimethylbutyramide[28] **(30)**. Other compounds were alkylated via the following general procedure.

To a solution of 1.3 mmol of lithium diisopropylamide (generated in situ from diisopropylamine and butyllithium) in 5 mL of anhydrous THF at −78 °C containing two crystals of 1,10-phenanthroline as an indicator was added 1 mmol of the active methylene compound. The rust-colored solution was stirred for about 45 min at −78 °C and then 0.3 mL (1.5 mmol) of **5** was added, followed by stirring for 30 min at −78 °C. The solution was slowly warmed to room temperature and stirred for 4–6 h. The reaction was then quenched with about 3 mL of water. The solvent was removed in vacuo and the residue was taken up in 15 mL of ether. This ether solution was washed twice with 0.1 N HCl and once with water. The ether layer was separated and dried over $MgSO_4$. Removal of the ether in vacuo left the crude 2-acetonyl compound which was purified by bulb-to-bulb distillation. The following compounds were obtained.

2-Acetonylheptanoic acid[29] **(34):** 85%; bp (0.02 Torr) 150–153 °C; ^1H NMR (CCl_4) δ 0.91 (m, 3 H), 1.0–1.8 (m, 8 H), 2.09 (s, 3 H), 2.35–2.95 (m, 3 H), 11.0 (s, 1 H); IR (neat) 1765 (C=O) 1710 (C=O), 2500–3600 cm^{-1} (COOH); mass spectrum (70 eV) 173 (M^+) (1), 129 (34), 111 (26), 73 (25), 55 (29), 43 (100).

2-Ethyl-4-oxopentanenitrile (35): 96%; bp (0.05 Torr) 85–87 °C; ^1H NMR (CCl_4) δ 1.08 (t, 3 H), 1.3–1.9 (m, 2 H), 2.13 (s, 3 H), 2.4–3.2 (m, 3 H); IR (neat) 2240 (C≡N), 1719 cm^{-1} (C=O); mass spectrum (70 eV) 125 (M^+) (1), 58 (30), 43 (100).

Methyl 2-ethyl-4-oxopentanoate (36): 74%; bp (0.1 Torr) 82–85 °C; ^1H NMR (CCl_4) δ 0.9 (t, 3 H), 1.2–1.8 (m, 2 H), 2.07 (s, 3 H), 2.0–2.8 (m, 3 H), 3.63 (s, 3 H); IR (neat) 1735 (C=O), 1720 cm^{-1} (C=O); mass spectrum (70 eV) 158 (M^+) (1), 101 (53), 87 (24), 55 (21), 43 (100).

2-Methyl-2-acetonyl-6-methoxy-1-tetralone (37): 81%; bp (0.05 Torr) 150 °C; ^1H NMR (CCl_4) δ 1.13 (s, 3 H), 2.05 (s, 3 H), 1.7–2.6 (m, 4 H), 2.7–3.1 (m, 2 H), 3.73 (s, 3 H), 6.4–6.9 (m, 2 H), 7.85 (d, 2 H); IR (neat) 1712 (C=O), 1669 (C=O), 1598 (C=C), 1253 cm^{-1} (OCH_3); mass spectrum (70 eV) 246 (M^+) (13), 188 (100), 148 (96), 120 (26).

***N,N*-Dimethyl-2-ethyl-4-oxopentanamide (38):** 44%; product decomposed upon attempted distillation; ^1H NMR (CCl_4) δ 0.87 (t, 3 H), 1.2–1.7 (m, 2 H), 2.07 (s, 3 H), 2.0–3.1 (m, 3 H), 2.87 (s, 3 H), 3.10 (s, 3 H); IR (neat) 1715 (C=O), 1640 cm^{-1} (C=O); mass spectrum (70 eV) 171 (M^+) (12), 128 (40), 127 (55), 119 (39), 117 (40), 114 (61), 100 (35), 99 (42), 72 (84), 58 (100), 43 (41).

Methyl 1-Acetonyl-2-oxocyclohexanecarboxylate (39): 80%; bp (0.05 Torr) 123–125 °C; ^1H NMR (CCl_4) δ 1.25–3.0 (m, 8 H), 2.10 (s, 3 H), 2.73 (s, 2 H), 3.71 (s, 3 H); IR (neat) 1735 (C=O), 1714 cm^{-1} (C=O); mass spectrum (70 eV) 212 (M^+) (1), 180 (45), 137 (47) 127 (37), 109 (43), 81 (69), 67 (33), 55 (40), 43 (100), 41 (44).

Alkylation of *N*-(1-Cyclohexenyl)pyrrolidine (33). To a solution of 2.00 g (13 mmol) of *N*-(1-cyclohexenyl)pyrrolidine[30] in 20 mL of dioxane was added 3 mL (15 mmol) of **5**. The red solution was stirred at reflux for 2 h. Hydrolysis and ring closure were accomplished by adding 5 mL of water, 2 g of acetic acid, and 1 g of sodium acetate. This was stirred at reflux overnight and then diluted with pentane. This pentane solution was washed with both dilute aqueous HCl and dilute aqueous NaOH, dried over $MgSO_4$, and filtered. The pentane and dioxane were removed and the product was purified by bulb-to-bulb distillation. The yield of bicyclo[4.3.0]non-6-en-8-one **(23)** was 0.80 g (45%) for this procedure.

Preparation of Diethyl (Acetonylethyl)malonate (40). This compound was prepared similarly to the procedure of Muchowski and co-workers.[11] A suspension of 11 mmol of sodium hydride in 20 mL of THF was heated to reflux and 1.87 mL (10 mmol) of diethyl ethylmalonate was added dropwise. After hydrogen evolution was complete, 12 mmol of **5** was added. After stirring for 3 h at reflux, the reaction mixture was poured into dilute HCl and extracted with ether. The ether layer was dried with $MgSO_4$ and filtered. All low-boiling material was removed in vacuo, leaving 2.99 g of crude product. Bulb-to-bulb distillation afforded 2.39 (94% yield) of pure diethyl (acetonylethyl)malonate **(40)**: bp (11 Torr) 150 °C; ^1H NMR (CCl_4) δ 0.83 (t, 3 H), 1.26 (t, 6 H), 2.03 (q, 2 H), 2.13 (s, 3 H), 3.00 (s, 2 H), 4.16 (q, 4 H); IR (CCl_4) 1725 cm^{-1} (C=O); mass spectrum (70 eV) 254 (M^+) (absent), 187 (57), 141 (67), 127 (26), 125 (65), 101 (29), 55 (32), 43 (100), 29 (44).

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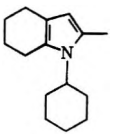

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Carbon-13 and Low-Temperature Proton Nuclear Magnetic Resonance Study of the Interaction of Acetylacetone with Diethylamine and Triethylamine[1a]

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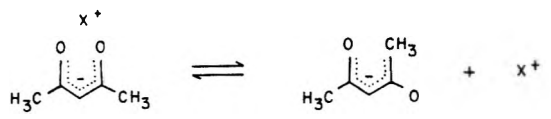
The ^1H NMR spectra of mixtures of acetylacetone with diethylamine and triethylamine have been examined at low temperature under conditions such that torsion about the partial double bonds in the acetylacetonate moiety is slow on the NMR time scale. Configurational assignments and distributions and NMR chemical shifts are used to define the nature of the interaction between the amine and acetylacetonate molecules in methanol and chloroform as solvents. The data suggest that, in methanol, mixtures of chelated ion pairs and solvent separated ions are found for both amines. Proton and carbon spectra indicate that in chloroform diethylamine gives rise to a chelated ion pair, while the diketone–triethylamine complex is best described as one in which the chelated enol form of acetylacetone is hydrogen bonded to triethylamine.

Reeves and Schneider have used proton nuclear magnetic resonance spectroscopy to study the interactions between acetylacetone (Hacac) with diethylamine and triethylamine.[2] Their study of spectra above room temperature was used to provide information about the rates of keto–enol tautomerism and proton exchange. We have shown that low-temperature ^1H NMR spectra of acetylacetonates[3-5] can be used to determine the configuration of the acetylacetonate moiety and draw conclusions about the degree and kind of association of the acac anion with alkali metal cations. For this reason, it seemed likely that examination of the low-temperature spectra of mixtures of Hacac and amines might provide further information about these interactions and could complement and extend the findings of Reeves and Schneider.

Results

The ^1H NMR spectrum of an equimolar mixture of acetylacetone (Hacac) and diethylamine in methanol-d_4 at −57 °C exhibits three singlets deriving from the acetyl methyl groups of the acac moiety. Two of these singlets at δ 1.89 and 2.27 are of equal intensity and must arise from species with the *E,Z* configuration, which have diastereotopic methyl groups. The signal at δ 1.85 arises from species with the *Z,Z* configuration in which the methyl groups are homotopic. Integration of the acetylmethyl signals indicated that the *Z,Z* configuration was present to the extent of 47% under these conditions. The use of triethylamine as base instead of diethylamine changed the situation only slightly. The proportion of acetylacetonate in the *Z,Z* form increased to ca. 60%.



When the solvent was changed to deuteriochloroform, both mixtures exhibited only single resonances for the acetyl methyl peaks at δ 1.92 at −57 °C. Unless the coalescence point for topomerization has been drastically lowered in this solvent, the observation of only a single resonance can be taken to mean that only the *Z,Z* form is present. The chemical shifts observed for the resonances both in the amine and acac moieties can provide further information about the states of association of these ammonium acetylacetonates. These data are given in Tables I and II. The ^{13}C NMR spectra of both mixtures in chloroform were also measured. The ^{13}C chemical shifts of the ethyl carbon atoms provide complementary information about protonation at nitrogen and are given together with the shifts in free amines and their benzoates in Table III.

Discussion

Reeves and Schneider concluded from their study that the keto–enol equilibrium of acetylacetone was markedly shifted

Table I. ^{1}H NMR Chemical Shifts (δ Units) in Methanol-d_4

	Hacac[d] Ambient	Et_2NH Ambient	Et_2NH·Hacac[a] −57 °C	Δδ[b]	Et_3N Ambient	Et_3N·Hacac[a] −57 °C	Δδ[b]
NCH_2CH_3		1.11	1.22	−0.11	1.05	1.18	−0.13
NCH_2CH_3		2.62	2.92	−0.30	2.56	2.95	−0.29
Acetyl	2.05		1.85 *Z,Z*			1.93 *Z,Z*	
Methyl			1.89 *E,Z*			1.93 *E,Z*	
			2.27 *E,Z*			2.21 *E,Z*	
Methine[c]	5.64						

[a] Amines were in slight excess (2–5%) over acetylacetone. [b] Shifts are defined as $\Delta\delta = \delta_{amine} - \delta_{complex}$. [c] Obtained in methanol. In methanol-d_4 this signal could not be observed due to facile H/D exchange. [d] Enolic.

Table II. ^{1}H NMR Chemical Shifts (δ Units) in Chloroform-*d*

	Hacac[c] Ambient	Et_2NH Ambient	Et_2NH·Hacac[a] −57 °C	Δδ[b]	Et_3N Ambient	Et_3N·Hacac[a] −57 °C	Δδ[b]
NCH_2CH_3		1.11	1.28	−0.17	1.03	1.07	−0.04
NCH_2CH_3		2.67	2.96	−0.30	2.53	2.61	−0.04
Acetyl	2.02		1.92	+0.10		2.10	−0.08
Methyl							
Methine	5.56		5.28	+0.28		5.57	−0.01

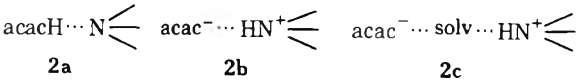
[a] Amines were in slight excess (2–5%) over acetylacetone. [b] Shifts are defined by $\Delta\delta = \delta_{amine} - \delta_{complex}$. [c] Enolic.

Table III. ^{13}C NMR Chemical Shifts (δ Units) in Chloroform-*d* at Ambient Temperature

	Et_2NH	Et_2NH·Hacac	Δδ[a]	$Et_2NH_2^+C_6H_5CO_2^-$	Δδ[a]
NCH_2CH_3	15.5	14.6	+0.9	11.4	+4.1
NCH_2CH_3	44.3	43.9	+0.6	41.9	+2.4
	Et_3N	Et_3N·Hacac	Δδ	$Et_3NH^+C_6H_5CO_2^-$	Δδ
NCH_2CH_3	11.9	12.1	−0.2	8.7	+3.2
NCH_2CH_3	46.6	46.6	0	44.9	+1.7

[a] Shifts are defined as $\Delta\delta = \delta_{amine} - \delta_{complex}$.

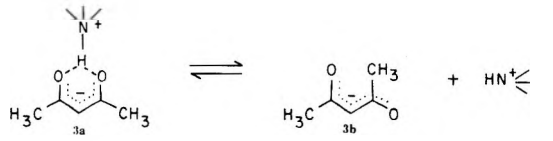
by amines to the point that such solutions are completely enolic. We, too, failed to observe resonances which could be attributed to the keto form. However, we can further differentiate between three limiting structures for "enolic" acetylacetone. Two of these structures, **2a** and **2b**, represent tightly associated complexes. Structure **2a** can be described



2a **2b** **2c**

as "enol-like" while **2b** is "enolate-like". The enolate-like form can also exist as solvent-separated ions **2c**, in addition to the intimate ion pair represented by **2b**.

Examination of the chemical shifts of the diethylamine–acac mixture indicates that the complex is completely ionized (or nearly so) in methanol. The acetyl methyl resonances are very similar to those observed for Na(acac), and the methyl and methylene resonances of the amine moiety experience downfield shifts from their positions in the free amine. We can thus represent the *Z,Z* configuration as **3a**. The similarity of

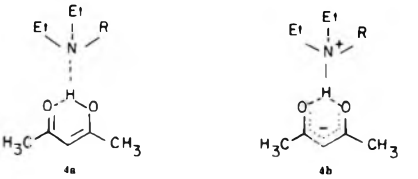


chemical shifts between this complex and those of Na(acac), which is known to be dissociated,[4,5] suggest that the *E,Z* form exists mostly as solvent-separated ions. Approximately the same interpretation can be given to the data for the triethylamine complex in methanol. The proportion of the *Z,Z* form is greater, suggesting that the conjugate acid of triethylamine is a stronger hydrogen-bond donor and thus better able to stabilize the *Z,Z* configuration in which the hydrogen is chelated by the two oxygen atoms.

This interpretation is in accord with the pK_a values for these three compounds (measured in aqueous solution at 30 °C): diethylamine (conjugate acid), 11.00;[6] triethylamine (conjugate acid), 10.74;[6] acetylacetone, 9.00.[7] Acetylacetone is substantially more acidic than the conjugate acids of either diethylamine or triethylamine, and essentially complete proton transfer is expected in aqueous solution or a comparable polar, ionizing solvent. The ions are not completely separated in methanol, and considerable association is observed, with a greater degree observed for the complex with the more acidic triethylammonium ion.

The situation is different in the less polar, poorly ionizing solvent chloroform. Here, relative acidities of Hacac and the amine conjugate acids must be changed. Acetylacetone is an uncharged acid and its acidity is reduced, while the conjugate acids of the amines are charged and dissociation does not increase the number of ions.

In this solvent the behavior of the two amines is different,



R = H, Et

reflecting their different relative acidities. The proton and carbon chemical shifts (Tables II and III) suggest that structure **4b** makes a major contribution to the structure of the diethylamine complex, which is best considered as an ion pair, while the triethylamine complex is essentially un-ionized and is best represented by structure **4a**.

The resonance of the protons in acetyl methyl groups of the diethylamine complex appears at δ 1.92, shifted upfield from that in the enol form of acetylacetone, as is the signal at δ 5.28 arising from the methine proton. The ethyl protons in the amine moiety exhibit downfield shifts comparable to those observed for both amines in methanol solution. These shifts are in accord with the behavior expected for ionic structure **4b**.

The shifts observed for triethylamine are quite different. The resonances from both the amine and acetylacetone moieties suffer very small downfield shifts. The small shifts observed suggest that the structures are not changed very much from the separate neutral compounds and that the complex is best represented by the un-ionized structure **4a**. Apparently, in this solvent the greater acidity of the conjugate acid of triethylamine (over that of diethylamine) is sufficient to suppress proton transfer, and the complex is one in which the triethylamine is only hydrogen bonded to the enolic proton of acetylacetone.

Carbon chemical shifts are also sensitive to amine protonation. Protonation is accompanied by characteristic upfield shifts of several ppm for the β carbons and smaller variable shifts for the α carbons.[8] Table III gives carbon chemical shifts for the two complexes and those in the free amines and the benzoate salts for comparison. Both amines exhibit upfield shifts for the β carbons (methyl carbons) upon conversion to the benzoates in accord with previous observations. The chemical shifts of both methyl and methylene carbon atoms in the triethylamine complex are essentially unchanged from those in the free amine, while those in the diethylamine complex experience upfield shifts which are about 25% of those in the benzoate. While these data may not quantitatively reflect the contributions of the two structures **4a** and **4b**, they do indicate that the contribution of **4b** is much greater for diethylamine.[9]

Experimental Section

Acetylacetone, diethylamine, triethylamine, and benzoic acid were obtained from commercial sources. The complexes were prepared in situ by mixing weighed amounts of the appropriate compounds.

^{1}H NMR spectra were measured on a Varian A60-A spectrometer (60 MHz). Chemical shifts are given in δ units relative to internal tetramethylsilane. Temperatures were controlled with a V-6040 variable-temperature controller and determined by measurement of methanol spectra as outlined in the Varian users manual. Carbon spectra were measured at ambient temperature on a JEOL FX-60 spectrometer (15.04 MHz) and are expressed in δ units relative to internal Me_4Si.

Registry No.—Et_2NH·Hacac, 62154-14-7; Et_3N·Hacac, 62154-15-8; $Et_2NH_2^+C_6H_5CO_2$, 940-90-9; $Et_3NH^+C_6H_5CO_2^-$, 941-02-6.

References and Notes

(1) (a) This work was supported by the National Science Foundation and the National Institute of General Medical Sciences. We also thank the National Science Foundation for an equipment grant used for the purchase of the FX-60 FT-NMR spectrometer used to obtained ^{13}C spectra for this study. (b) Alfred P. Sloan Foundation Fellow, 1972–1976. (c) On leave from the University of Tokyo.
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(7) L. Laloi and P. Rumpf, *Bull. Soc. Chim. Fr.*, **1961**, 1645.
(8) K. F. Koch, J. A. Rhoades, E. W. Hagaman, and E. Wenkert, *J. Am. Chem. Soc.*, **96**, 3300 (1974).
(9) The changes in the chemical shifts of the acetylacetone moiety are also greater when diethylamine is added. The chemical shifts for the carbonyl, methine, and methyl groups were: Hacac, 191.2, 100.3, 24.7; Hacac·$NHEt_2$, 190.5, 99.4, 26.0; Hacac·NEt_3, 191.2, 100.1, 25.0.

Alkylation and Ring Contraction Reactions of 1,3,4-Benzotriazepine-2,5-dione Systems

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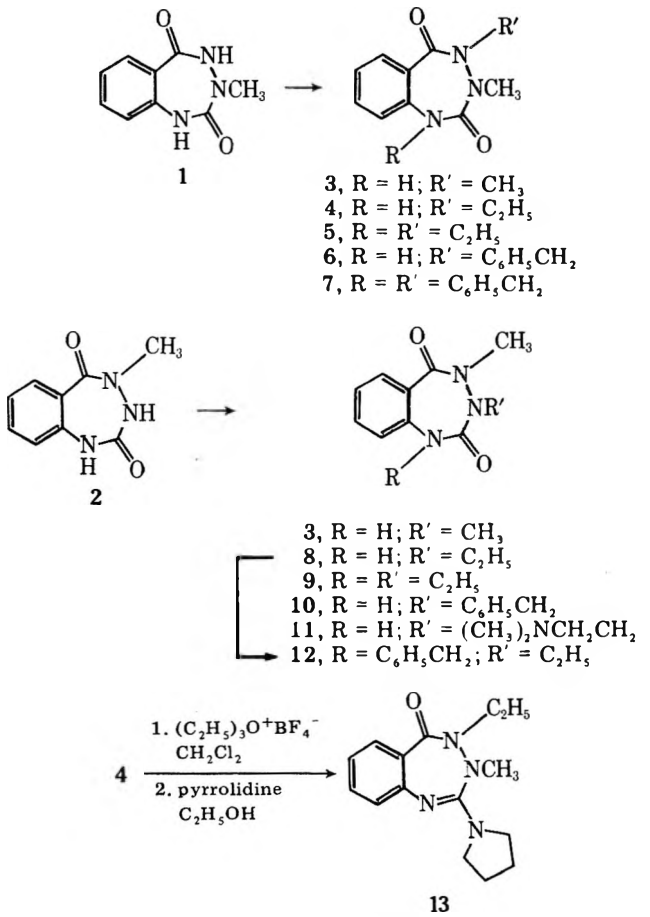
Alkylation studies on 3,4-dihydro-3-methyl-1*H*-1,3,4-benzotrazepine-2,5-dione (**1**) and its 4-methyl isomer **2** have led to a method for the regiospecific introduction of one or two (similar or dissimilar) alkyl groups to these systems, which allows the preparation of a wide variety of 1,3,4-trialkyl-3,4-dihydro-3-methyl-1*H*-1,3,4-benzotriazepine-2,5-diones. When ethyl bromoacetate was employed as the alkylating agent, ring contraction reactions occurred to produce 3-methyl-2,4(1*H*,3*H*)-quinazolinedione (**15**) from both **1** and **2**. Treatment of **2** with aqueous base also resulted in ring contraction to produce 3-(methyl)amino-2,4(1*H*,3*H*)-quinazolinedione (**30**), whereas **1**, under the same conditions, yielded 2-(*o*-aminobenzoyl)-1-methylhydrazine (**25**). Further utility of 1-acetyl-1-methylhydrazine was demonstrated in the preparation of authentic samples of **25** and **30**. Mechanisms of the ring contraction reactions are discussed.

We have recently reported[1] syntheses of 3,4-dihydro-3-methyl-1*H*-1,3,4-benzotriazepine-2,5-dione (**1**) and its 4-methyl isomer **2**. It was found that both **1** and **2** undergo selective monomethylations with sodium hydride and methyl iodide in dimethylformamide, to yield the same benzotriazepinedione **3**.[2] In this report we describe additional alkylation studies on **1** and **2**, some of which have led to interesting ring contraction reactions.

Alkylation reactions which were performed with **1** and **2** are described in Scheme I. All of the depicted reactions generally produced a single product in good yield. The selectivity of the monoalkylation reactions which produced 4-alkyl derivatives of **1** and 3-alkyl derivatives of **2** allowed the systematic introduction of a variety of alkyl groups into the benzotriazepinediones. In all cases, sodium hydride was the base employed and the solvent was dimethylformamide. Thus,

Scheme I



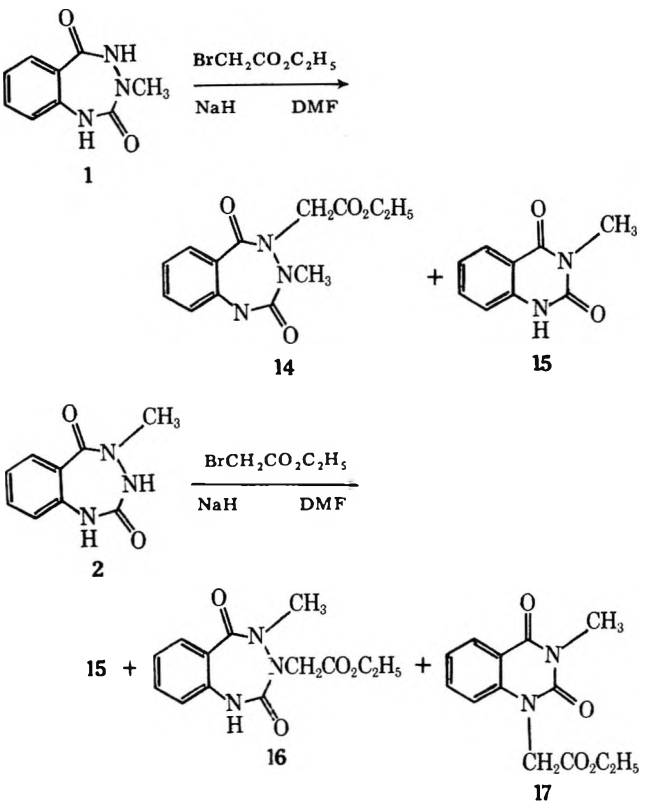
monoalkylation of **1** using equivalent amounts of sodium hydride and ethyl iodide or benzyl bromide yielded the 4-ethyl and 4-benzyl derivatives **4** and **6**, respectively. Dialkylation using 2 equiv each of sodium hydride and the same alkylating agents produced the respective 1,4-diethyl and 1,4-dibenzyl derivatives **5** and **7**.

Similar alkylations of benzotriazepinedione **2** yielded the 3-ethyl (**8**), 1,3-diethyl (**9**), and 3-benzyl (**10**) derivatives of **2**. 2-Dimethylaminoethyl chloride, under conditions of monoalkylation, gave **11**. The preparation of compound **12**, 3-ethyl-3,4-dihydro-4-methyl-1-(phenylmethyl)-1*H*-1,3,4-benzotriazepine-2,5-dione, from **2** via **8** in two successive monoalkylation reactions demonstrates the utility of the alkylation procedure in preparing a 1*H*-1,3,4-benzotriazepine-2,5-dione bearing three different alkyl groups. Treatment of **4** with triethyloxonium tetrafluoroborate followed by quenching with pyrrolidine gave **13**.

Alkylations of **1** and **2** with ethyl bromoacetate led to mixtures resulting from ring contraction reactions of the benzotriazepinediones. The product mixture from **1** gave the expected 4-carbethoxymethyl derivative **14**, and 3-methyl-2,4(1*H*,3*H*)-quinazolinedione (**15**). In the gross transformation of **1** to **15**, an NH group had been removed from the ring and its residue was not to be found on the contracted ring. Even more interesting was the finding that quinazolinedione **15** also resulted from the alkylation of **2** with ethyl bromoacetate. In addition, we isolated the expected 3-carbethoxymethyl derivative **16**, and 1,2,3,4-tetrahydro-3-methyl-2,4-dioxo-1-quinazolineacetic acid ethyl ester (**17**), which was apparently derived from **15**, after its in situ formation, by alkylation. Thus, the unmethylated nitrogen atom in the 3 and 4 positions of benzotriazepinediones **2** and **1**, respectively, could be completely removed by reaction with ethyl bromoacetate. See Scheme II.

Scheme III indicates some possible mechanistic pathways

Scheme II



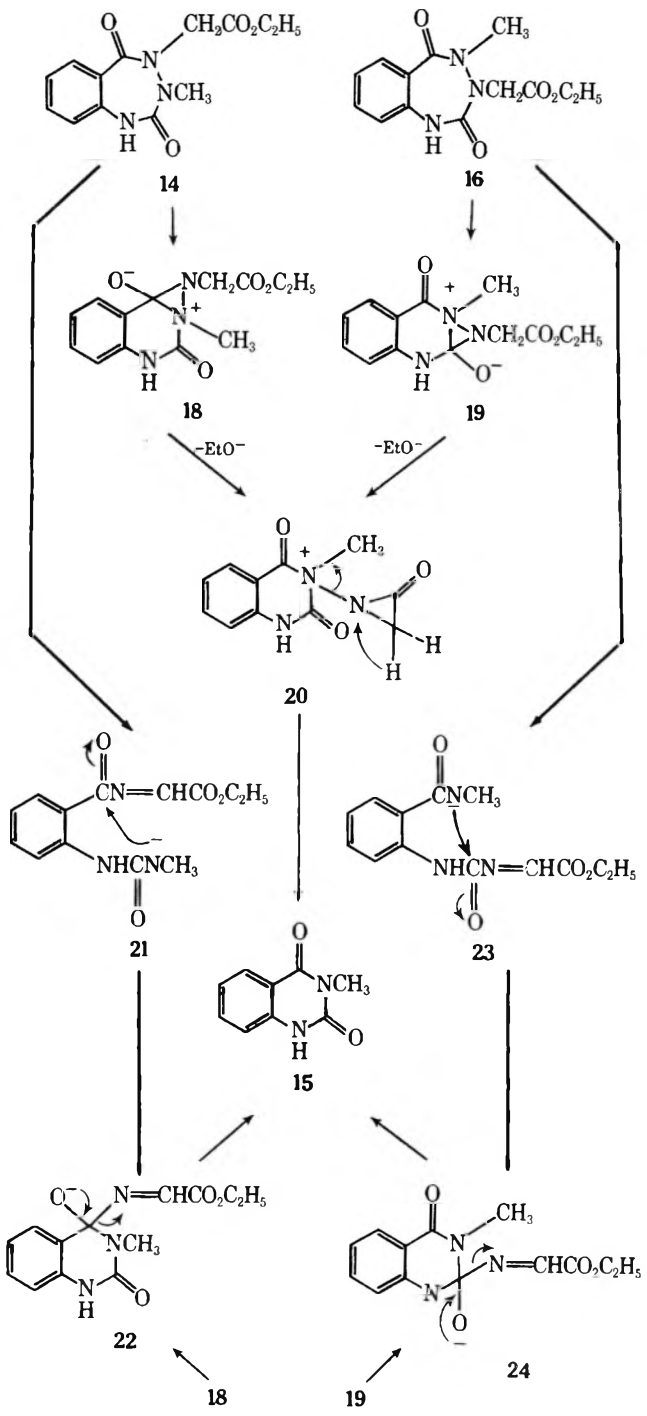
for the conversions of **14** and **16** to **15**. One set of mechanistic pathways avoids the intermediacy of acyclic precursors and invokes the aziridinone **20** as a common intermediate, which could arise from diazirine intermediates **18** and **19**, and which could liberate the constituents of HCN and CO to yield quinazolinedione **15**. Alternatively, methylene proton abstraction could lead to acyclic intermediates **21** and **23**, which then could reclose to the six-membered intermediates **22** and **24**. These latter intermediates could also arise from intermediates **18** and **19**, respectively. Extrusion of the imine salt of ethyl glyoxylate from intermediates **22** and **24** would then yield quinazolinedione **15**. It is clear that the mechanisms for these transformations involve the carbethoxymethyl group in some special manner, as do the mechanisms depicted in Scheme III, since no ring contraction reactions were observed with other monoalkylated derivatives of **1** or **2** under the same reaction conditions.

It was necessary for us to verify that quinazolinedione **15** was being produced in situ from benzotriazepinediones **14** and **16**. Experiments which strongly suggested this were alkylations of **1** and **2** with ethyl bromoacetate at a low, controlled temperature (10 °C). In these reactions, the major products were the unrearranged, alkylated benzotriazepinediones **14** and **16**, which were obtained in 69 and 64% yields, respectively. These reactions supplied sufficient quantities of **14** and **16** for subsequent experiments which established the intermediacy of these compounds in the formation of quinazolinedione **15** in the original alkylations. Treatment of **14** and **16** with equivalent amounts of sodium hydride in dimethylformamide at 90–100 °C for 2 h produced **15** in isolated yields of 82 and 88%, respectively.

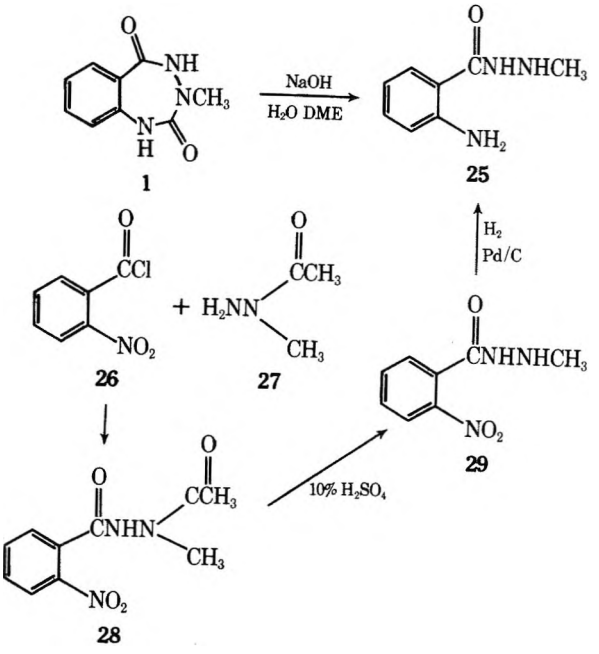
Recently reported dihydro-5*H*-1,3,4-benzotriazepin-5-ones[3,4] have been shown to undergo base-induced rearrangements to quinazolinones.[5] A review of ring contraction reactions of seven-membered ring heterocycles,[6a] including a recent report on the ring contraction of a benzo-1,2,5-triazepin-4-one,[6b] has appeared.

We have also examined the reactions of benzotriazepines **1** and **2** with aqueous base. Simple hydrolytic cleavage appears

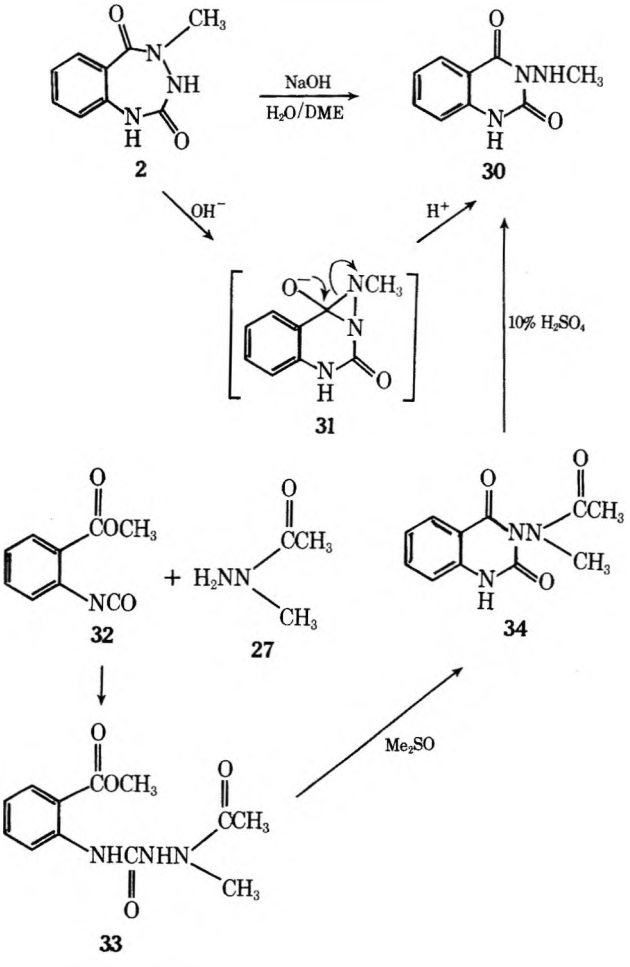
Scheme III



Scheme IV



Scheme V



to account for the formation of 2-(o-aminobenzoyl)-1-methylhydrazine (**25**) from **1**. The identity of **25** was established by comparison with an authentic sample, whose synthesis[7] is shown in Scheme IV. Acylation of 1-acetyl-1-methylhydrazine (**27**) with o-nitrobenzoyl chloride (**26**) gave hydrazide **28**, which was hydrolyzed with dilute sulfuric acid to produce **29**. Catalytic reduction of **29** gave **25**.

Treatment of **2** with aqueous base resulted in its rearrangement to 3-methylamino-2,4(1*H*,3*H*)-quinazolinedione (**30**). A possible intermediate (**31**) in this transformation is shown in Scheme V, which is reminiscent of intermediates **18** and **19** in the rearrangements of **14** and **16** to **15**.

Our preparation of an authentic sample of quinazolinedione **30** demonstrates once again the utility of 1-acetyl-1-methylhydrazine (**27**) in heterocyclic synthesis.[7] Treatment of 2-carbomethoxyphenyl isocyanate (**32**) with **27** gave semicarbazide **33**. A good method for the quantitative conversion of **33** to quinazolinedione **34** presented itself while we were recording the NMR spectrum of **33** in dimethyl sulfoxide-d_6. The conversion of **33** to **34** in dimethyl sulfoxide at room temperature was easily followed by NMR spectroscopy, and was 60% complete after 30 min, and 90% complete after 2.5 h. The disappearance of the three methyl singlets of **33** was accompanied by the appearance of a methanol signal and two pairs of singlets for the methyl groups of **34**. The pairs of sin-

glets indicated restricted rotation about the acetyl–nitrogen or nitrogen–nitrogen bond in **34**. It was also observed that **33** thermally cyclized to **34** at its melt temperature (180–182 °C). The final step in the preparation of authentic **30** was accomplished by removal of the acetyl group in **34** with 10% sulfuric acid.

The NMR spectra of alkylated 1,3,4-benzotriazepin-5-ones bearing substituted methylene groups, i.e., ethyl, benzyl, carbethoxymethyl, or 2-(dimethylamino)ethyl groups, at positions 1, 3, or 4, showed the methylene protons to be distinctly nonequivalent (see Experimental Section). For example, the chemical shift difference for the methylene protons in **6** is greater than 1 ppm. In contrast to this observation, the methylene group in quinazolinedione **17** appears as a singlet. The NMR spectrum of compound **11** was particularly interesting in that the nonequivalence of the methylene protons attached to the ring caused the methylene group adjacent to the dimethylamino group to appear as a pair of doublets (A_2 of A_2XY pattern where $J_{AY} = 7$ and $J_{Ax} = 6$ Hz).

Experimental Section[8]

4-Ethyl-3,4-dihydro-3-methyl-1*H*-1,3,4-benzotriazepine-2,5-dione (4). To a mixture of 0.960 g (40.0 mmol) of NaH in 25 mL of dimethylformamide (DMF) was added 7.64 g (40.0 mmol) of **1**. After 5 min, 6.24 g (40.0 mmol) of ethyl iodide was added to the clear solution. The addition was exothermic, and the temperature of the reaction solution rose to 80 °C. After 4 h, the solution was poured into water and extracted with several portions of CH_2Cl_2. The combined extracts were dried (Na_2SO_4), concentrated, and diluted with ether. The resulting solid was collected and air dried to afford 5.76 g (65%) of **4**: mp 128–130 °C; mp 129–130 °C (CH_2Cl_2–hexane); IR (Nujol) 3225 (NH), 1685 (C=O), 1645 cm^{-1} (C=O); NMR (Me_2SO-d_6) δ 9.65 (s, 1, NH), 8.10–7.17 (m, 4, aromatic), 4.70–3.98 (d of q, Y of A_3XY pattern, $J_{XY} = 14.5$, $J_{AY} = 7.5$ Hz, 1, one CH_2 proton), 3.83–3.12 (d of q, X of A_3XY pattern, $J_{XY} = 14.5$, $J_{AX} = 7.5$ Hz, 1, one CH_2 proton), 3.03 (s, 3, NCH_3), 1.17 (t, A_3 of A_3XY pattern, $J_{AX} = J_{AY} = 7.5$ Hz, 3, CH_2CH_3).

Anal. Calcd for $C_{11}H_{13}N_3O_2$: C, 60.26; H, 5.98; N, 19.15. Found: C, 60.55; H, 6.02; N, 19.23.

1,4-Diethyl-3,4-dihydro-3-methyl-1*H*-1,3,4-benzotriazepine-2,5-dione (5). To a mixture of 0.300 g (12.5 mmol) of NaH in 20 mL of DMF was added 1.19 g (6.25 mmol) of **1**. After 5 min, 3 mL of ethyl iodide was added (exothermic). After 2 h the solution was diluted with water and extracted with CH_2Cl_2, and the combined extracts were dried (Na_2SO_4) and concentrated to leave 980 mg of thick oil. Trituration with ether afforded 800 mg (52%) of **5**: mp 98–99 °C; IR (Nujol) 1675 (C=O) and 1650 cm^{-1} (C=O); NMR (Me_2SO-d_6) δ 8.07–7.20 (m, 4, aromatic), 4.70–3.18 (m, 4, both CH_2 groups), 2.04 (s, 3, NCH_3), 1.10 (t, $J = 7.5$ Hz, 6, both CH_2CH_3 groups).

Anal. Calcd for $C_{13}H_{17}N_3O_2$: C, 63.14; H, 6.93; N, 16.99. Found: C, 63.00; H, 6.98; N, 17.05.

3,4-Dihydro-3-methyl-4-(phenylmethyl)-1*H*-1,3,4-benzotriazepine-2,5-dione (6) and 3,4-Dihydro-3-methyl-1,4-bis(phenylmethyl)-1*H*-1,3,4-benzotriazepine-2,5-dione (7). To a mixture of 0.384 g (16.0 mmol) of NaH in 25 mL of DMF was added 2.87 g (16.0 mmol) of **1**. After 5 min, 2.57 g (15.0 mmol) of benzyl bromide was added (exothermic). After 15 h, the solution was diluted with water and extracted with CH_2Cl_2 and the combined extracts were dried (Na_2SO_4) and concentrated to a thick oil which crystallized upon standing to yield 2.80 g (66%) of **6**: mp 147–148 °C; mp 150–151 °C (ethanol); IR (Nujol) 3240 (NH), 1690 (C=O), 1630 cm^{-1} (C=O); NMR ($CDCl_3$) δ 8.05–7.87 (d of d, $J_{ortho} = 7$, $J_{meta} = 2$ Hz, 1, H ortho to C=O), 7.78 (s, 1, NH, D_2O exchangeable), 7.50–7.03 (m, 7, aromatic), 6.90–6.74 (d of d, $J_{ortho} = 7$, $J_{meta} = 1.5$ Hz, 1 aromatic), 5.50 (d, $J = 16$ Hz, 1, one CH_2 proton), 4.42 (d, $J = 16$ Hz, 1, one CH_2 proton), 2.97 (s, 3, CH_3).

Anal. Calcd for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.38; N, 14.94. Found: C, 68.00; H, 5.49; N, 15.04.

When the above experiment was performed with a 25% excess of NaH,[9] workup afforded an oil from which preferentially crystallized, in 24% yield, compound **7**: mp 173–174 °C; IR (Nujol) 1670 (C=O), 1650 cm^{-1} (C=O); NMR (Me_2SO-d_6) δ 8.03–6.85 (m, 14, aromatic), 5.48 (d, $J = 16$ Hz, 1, one 1-benzyl CH_2 proton), 4.79 (s, 2, 4-benzyl CH_2 group), 4.69 (d, $J = 16$ Hz, 1, one 1-benzyl CH_2 proton), 3.07 (s, 3, CH_3).

Anal. Calcd for $C_{23}H_{21}N_3O_2$: C, 74.37; H, 5.70; N, 11.31. Found: C, 74.70; H, 5.89; N, 11.24.

3-Ethyl-3,4-dihydro-4-methyl-1*H*-1,3,4-benzotriazepine-2,5-dione (8). To a mixture of 0.960 g (40.0 mmol) of NaH in 15 mL of DMF was added 7.60 g (39.8 mmol) of **2**. To the slurry, after 5 min of stirring, was added 6.24 g (40.0 mmol) of ethyl iodide (exothermic). After 3 h, the solution was diluted with water and extracted with CH_2Cl_2 and the combined extracts were dried (Na_2SO_4) and concentrated to a small volume. The white, crystalline product which formed was collected to yield 6.65 g (76%) of **8**: mp 186–188 °C; IR (Nujol) 3270 (NH), 1700 cm^{-1} (C=O); NMR (Me_2SO-d_6) δ 9.72 (s, 1, NH), 8.08–7.13 (m, 4, aromatic), 3.90–2.94 (m, 5, NCH_3 and NCH_2CH_3, with NCH_3 s at 3.16), 0.94 (t, $J = 7.2$ Hz, 3, NCH_2CH_3).

Anal. Calcd for $C_{11}H_{13}N_3O_2$: C, 60.26; H, 5.98; N, 19.15. Found: C, 60.50; H, 5.91; N, 19.01.

1,3-Diethyl-3,4-dihydro-4-methyl-1*H*-1,3,4-benzotriazepine-2,5-dione (9). To a mixture of 0.349 g (14.2 mmol) of NaH in 20 mL of DMF was added 1.20 g (6.28 mmol) of **2**. To the slurry, after 5 min of stirring, was added an excess (3.2 mL) of ethyl iodide (exothermic). After 3 h, the solution was diluted with water and extracted with CH_2Cl_2 and the combined extracts were dried (Na_2SO_4) and concentrated to an oil which crystallized upon trituration with ether to yield 1.14 g (73%) of **9**: mp 77–79 °C; IR (Nujol) 1680 (C=O) and 1660 cm^{-1} (C=O); NMR ($CDCl_3$) δ 8.17–7.23 (m, 4, aromatic), 4.30–3.00 (m, 7, both CH_2 groups and NCH_3 group, with NCH_3 s at 3.17), 1.14 (t, $J = 7.2$ Hz, 3, NCH_2CH_3), 0.87 (t, $J = 7.2$ Hz, 3, NCH_2CH_3).

Anal. Calcd for $C_{13}H_{17}N_3O_2$: C, 63.14; H, 6.93; N, 16.99. Found: C, 63.00; H, 6.85; N, 17.11.

3,4-Dihydro-4-methyl-3-(phenylmethyl)-1*H*-1,3,4-benzotriazepine-2,5-dione (10). To a mixture of 0.900 g (37.5 mmol) of NaH in 15 mL of DMF was added 5.74 g (30.0 mmol) of **2**. To the slurry, after 5 min of stirring, was added 5.13 g (30.0 mmol) of benzyl bromide (exothermic). After 3 h the solution was diluted with water and extracted with CH_2Cl_2 and the combined extracts were dried (Na_2SO_4) and concentrated to yield a white solid which was recrystallized from CH_2Cl_2–hexane to yield 5.70 g (68%) of **10**: mp 183–184 °C; IR (Nujol) 3240 (NH), 1695 (C=O), 1660 cm^{-1} (C=O); NMR ($CDCl_3$) δ 9.87 (s, 1, NH), 7.98–7.05 (m, 9, aromatic), 4.95 (d, $J = 15$ Hz, 1, one CH_2 proton), 4.46 (d, $J = 15$ Hz, 1, one CH_2 proton), 3.23 (s, 3, CH_3).

Anal. Calcd for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.38; N, 14.94. Found: C, 68.50; H, 5.34; N, 14.85.

3-[2-(Dimethylamino)ethyl]-3,4-dihydro-4-methyl-1*H*-1,3,4-benzotriazepine-2,5-dione (11). To a mixture of 2.00 g (83.3 mmol) of NaH in 25 mL of DMF was added 5.74 g (30.0 mmol) of **2**. To the slurry, after 5 min of stirring, was added 4.32 g (30.0 mmol) of 2-dimethylaminoethyl chloride hydrochloride (Aldrich) in portions. The addition was exothermic and the temperature was controlled below 35 °C. After stirring overnight, the solution was diluted with water and extracted with CH_2Cl_2. The combined extracts were concentrated to a light oil which was taken up in ether and treated with HCl gas. The resulting white, hygroscopic material was partitioned between CH_2Cl_2 and 20% NaOH. The organic layer was dried (Na_2SO_4) and concentrated to yield ca. 2 g of light oil from which crystallized, upon trituration with ether, compound **11** (mp 154–156 °C): mp 158–159°C (CH_2Cl_2–hexane); IR (Nujol) 3250 (NH), 1690 (C=O), 1630 cm^{-1} (C=O); NMR ($CDCl_3$) δ 8.03–7.87 (m, 1, H ortho to C=O, 7.56–7.07 (m, 3, NH and 2 aromatic protons), 7.04–6.87 (m, 1, H ortho to NH), 4.17–3.79 (d of t, Y of A_2XY pattern, $J_{AY} = 7$, $J_{XY} = 14.5$ Hz, 1, one ring-adjacent CH_2proton), 3.49–3.12 (d of t, X of A_2XY pattern, $J_{AX} = 6$, $J_{XY} = 14.5$ Hz, 1, one ring-adjacent CH_2 proton), 3.33 (s, 3, NCH_3), 2.50–2.20 [d of d, A_2 of A_2XY pattern, $J_{AX} = 6$, $J_{AY} = 7$ Hz, 2, $CH_2N(CH_3)_2$], 2.07 [s, 6, $N(CH_3)_2$]; mass spectrum (70 eV, chemical ionization, methane) *m/e* 263 ($M^+ + 1$), 291 ($M^+ + 29$).

Anal. Calcd for $C_{13}H_{18}N_4O_3$: C, 59.52; H, 6.92; N, 21.36. Found: C, 59.30; H, 6.97; N, 21.41.

3-Ethyl-3,4-dihydro-4-methyl-1-(phenylmethyl)-1*H*-1,3,4-benzotriazepine-2,5-dione (12). To a mixture of 0.619 g (25.8 mmol) of NaH in 25 mL of DMF was added 5.65 g (25.8 mmol) of **8**. To the slurry, after 5 min of stirring, was added 4.41 g (25.8 mmol) of benzyl bromide (exothermic). After 15 h, the solution was concentrated and the residue was partitioned between CH_2Cl_2 and water. The organic layer was dried (Na_2SO_4) and concentrated to leave 7.98 g (100%) of **12** as a colorless oil: IR (Nujol) 1660 cm^{-1} (broad C=O); NMR ($CDCl_3$) δ 8.03–7.75 (m, 1, H ortho to C=O), 7.60–7.00 (m, 8, remaining aromatic), 5.23 (d, $J = 7.5$ Hz, 1, one benzyl CH_2 proton), 4.75 (d, $J = 7.5$ Hz, 1, one benzyl CH_2 proton), 3.87–3.08 (m, 5, NCH_2CH_3 and NCH_3 s at 3.30), 1.03 (t, $J = 7$ Hz, 3, NCH_2CH_3); mass spectrum (70 eV) *m/e* 309 (molecular ion).

4-Ethyl-3-methyl-2-(1-pyrrolidinyl)-3*H*-1,3,4-benzotriaze-

pin-5(4*H*)-one (13). To a solution of 4.38 g (20.0 mmol) of **4** in 50 mL of CH_2Cl_2 under a nitrogen atmosphere was added 20 mL (0.200 mol) of 1 M triethyloxonium tetrafluoroborate in CH_2Cl_2 (Aldrich). After 24 h at room temperature, the solution was concentrated and the residual oil was reconstituted in 200 mL of absolute ethanol. Excess (20 g) pyrrolidine was added and the solution was heated at reflux for 15 h. The solution was concentrated and a CH_2Cl_2 solution of the residue was washed with water and then extracted with aqueous hydrochloric acid. The aqueous layer was neutralized with sodium hydroxide and extracted with CH_2Cl_2 to leave, after drying (Na_2SO_4) and concentration, 2.34 g of oil. GLC (5% SE-30, 5 ft × 0.125 in., 250 °C, 30 mL/min of He) indicated two well-separated components (1.4 and 3.7 min) as did TLC. A 2.07-g quantity of the oil was applied to 120 g of alumina (Fisher A-540) and eluted with 1 L of ether to cleanly remove the component which eluted at 3.7 min by GLC. Concentration of the ether solution afforded 0.820 g of oil which crystallized upon trituration with ether–hexane to yield **13** as a white solid: mp 71–72 °C; IR (Nujol) 1655 cm^{-1} (C=O); NMR ($CDCl_3$) δ 8.08–7.80 (m, 1, H ortho to C=O), 7.57–6.87 (m, 3, remaining aromatic), 4.18–3.27 (m, 6, CH_2NCH_2 and NCH_2CH_3), 2.70 (s, 3, NCH_3), 2.31–1.83 (m, 4, $NCH_2CH_2CH_2$), 1.32 (t, J = 7.2 Hz, 3, NCH_2CH_3); mass spectrum (70 eV) m/e 272 (molecular ion).

Anal. Calcd for $C_{15}H_{20}N_4O$: C, 66.15; H, 7.40; N, 20.57. Found: C, 65.90; H, 7.45; N, 20.26.

The remaining component was cleanly removed from the column by elution with ethyl acetate, but it was not identified.

Alkylation of 1 with Ethyl Bromoacetate. To a mixture of 0.960 g (40.0 mmol) of NaH in 25 mL of DMF was added 7.64 g (40.0 mmol) of **1**. To the slurry, after 5 min of stirring, was added 6.68 g (40.0 mmol) of ethyl bromoacetate, dropwise. The temperature of the reaction mixture during the exothermic addition was kept at 50–55 °C. After 2.5 h, the red solution was poured into water. A 500-mg quantity of **1**, which was soluble in neither phase, was recovered by filtration. (Concentration of the aqueous phase afforded an additional 295 mg of **1**.) The organic phase was dried (Na_2SO_4) and concentrated to leave 11.9 g of semisolid from which was removed, by filtration, 1.19 g of 3-methyl-2,4(1*H*,3*H*)-quinazolinedione (**15**): mp 233–235 °C (CH_2Cl_2) (lit. mp 236[10] and 236–238 °C[11]); IR (Nujol) 1715 (C=O), 1665 cm^{-1} (C=O); NMR (Me_2SO-d_6) δ 8.07–7.85 (m, 1, H ortho to C=O), 7.85–7.52 (m, 1, aromatic), 7.38–7.05 (m, 2, aromatic), 3.30 (s, 3, CH_3); mass spectrum (70 eV) m/e 176 (molecular ion).

Anal. Calcd for $C_9H_8N_2O_2$: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.50; H, 4.51; N, 16.04.

From an ether solution of the filtrate was obtained, by crystallization, 2.07 g of 1,2,3,5-tetrahydro-3-methyl-2,5-dioxo-4*H*-1,3,4-benzotriazepine-4-acetic acid ethyl ester (**14**, mp 137–139 °C): mp 138–140 °C (ethanol–hexane); IR (Nujol) 3300 (NH), 1730 (ester C=O), 1705 (C=O), 1630 cm^{-1} (C=O); NMR ($CDCl_3$) δ 8.10–7.84 (m, 2, NH and H ortho to C=O), 7.63–6.90 (m, 3, aromatic), 4.80 (d, J = 18 Hz, 1, one NCH_2 proton), 4.28 (d, J = 18 Hz, 1, one NCH_2 proton), 4.27 (q, J = 7.2 Hz, 2, OCH_2), 1.30 (t, J = 7.2 Hz, 3, OCH_2CH_3); mass spectrum (70 eV) m/e 277 (molecular ion).

Anal. Calcd for $C_{13}H_{15}N_3O_4$: C, 56.31; H, 5.45; N, 15.16. Found: C, 56.10; H, 5.41; N, 14.96.

When the alkylation was performed with 4.59 g (24.0 mmol) of **1**, 0.660 g (27.5 mmol) of NaH, and 4.59 g (27.5 mmol) of ethyl bromoacetate, and the reaction temperature was controlled at 10–13 °C, workup as above afforded 3.72 g (69%) of **14**.

Alkylation of 2 with Ethyl Bromoacetate. To a mixture of 0.700 g (29.2 mmol) of NaH in 20 mL of DMF was added 4.59 g (24.0 mmol) of **2**. To the slurry, after 5 min of stirring, was added 4.80 g (28.7 mmol) of ethyl bromoacetate. The addition was exothermic and the reaction temperature was not controlled. The red solution was stirred at room temperature for 2.5 h, diluted with water, and extracted with CH_2Cl_2. The combined extracts were dried (Na_2SO_4) and concentrated to a small volume. Filtration afforded 815 mg of **17**. An ether solution of the filtrate yielded 950 mg of 2,3,4,5-tetrahydro-4-methyl-2,5-dioxo-1*H*-1,3,4-benzotriazepine-3-acetic acid ethyl ester (**16**): mp 146–148 °C (ethanol–hexane); IR (Nujol) 3250 (NH), 1750 (ester C=O), 1690 (C=O), 1630 cm^{-1} (C=O); NMR (Me_2SO-d_6) δ 9.77 (s, 1, NH), 8.17–7.17 (m, 4, aromatic), 4.67 (d, J = 18 Hz, 1, one NCH_2 proton), 4.42 (d, J = 18 Hz, 1, one NCH_2 proton), 4.12 (q, J = 7.2 Hz, 2, OCH_2), 3.30 (s, 3, NCH_3), 1.08 (t, J = 7.2 Hz, 3, OCH_2CH_3); mass spectrum (70 eV) m/e 277 (molecular ion).

Anal. Calcd for $C_{13}H_{15}N_3O_4$: C, 56.31; H, 5.45; N, 15.16. Found: C, 56.50; H, 5.49; N, 15.13.

The ether filtrate subsequently yielded 200 mg of 1,2,3,4-tetrahydro-3-methyl-2,4-dioxo-1-quinazolineacetic acid ethyl ester (**17**, mp 128–130 °C); mp 132–133 °C (ethanol–hexane); IR (Nujol) 1740 (ester C=O), 1705 (C=O), 1670 cm^{-1} (C=O); NMR (Me_2SO-d_6) δ 8.43–8.15 (m, 1, H ortho to C=O), 8.15–7.78 (m, 1, aromatic), 7.72–7.34 (m, 2, aromatic), 5.09 (s, 2, NCH_2), 4.32 (q, J = 7.2 Hz, 2, OCH_2), 3.42 (s, 3, NCH_3), 1.27 (t, J = 7.2 Hz, 3, OCH_2CH_3); mass spectrum (70 eV) m/e 262 (molecular ion).

When the alkylation was repeated with 4.59 g (24.0 mmol) of **2**, 0.900 mol (37.5 mmol) of NaH, and 4.95 g (29.6 mmol) of ethyl bromoacetate, and the reaction temperature was controlled at 10–13 °C, workup as above afforded 3.52 g (64%) of **18** and 0.800 g (13%) of **17**.

Preparation of 15 from 14 and 16. To a solution of 0.500 g (1.80 mmol) of **14** in 25 mL of DMF was added 0.480 g (2.00 mmol) of NaH and the mixture was heated in an oil bath at 90–100 °C for 2 h. The solution was cooled, diluted with water, and extracted with CH_2Cl_2. The combined extracts were dried (Na_2SO_4) and concentrated, and the residue was washed with ether to afford 0.260 g (82%) of **15**, mp 235–239 °C. On the same scale was prepared **15** (mp 238–240 °C) from **16** in 88% yield.

Treatment of 1 with Aqueous Base. A 1.00-g (5.23 mmol) quantity of **1** was dissolved in a mixture of 10 mL of 2 N NaOH solution and 10 mL of dimethoxyethane and heated at reflux for 2 h. The solution was diluted with 125 mL of water and acidified with concentrated HCl. A crop of white crystals afforded, after filtration and drying, 0.26 g of **1**. The filtrate was made basic with $NaHCO_3$ solution and extracted with CH_2Cl_2. The combined extracts were dried (Na_2SO_4) and concentrated to yield 0.38 g of material which was slurried with ether and filtered to remove an additional 40 mg of **1** (20% total yield). The filtrate, by evaporative crystallization from ether–hexane, afforded 150 mg (17%) of 2-aminobenzoic acid 2-methylhydrazide (**25**), mp 70–77 °C (lit.[7] mp 90–91 °C), whose IR (Nujol) and NMR ($CDCl_3$) spectra were identical with those of authentic **25**.[7] A mass spectrum (70 eV) of **25** displayed a molecular ion at m/e 165.

Treatment of 2 with Aqueous Base. A 1.00-g (5.23 mmol) quantity of **2** was dissolved in 10 mL of 2 N NaOH solution and 10 mL of dimethoxyethane and heated at reflux for 2 h. The solution was cooled, acidified with concentrated HCl, and basified with $NaHCO_3$ solution. Extraction with CH_2Cl_2 removed, after drying (Na_2SO_4) and concentrating the combined extracts, 0.45 g of oil which, when triturated with ether–ethanol, afforded 100 mg (10%) of 3-(methyl)amino-2,4(1*H*,3*H*)-quinazolinedione (**30**), mp 186–188 °C, which was spectrally identical with an authentic sample whose preparation follows.

2-[[(2-Acetyl-2-methylhydrazino)carbonyl]amino]benzoic Acid Methyl Ester (33). To a stirring solution of 8.86 g (0.500 mol) of 2-carbomethoxyphenyl isocyanate[12] in 50 mL of CH_2Cl_2 with ice-bath cooling was added 4.41 g (0.500 mol) of 1-acetyl-1-methylhydrazine.[7] After 30 min at room temperature, the solution was concentrated to a small volume and the resulting solid was collected and air dried to yield 12.9 g (97%) of **33**: mp 180–182 °C, followed by resolidification and remelt at 291–293 °C (2-propanol); IR (Nujol) 3270 and 3230 (NH), 1715 (ester C=O), 1695 (amide C=O), 1640 cm^{-1} (semicarbazide C=O); NMR ($CDCl_3$) δ 10.90 (s, 1, NH), 8.60–8.43 (m, 1, aromatic), 8.08–7.80 (m, 1, aromatic), 7.80 (s, 1, NH), 7.64–7.30 (m, 1, aromatic), 7.16–6.84 (m, 1, aromatic), 3.87 (s, 3, OCH_3), 3.29 (s, 3, NCH_3), 2.20 (s, 3, $COCH_3$).

Anal. Calcd for $C_{12}H_{15}N_3O_4$: C, 54.33; H, 5.70; N, 15.84. Found: C, 54.60; H, 5.65; N, 15.55.

***N*-(1,4-Dihydro-2,4-dioxo-3(2*H*)-quinazolinyl)-*N*-methylacetamide (34).** A 3.75-g (14.1 mmol) quantity of **33** was dissolved in 20 mL of dimethyl sulfoxide, warmed at 60 °C for 30 min, and allowed to stand at room temperature for 15 h. With the addition of a small volume of water, crystallization commenced to yield, after collection, washing with water, and air drying, 3.30 g (100%) of **34**: mp 291–293 °C (ethanol); IR (Nujol) 3270 and 3220 (NH), 1730 (C=O), 1685 (C=O), 1665 cm^{-1} (C=O); NMR (Me_2SO-d_6) δ 8.07–7.44 (m, 1, aromatic), 7.74–7.50 (m, 1, aromatic), 7.40–7.04 (m, 2, aromatic), 3.24 and 3.10 (2 singlets, in a ratio of ca. 1:2.5, respectively, 3, NCH_3), 2.18 and 1.80 (2 singlets, in a ratio of ca. 1:2.5, respectively, 3, $COCH_3$).

Anal. Calcd for $C_{11}H_{11}N_3O_3$: C, 56.65; H, 4.75; N, 18.02. Found: C, 56.70; H, 4.79; N, 18.17.

Preparation of 30 from 34. A 3.30-g (12.4 mmol) quantity of **34** in 60 mL of 10% H_2SO_4 was heated at reflux for 15 h. The clear solution was cooled and neutralized with cold, dilute NaOH solution. The precipitate which resulted was collected and air dried to yield 2.10 g (89%) of **30** (mp 194–196 °C): mp 195–196 °C (ethanol); IR (Nujol) 3400–3000 (broad NH), 1720 (C=O), 1670 cm^{-1} (C=O); NMR ($CDCl_3$ + Me_2SO-d_6) δ 8.20–7.97 (m, 1, H ortho to C=O), 7.78–7.00 (m, 3, remaining aromatic), 5.63 (broad signal, 1, NH, D_2O exchangeable), 2.84 (broad s, 3, CH_3).

Anal. Calcd for $C_9H_9N_3O_2$: C, 56.54; H, 4.75; N, 21.98. Found: C,

56.31; H, 4.60; N, 21.70.

Registry No.—**1**, 55043-79-3; **2**, 55043-81-7; **4**, 62493-12-3; **5**, 62493-13-4; **6**, 62493-14-5; **7**, 62493-15-6; **8**, 62493-16-7; **9**, 62493-17-8; **10**, 62493-18-9; **11**, 62493-19-0; **12**, 62493-20-3; **13**, 62493-21-4; **14**, 62493-22-5; **15**, 607-19-2; **16**, 62493-23-6; **17**, 62493-24-7; **25**, 59169-47-0; **27**, 3530-13-0; **30**, 62493-25-8; **32**, 1793-07-3; **33**, 62493-26-9; **34**, 62493-27-0; ethyl iodide, 75-03-6; benzyl bromide, 100-39-0; 2-dimethylaminoethyl chloride HCl, 4584-46-7; pyrrolidine, 123-75-1; ethyl bromoacetate, 105-36-2.

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Cycliacylation Studies on 3,5-Disubstituted Phenylalkanoic Acids[1]

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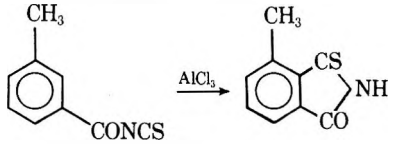
The syntheses of 4-(3-chloro-5-methylphenyl)butanoic acid (**1**), 4-(3-methoxy-5-methylphenyl)butanoic acid (**4**), 3-(3-chloro-5-methylphenyl)propanoic acid (**7**), and 3-(3-methoxy-5-methylphenyl)propanoic acid (**10**) are described. The ring closure of these acids to mixtures of 6,8-disubstituted tetralones and 5,7-disubstituted indanones by five reagents (anhydrous HF, polyphosphoric acid, $AlCl_3$ on RCOCl in benzene and in nitroethane, and $SnCl_4$ on RCOCl in benzene) were studied. For acids **1** and **7**, ring closure took place predominantly (2:1) at the position para to the chlorine. For acids **4** and **10**, ring closure took place predominantly (66–91%) para to the methoxy group.

Relatively little systematic study has been made on preferential intramolecular Friedel–Crafts-type acylation reactions. The cases studied include mainly the cyclization of dibasic acids which gave six-membered ring compounds in preference to five- and seven-membered rings,[3] and monobasic acids which can react with either of two different rings or with one ring in two different locations.[3] One interesting such reaction involves the cyclization of *m*-tolyl isothiocyanate exclusively to 2a-thio-3-methylphthalimide[4] although the para position is available.



The primary objective of the research reported herein was to study the intramolecular cyclization of unsymmetrical 4-(3,5-disubstituted phenyl)butanoic acids to isomeric 6,8-disubstituted tetralones. We hoped to learn something about the relative directive influence of substituents on the aromatic ring in cyclization experiments and about the effect of cyclizing reagent on the proportions of isomers found. The products obtained might provide new intermediates for the synthesis of trisubstituted naphthalenes desired as starting materials in certain projected syntheses. As the work progressed, we included studies on the cyclization of unsymmetrical 3-(3,5-disubstituted phenyl)propanoic acids to yield isomeric 5,7-disubstituted indanones because, by so doing, the effects in ring closures to five-membered rings might be compared to the effects in six-membered rings. The substituents chosen for study involved methyl vs. chlorine and methyl vs. methoxy.

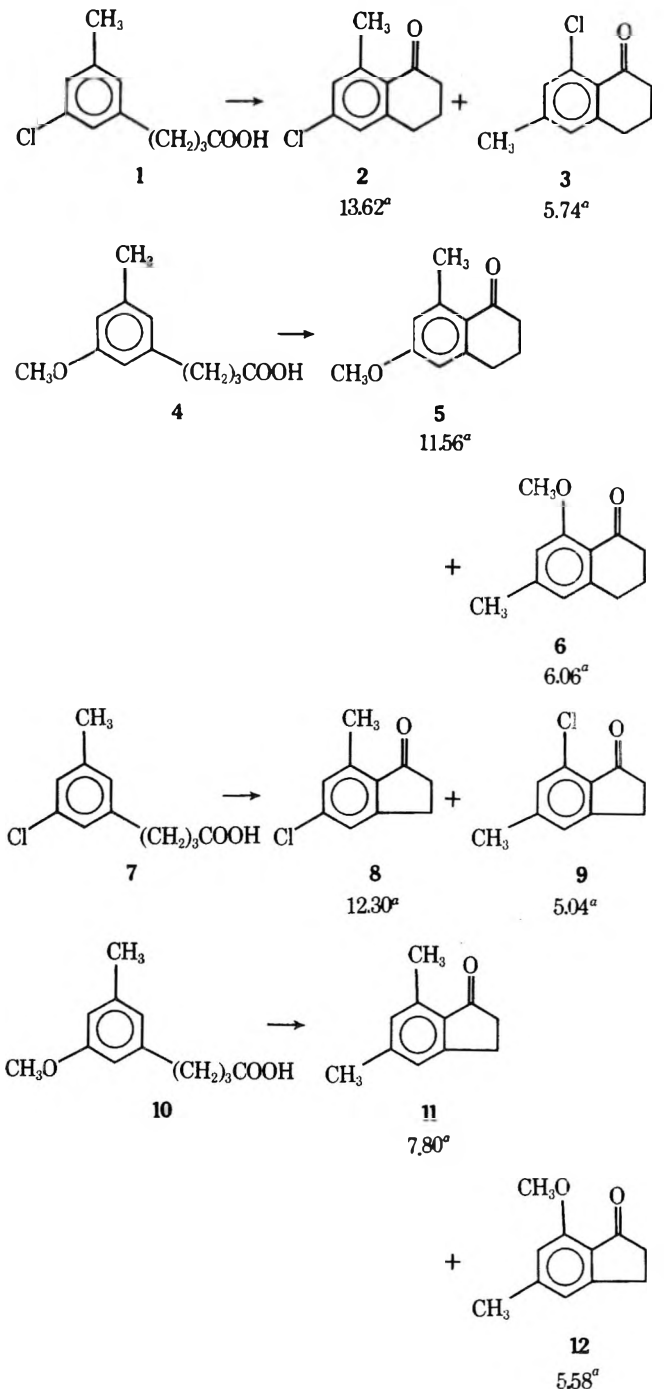
To fulfill the above objectives, we synthesized 4-(3-chloro-5-methylphenyl)butanoic acid (**1**), 4-(3-methoxy-5-methylphenyl)butanoic acid (**4**), 3-(3-chloro-5-methylphenyl)propanoic acid (**7**), and 3-(3-methoxy-5-methylphenyl)propanoic acid (**10**). All were cyclized to the tetralones and indanones shown in Scheme I.

The cyclizations of the acids were accomplished by means of the following reagents: (A) hydrogen fluoride, (B) polyphosphoric acid (PPA), (C) aluminum chloride in benzene using acid chloride, (D) aluminum chloride in nitroethane using acid chloride, and (E) stannic chloride in benzene using acid chloride. The results are summarized in Table I.

The results listed in Table I show that the proportions of isomers formed are essentially the same in comparable cases when a five- or six-membered ring ketone was formed. Furthermore, there is very little effect on the proportions of isomers formed when the cyclization conditions were changed. In the cases of both the chloro- and methoxy-substituted compounds, the reagent which gave the least selectivity was the action of aluminum chloride on the acid chloride in benzene. This lack of selectivity was more pronounced in the methoxy compounds than in the chloro compounds. The best selectivity was obtained with the methoxy compounds using aluminum chloride in nitroethane to give products in which the ketone function was produced by cyclization para to the methoxy group.

The proportions of isomeric ketones formed in each case represents the resultant of a number of parameters which must relate to the tendencies to react para to one function and ortho to the other. Since no quantitative data relating to ortho substitution in Friedel–Crafts acylations are at hand, no attempt to calculate the expected ratios was made.

Scheme I



a Extrapolated molar-shift values obtained with Eu(DPM)$_3$ (see Experimental Section).

The acids **1**, **4**, **7**, and **10**, were synthesized as shown in Scheme II.

Several unsuccessful attempts were made to isomerize 2,5-dimethylchlorobenzene to 3,5-dimethylchlorobenzene by acidic catalysts since acid-catalyzed rearrangements of trimethylbenzenes to mesitylene are known.[5] The desired 3,5-dimethylchlorobenzene was readily obtained from 3,5-dimethylaniline.[6]

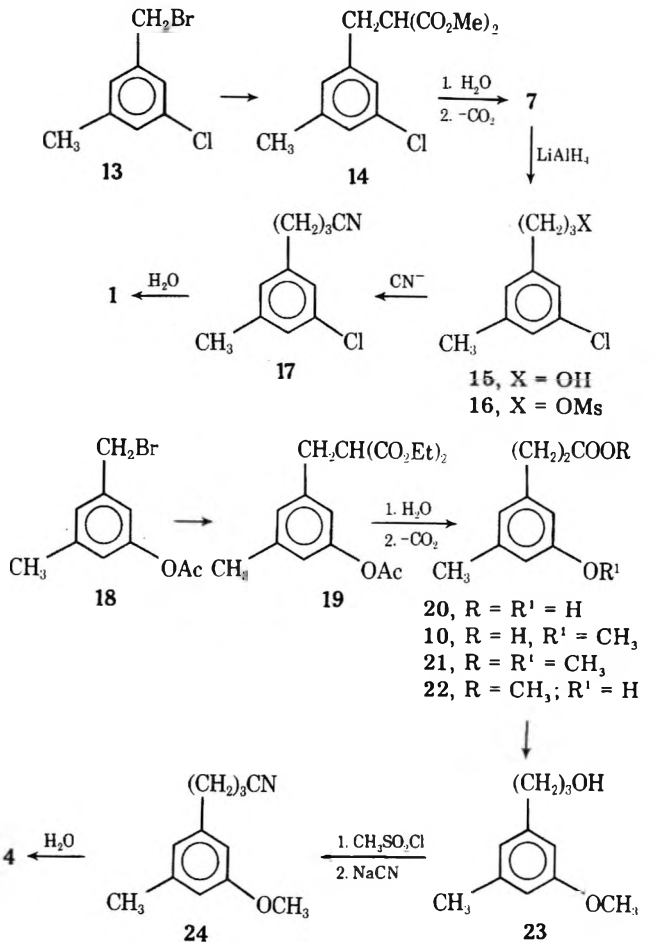
In general, all of the steps outlined in Scheme II proceeded in high yields and are described in the Experimental Section. The introduction of a bromine atom into a methyl group of 3,5-dimethylphenol by means of *N*-bromsuccinimide (NBS) could be accomplished only with 3,5-dimethylphenyl acetate. If the free phenol or the methyl ether were used, only nuclear bromination, mainly in the 4 position, occurred. The conversion of 3-hydroxy-5-methylphenylpropanoic acid (**20**) into methyl 3-(3-methoxy-5-methylphenyl)propanoate (**21**) was best accomplished (overall yield 84.6%) by esterification to methyl 3-(3-hydroxy-5-methylphenyl)propanoate (**22**), followed by treatment with sodium hydride and methyl iodide in DMF. The preparation of 3-(3-methoxy-5-methylphenyl)-propanoic acid (**10**) from **20** was carried out in 85% yield by treatment of the disodium salt of **20** in DMF with 1 equiv of methyl iodide. This reaction represents the advantage of using a bis-anion for selective alkylation.

Table I. Effect of Cyclizing Agent on Relative Yields of Major Product Isomer of Selected 3,5-Disubstituted Phenylalkanoic Acids

Reagent	2[a]	8[a]	5[a]	11[a]
1. HF[b]	66	64	84	82
2. PPA[b]	67	65	84	83
3. 3. $AlCl_3/C_6H_6$[b]	61	62	66	69
4. $AlCl_3/C_2H_5NO_2$[b]	66	65	91	91
5. $SnCl_4/C_6H_6$[b]	68	70	87	86

[a] Major isomer, the remainder consisted of the compounds **3**, **9**, **6**, and **12**, respectively. [b] See Experimental Section for description of experimental details.

Scheme II



Experimental Section[7]

Attempts to Isomerize 2,5-Dimethylchlorobenzene. (1) A mixture of 10 mL of 2,5-dimethylchlorobenzene, 50 mL of HF, and 7 g of BF_3 (loss of weighed cylinder) was held at room temperature in a stainless-steel bomb for 3 h. Only starting chloro compound was present, as shown by gas-chromatographic analysis. (2) A mixture of 27 mL of chloro compound and 7 g of $SnCl_4$ showed only starting compound up to 5 days at room temperature. (3) In an experiment similar to (2), except that 3.5 g of $AlCl_3$ and 1 mL of concentrated HCl

Table II. Proton Shift Data

Compd[a]	Parent Peak		Shift	
	CH_3	OCH_3	CH_3	OCH_3
2	2.50		0.137	
3	2.36		0.057	
5	2.48	3.66	0.117	0.026
6	2.35	3.74	0.060	0.073
8	2.46		0.123	
9	2.38		0.050	
11	2.47	3.75	0.078	0.016
12	2.32	3.79	0.056	0.067

[a] All spectra were taken in CCl_4, $(CH_3)_4Si$ standard, δ, and in tared NMR tubes for quantitative solution preparation. Each shift was determined with five different compound/LSR ratios. The average of five closely agreeing shift ratios is reported in the shift column.

was used instead of $SnCl_4$, analysis showed many products, including *p*-xylene and higher molecular weight substances.

3,5-Dimethylchlorobenzene. Using essentially the procedure described,[8] 3,5-dimethylaniline was converted into 3,5-dimethylchlorobenzene, bp 73 °C at 15 mm, in 72% yield.

Dimethyl 3-Chloro-5-methylbenzylmalonate* (14). A mixture of 140.5 g (1.0 mol) of 3,5-dimethylchlorobenzene, 141 g (0.8 mol) of *N*-bromosuccinimide, 5 g of benzoyl peroxide, and 1 L of CCl_4 was refluxed for 6 h and cooled. After filtration of the succinimide, the product in the filtrate was fractionated to yield 45 g (0.32 mol) of 3,5-dimethylchlorobenzene, bp 73 °C at 15 mm, and 132 g (0.60 mol, 72% yield based on unrecovered chloro compound) of 3-chloro-5-methylbenzyl bromide (**13**), bp 145 °C at 15 mm, 78 °C at 0.2 mm, mp 57–58 °C. Because of instability in air, **13** was used as soon as distilled. No sample was sent for elemental analyses. To the sodium methoxide solution prepared from 30 g (1.3 mol) of sodium and 1 L of absolute methanol was added 300 g (2.5 mol) of dimethyl malonate under N_2 followed by 214 g (1.2 mol) of **13** during 30 min. After 16 h at reflux, most of the methanol was distilled, the residue was diluted with dilute acid, and the product was isolated as usual to yield 157 g of dimethyl malonate and 294 g (91%) of **14**, bp 154 °C at 1 mm.

3-(3-Chloro-5-methylphenyl)propanoic Acid* (7). A mixture of 122 g of **14**, 100 g of NaOH, and 1.2 L of water was refluxed for 8 h. The homogeneous solution was cooled and acidified with 400 mL of concentrated HCl. After 2 h of reflux, decarboxylation was complete. A conventional work-up afforded 79 g (88%) of **7**, bp 110 °C at 0.2 mm.

3-(3-Chloro-5-methylphenyl)-1-propanol* (15). To a mixture of 38 g of $LiAlH_4$ and 700 mL of anhydrous ether which had been refluxed for 1 h was added dropwise a solution of 65 g of **14** in 50 mL of ether. After 18 h at reflux, the cooled mixture was treated as described.[9] Distillation of the product afforded 58.0 g (95%) of **15**, bp 110 °C at 1 mm.

3-(3-Chloro-5-methylphenyl)-1-propyl Methanesulfonate* (16). To an ice-cooled solution of 41.0 g of **15** and 25 g of triethylamine in 400 mL of benzene was added dropwise a solution of 27 g of mesyl chloride in 150 mL of benzene. The mixture was allowed to stand at 20–25 °C for 3 h and the $(Et)_3NHCl$ was filtered. From the filtrate after work-up in the usual manner (dilute HCl extraction) was obtained 57 g (98%) of **16** which was analytically pure without recrystallization, and used in the next step.

3-(3-Chloro-5-methylphenyl)-1-propyl Cyanide* (17). A phase-transfer[10] mixture containing 40.0 g of **16**, 23 g of KCN, 1 g of Aliquat-336,[11] 20 mL of water, and 200 mL of benzene was stirred and heated to reflux for 5 h. After the usual work-up, distillation afforded 25.0 g (85%) of **17**, bp 126 °C at 0.75 mm.

4-(3-Chloro-5-methylphenyl)butanoic Acid* (1). A mixture of 22.0 g of **17**, 40 g of NaOH, 10 mL of methanol, and 400 mL of water was refluxed for 2 days. After acidifying with 200 mL of concentrated HCl, the mixture was refluxed for 8 h. The organic acid fraction of the product was distilled to yield 22.5 g (94%) of **1**, bp 155 °C at 0.2 mm, mp 45.0–46.5 °C when crystallized from hexane.

3,5-Dimethylphenyl Acetate. To a solution of 244 g of 3,5-dimethylphenol (Aldrich) in 170 g of pyridine and 2 L of ether was added dropwise 156 g of acetyl chloride. After 16 h at reflux, the mixture was filtered and the filtrate was washed with 5% HCl and worked up as usual to yield 320 g (97%) of 3,5-dimethylphenyl acetate, bp 125 °C at 15 mm (lit.[12] bp 115–117 °C at 14 mm).

3-(Bromomethyl)-5-methylphenyl Acetate* (18). A mixture of 164 g (1.0 mol) of 3,5-dimethylphenyl acetate, 141 g (0.80 mol) of NBS, 5 g of benzoyl peroxide, and 1 L of CCl_4 was stirred and heated at reflux for 6 h, cooled, and filtered. After working up as usual, fractionation through a Widmer column (18 in.) yielded 53 g (32%) of recovered 3,5-dimethylphenyl acetate, bp 50 °C at 0.2 mm, and 158 g (96% allowing for recovered starting acetate) of **18**, bp 95 °C at 0.2 mm. The yield was much better than when equivalent amounts of NBS were used. The compound is an extremely irritating lachrymator.

Dimethyl (3-Acetoxy-5-methylbenzyl)malonate (19). Dimethyl malonate was alkylated with **18** essentially as described for the preparation of **14**. The product, **19**, bp 168–170 °C at 0.2 mm, was obtained in 52% yield: NMR (CCl_4) δ 2.09 (s, 3, ArO_2CCH_3), 2.23 (s, 3, $ArCH_3$), 3.06 (d, 2, CH_2CH), 3.53 (t, 1, CH_2CH), 3.55 (s, 6, $COOCH_3$), 6.68 (m, 3, ArH); ms *m/e* 294. Because of a slight impurity which was not removed on distillation, the C,H analyses were off. This material was used for the next step.

3-(3-Hydroxy-5-methylphenyl)propanoic Acid* (20). A mixture of 120 g of **19**, 120 g of NaOH, and 1.2 L of water was boiled for 6 h. After careful acidification with 500 mL of concentrated HCl, boiling was continued for 18 h (no further evolution of CO_2). After the usual work-up, distillation yielded 66 g (89%) of **20**, bp 190–200 °C at 1 mm, mp 83–84 °C after crystallization from pentane and heptane.

3-(3-Methoxy-5-methylphenyl)propanoic Acid* (10). To a stirred solution of 36.0 g (0.2 mol) of **20** in 350 mL of pure dimethylformamide (DMF) was added 10 g (0.42 mol) of NaH. After gas evolution had subsided, 29.0 g (0.2 mol) of CH_3I was added dropwise. The reaction mixture was warmed and then heated nearly to reflux of DMF during 1 h. After the usual work-up, the product was distilled to yield 33.0 g (85%) of **10**, bp 138 °C at 0.8 mm. The same compound was obtained in 73% yield when the methylation was performed in absolute methanol using 2 equiv of $NaOCH_3$ and 1 equiv of CH_3I.

Methyl 3-(3-Hydroxy-5-methylphenyl)propanoate* (22). Esterification of 90 g of **20** with methanolic H_2SO_4 afforded 89 g (92%) of **22**, bp 170–172 °C at 0.8 mm.

Methyl 3-(3-Methoxy-5-methylphenyl)propanoate* (21). Esterification of 97.5 g of **10** with methanolic H_2SO_4 afforded 97.0 g (93%) of **21**, bp 143–149 °C at 0.8 mm. By treatment of 39.0 g of **20** with a solution of 10 g of NaOH in 175 mL of water followed by addition of 25 g of $(CH_3)_2SO_4$ there was obtained 32 g (72%) of **21**.

Alternately, a mixture of 19.4 g (0.1 mol) of **22** in 175 mL of DMF was treated with 2.4 g (0.1 mol) of NaH in portions. When hydrogen was no longer evolved, 15 g (0.11 mol) of CH_3I was added dropwise. After 1 h of reflux, the mixture was added to 1 L of water and worked up as usual to yield 19.3 g (92%) of **21**.

3-(3-Methoxy-5-methylphenyl)-1-propanol* (23). A solution of 104 g of **21** in 400 mL of ether was added during 1 h to a mixture of 40 g of $LiAlH_4$ in 600 mL of ether. After being held at reflux for 16 h, the mixture was worked up as described[9] to yield 87 g (96%) of **23**, bp 166–167 °C at 0.8 mm.

4-(3-Methoxy-5-methylphenyl)-1-propyl Cyanide* (24). By treatment similar to that described above for conversion of **15** to **16**, 45 g of **23** was converted into the mesylate of **23**, mp 47–48 °C, in 91% yield (characterized by *m/e* 242 and NMR[2]). This mesylate was treated as described for **17** to yield **24**, bp 140–141 °C at 0.1 mm, in 95% yield.

4-(3-Methoxy-5-methylphenyl)butanoic Acid* (4). Hydrolysis of **24** was carried out essentially as described above for **1** to yield 91% of **4**, mp 50.5–51.5 °C.

5-Chloro-7-methyl-1-indanone* (8) and 7-Chloro-5-methyl-1-indanone* (9). To 35 mL of HF in a polyethylene bottle was added 5.0 g of **7**. After standing for 6 h, the residue was treated with ice and the products were extracted by ether. After the usual work-up, distillation afforded 4.0 g (88%) of a mixture of **8**, mp 67–68 °C, and **9**, mp 37–38 °C, separated by preparative GLC[7] (see Table I). The assignments of structure to **8** and **9** were made with the aid of tris(2,2,6,6-tetramethylheptane-3,5-dionato)europium[13], Eu(DPM)$_3$ (see Table II for NMR assignments).

6-Chloro-8-methyl-3,4-dihydro-1(2*H*)-naphthalenone* (2) and 8-Chloro-6-methyl-3,4-dihydro-1(2*H*)-naphthalenone* (3). The cyclization of **1** into a mixture of **2**, mp 65.5–66.5 °C, and **3**, mp 122–123 °C, was accomplished in 92% yield as described for the preparation of **8** and **9**. The separation was performed by preparative GLC.[7] See Tables I and II for the proportions of **2** and **3** and their structure proofs.

5-Methoxy-7-methyl-1-indanone* (11) and 7-Methoxy-5-methyl-1-indanone* (12). The cyclization of **10** was performed as in the case of **7** to yield 74% of a mixture of **11**, mp 83–85 °C, and **12**, mp 35–41 °C,[14] which were separated by preparative GLC.[7] See Ta-

bles I and II for relative amounts formed and assignment of structure.

6-Methoxy-8-methyl-3,4-dihydro-1(2*H*)-naphthalenone* (5) and **8-Methoxy-6-methyl-3,4-dihydro-1(2*H*)-naphthalenone (6).** The cyclization of **4** as described for **7** afforded 93% of a mixture of **5**, mp 69–70 °C (lit.[3b] mp 70.5 °C), and **6**, separated by GLC.[7] The amounts formed and assignments of structure are listed in Tables I and II.

Standard Cyclization Procedures. Method A (HF). To 30 mL of HF in a 50-mL polyethylene bottle was added about 2 g of the acid to be cyclized. After 3–6 h at room temperature, the contents was treated with ice and the organic product was taken into ether. After removal of uncyclized acid by alkaline extraction, the ketone mixture was isolated as usual. The yields were generally high. In the case of cyclization of **10**, the HF solution was worked up after 3 h because on longer standing the formation of high-molecular-weight products occurred.

Method B (PPA). The acids were dissolved in PPA at 80 °C and the reaction was interrupted after 10–30 min. In general, about 80% yields of ketones were obtained.

Method C (RCOCl, $AlCl_3$, Benzene). The requisite acid chlorides were prepared by treatment of the acids in CH_2Cl_2 with 1 equiv of PCl_5 at reflux. The solvent and $POCl_3$ were removed in vacuo and solutions of the acid chlorides in benzene were added to stirred suspensions of $AlCl_3$ in benzene.[15] The cyclizations were run from 30 to 60 min at room temperature, after which the mixtures were poured on ice and the ketonic fraction of the products was isolated in high yield as usual.

Method D (RCOCl, $AlCl_3$, $C_2H_5NO_2$). These reactions were run in purified nitroethane and the ketone fractions were isolated as described above in method C.

Method E (RCOCl, $SnCl_4$, Benzene). In these reactions the acid chloride was purposely contaminated with small amounts of $POCl_3$[16] and dissolved in benzene. Stannic chloride was added to the mixture at 10–20 °C and the reactions were interrupted after 10–30 min. The ketone fraction was isolated in high yield in the usual way.

Analyses of Ketone Mixtures. The isomeric ketone mixtures obtained by the above cyclization procedures were analyzed by quantitative GLC techniques[7] and the individual isomers in each mixture were separated by preparative GLC.[7] The assignments of structure to the cyclized ketones were made on the basis of the shifts in the NMR spectra caused by tris(2,2,6,6-tetramethylheptane-3,5-dionato)europium ($Eu(DPM)_3$). Since all lanthanide shift-reagent (LSR) studies were done at essentially the same concentration and temperature, it was possible to extrapolate what the induced shifts would be under these conditions and equimolar amounts of LSR and substrate. Linear-regression analysis of the shift data using the regression function of the SPSS[17] showed a high correlation between shift and LSR concentration for each isomer. Extrapolation for 100% $Eu(DPM)_3$ using linear-equation solutions provide the molar-shift values listed by the ketones in Scheme I. The order of decreasing molar shift lists ketones before others.[13]

In order to determine if the ketone mixtures formed were the result of kinetic rather than thermodynamic factors, portions of ketones rich in the minor isomer were subjected to the same experimental conditions which controlled their formation. In no case was a difference noted in the ratio of isomeric ketones after treatment. Thus, the results reflect kinetic control.

Registry No.—**1**, 62358-67-2; **2**, 62358-75-2; **3**, 62358-76-3; **4**, 18458-09-8; **5**, 62358-79-6; **6**, 62358-80-9; **7**, 62358-63-8; **8**, 62358-73-0; **9**, 62358-74-1; **10**, 22524-05-6; **11**, 62358-77-4; **12**, 62358-78-5; **13**, 62358-81-0; **14**, 62358-62-7; **15**, 62358-64-9; **16**, 62358-65-0; **17**, 62358-66-1; **18**, 62358-68-3; **19**, 62358-82-1; **20**, 60549-28-2; **21**, 62358-71-8; **22**, 62358-70-7; **23**, 22524-06-7; **24**, 62358-72-9; 3,5-dimethylchlorobenzene, 556-97-8; dimethyl malonate, 108-59-8; 3,5-dimethylphenyl acetate, 877-82-7; 3,5-dimethylphenol, 108-68-9.

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(6) This route is simple but expensive because of the high cost of 3,5-dimethylaniline (Aldrich Chemical Co.). See ref 2 for alternate syntheses.
(7) All melting points and boiling points are uncorrected. Single boiling points refer to the boiling point of a small sample taken from the center of a fraction. This sample was used for analyses, NMR, and mass spectra. All compounds marked with an asterisk gave C, H analyses (done by Robertson Labs, Florham Park, N.J.) within ±0.3% of theory; NMR and mass spectra were consistent with expected values (see ref 2 for details). Quantitative GLC analyses were done on a F&M Model 609 instrument (flame-ionization detector) using a 10 ft × 0.25 in. column packed with 20% Carbowax 20M on 60–80 mesh Chromosorb W. Preparative GLC was done on a F&M Model 500 Instrument (thermal-conductivity detector) using a 20 ft × 0.25 in. column packed with 20% Se-30 on 60–80 mesh Chromosone W. Flow rates were usually 15 mL/min and temperatures of 180 and 200 °C were used. Mass spectra were done by M. R. Weisenberger using a CEC-MS9 instrument (70 eV). The term "worked up in the usual way" means that an ether or ether–benzene solution of the products was washed with dilute Na_2CO_3 and/or HCl, and saturated NaCl solution, and was then dried by passing through a cone of $MgSO_4$. Solvent was then removed on a rotary evaporator.
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(16) M. S. Newman, H. V. Anderson, and K. H. Takemura, *J. Am. Chem. Soc.*, **75**, 347 (1953).
(17) Statistical Package for the Social Sciences (SPSS) was developed by the National Opinion Research Center, University of Chicago. Version 5.4 of SPSS, as supported by the Ohio State University Instruction and Research Computer Center, was used for the linear-regression analyses.

Electrolytic Reductive Coupling of 1,3-Diphenyl-1,3-propanedione and Derivatives[1]

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The electrolytic reductive coupling of 1,3-diketones leads to pinacols which are sersitive to both acids and bases. Electrolysis of slightly acidic solutions of 1,3-diphenyl-1,3-propanedione gives stable products but does not give the open-chain pinacol **2a**. Instead, the cyclized forms **6a** and a tricyclotrioxanonane **3a** are produced. The fluoro, chloro, and bromo derivatives **1b–d** produce the pinacols **2b–d**, whereas the methyl and methoxy derivatives **1f,g** produce pinacols which are quite susceptible to dehydration to hexadienediones **4f,g**, which undergo further reduction. All pinacols (as well as **3a** and **6a**) are readily dehydrated by acid forming the hexadienediones **4**. **4a** was reduced in good yield to the hexenedione **5a**.

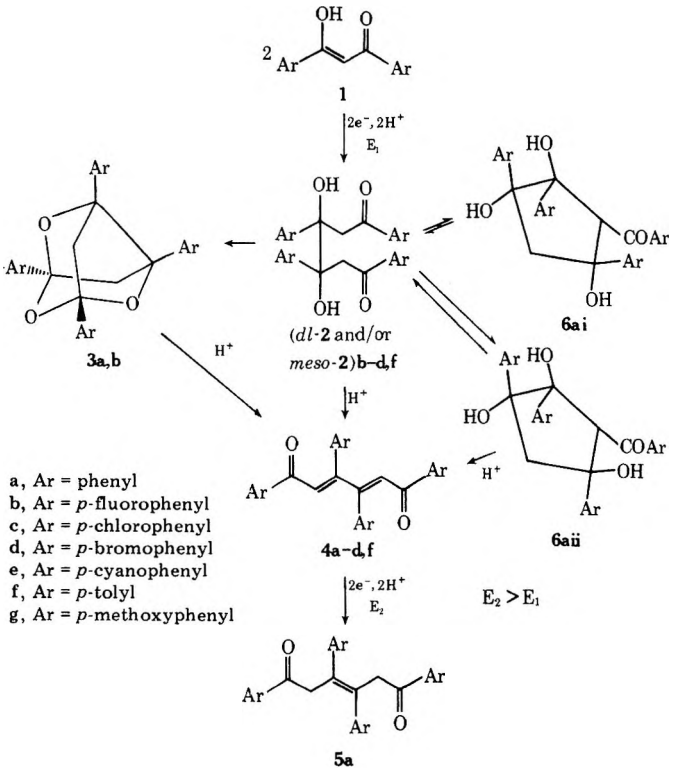
Several years ago Evans and Woodbury[2] reported that 1,3-diphenyl-1,3-propanedione (**1a**) could be electrochemically reduced in ethanol–water with the uptake of one, two, or four electrons depending on solution pH and cathode potential. Since that time the reduction of **1a** and related compounds has been studied in aprotic media[3–5] and the products from electrolysis of numerous other 1,3-diketones have been characterized.[6–14] Of particular interest in these studies has been the nature of the two-electron product with attention being focused on the possibility of cyclopropanediol formation.[6,10,13,14] The nature of the dimeric products formed by one-electron reduction has received less attention.[10,13,15]

The reductive coupling of **1a** was reported to give the pinacol **2a**.[2] We have extended our investigation of this interesting process and we now report a variety of other products formed in the reduction and information about the generality of the reaction.

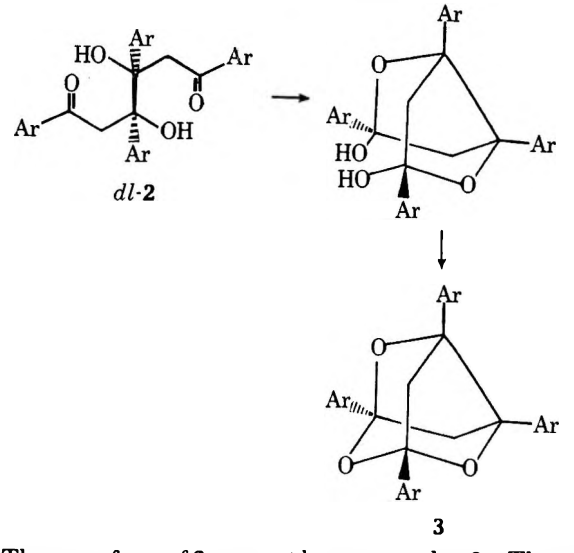
Results and Discussion

1,3-Diphenyl-1,3-propanedione (1a). Controlled potential coulometry has shown that **1a** is reduced in a one-electron process at −1.15 V in pH 4.2 buffer.[2] The product was previously reported to be the pinacol **2a** but the 100-MHz NMR spectrum indicates that one of the isomers of **6a** is a more likely assignment (Scheme I). **6a** is formed by an intramolecular aldol condensation of **2a**. In the two isomers of **6a** shown, it is assumed on steric grounds that the phenyl and benzoyl groups will be oriented trans to each other in the cyclic ketol. In addition, this communication reports the isolation of a new product, the trioxatricyclononane **3a**. **3a** can be obtained more reliably and in better yield using the 80% ethanol–water acetate buffer. This product may be obtained from *dl*-**2a** by double intramolecular ketalization followed by dehydration (Scheme II). It was found that stirring a suspension of **6a** in the acetate buffer caused partial conversion to **3a**.

Scheme I

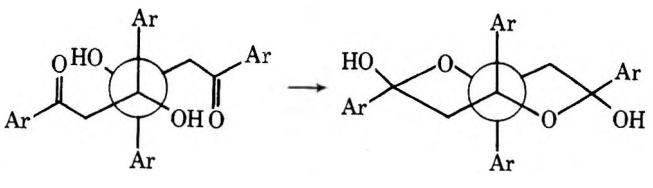


Scheme II



The meso form of **2a** cannot be converted to **3a**. Though it may form the bishemiketal, the dehydration step is impossible because the two OH groups are rot properly situated (Scheme III). It is on the basis of its conversion to **3a** that **6a** is thought

Scheme III



to be derived from *dl*-**2a**. A tetramethyl analogue of **3a** is formed during chemical reduction (magnesium/acetic acid) of acetylacetone.[16]

A slightly soluble gray powder was also formed during re-

duction in the pH 4.2 buffer.[2] In the present work it was found that small quantities of this substance could be recrystallized from benzene giving a compound (mp 259 °C) whose spectral properties and elemental analysis are consistent with its being one of the isomers of **6a** derived from *meso*-**2a** (not shown in Scheme I). This compound could not be converted to **3a** but it was dehydrated in high yield (72%) to dienedione **4a.**

Thus, the electrochemical reduction of **1a** would appear to produce initially both diastereomers of the pinacol, a reaction which is common in the reduction of many aromatic carbonyl compounds.[16-23] In this case, however, the pinacols are susceptible to a number of reactions leading to **3a, 4a,** and isomers of **6a.** It was of interest to see if similar product distributions would be obtained in the reduction of related compounds.

Reduction of Some *p,p'*-Substituted 1,3-Diphenyl-1,3-propanediones. Buffer 2 was selected for these electrolyses because the starting materials are more soluble in this medium.

It was found that the fluoro derivative **1b** gave a pinacol **2b** as well as a small amount of the trioxatricyclononane **3b.** A pinacol was isolated from electrolysis of the chloro and bromo derivatives but neither gave any trioxatricyclononane. In each case only one pinacol was isolated. In contrast to the reduction of **1a,** the NMR data indicated that the major products of the halo derivatives were the open-chain pinacols but it was not determined whether the isolated materials were meso or *dl.* The pinacols were readily converted to the dienediones **4b-d.**

These results indicate that reductive coupling to the pinacol can be achieved for 1 derivatives with electron-withdrawing substituents. However, the cyclic ketols **6** were not obtained. Electrolysis of the cyano derivative **1e** was not practical due to its low solubility.

The preparation was less successful with electron-donating substituents such as methyl (**1f**) or methoxy (**1g**). The electrolysis solution became yellow owing to the dehydration of the initially formed pinacol. For **1g,** the dienedione **4g** was detected in a partially electrolyzed solution by polarography. The dienediones have reduction waves positive of the wave of the 1,3-diketones so they will be reduced if formed during the electrolysis. Presumably, the electron-donating substituents accelerate acid-catalyzed dehydration of the pinacols, causing failure of the pinacol preparation from **1g.** Use of less acidic buffers did not give isolable quantities of pinacol **2g.**

Although dienedione was formed in the electrolysis of **1f,** a small amount of pinacol **2f** was isolated using buffer 2. On performing the electrolysis in a pH 6.1 buffer (buffer 3), a mixture of the open-chain pinacol **2f** and a cyclic ketol **6f** was obtained.

Reduction of Hexadienedione 4a. Reduction in buffer 2 produced a good yield of the hexenedione **5a.** Reductions of conjugated enediones are thought to occur by $2e^-$, $2\ H^+$ 1,ω-reduction followed by tautomerization of the bisenols so formed.[23,24] The syntheses of the 2,4-hexadiene-1,6-diones **4** and the 3-hexene-1,6-dione **5a** along with the production of 1,6-hexanediones by reductive coupling of chalcones[23] demonstrates that electrochemical routes exist for a number of 1,3,4,6-tetraarylhexyl systems.

Experimental Section

Melting points are uncorrected. Microanalyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich. Infrared spectra were recorded using a Perkin-Elmer Model 137, mass spectra were obtained using an A.E.I. MS-9 spectrometer, and the NMR spectrometers were a Jeolco MH100 or Bruker WH270. Unless otherwise indicated, NMR spectra were obtained using $CDCl_3$ solvent and Me_4Si reference.

Electrochemical Apparatus. The potentiostats used were a Wenking (Brinkmann Instruments, Westbury, N.Y.) Model 61R and a Princeton Applied Research (Princeton, N.J.) Model 173. The large electrolysis cell (cell 1) constructed from a reaction kettle has been described.[2] A smaller cell (cell 2) like the one used for coulometry[3] was employed in some electrolyses. Its capacity was about 100 mL.

All reductions were performed on mercury-pool cathodes with stirring effected by a Teflon-coated magnetic stirring bar. The platinum-wire auxiliary electrode was in a compartment separated from the cathode compartment by a medium-porosity glass frit. The anolyte was the same buffer solution used in the cathode compartment unless indicated otherwise. The cathode compartment was continuously purged with nitrogen. An aqueous saturated calomel reference electrode was used.

All experiments were carried out at room temperature (23 ± 1 °C) and no special precautions were taken to maintain a constant temperature. The currents were small enough to preclude large-temperature increases, although in the longer experiments the cell was warmed (never above 30 °C) by the motor of the magnetic stirrer.

Reagents. The 1,3-diketones were either commercially available or were prepared by standard literature procedures. They were purified by crystallization as required.

Three buffer solutions were used. Buffer 1 was the pH 4.2 citrate buffer in 50% ethanol–water which was employed previously.[2] Buffer 2 was prepared from 1 mol of potassium acetate and 6 mol of acetic acid made up to 1 L with 80% ethanol–water, and its apparent pH was also 4.2 as measured using a glass electrode calibrated with standard aqueous buffers. Buffer 3 was the pH 6.1 citrate buffer in 50% ethanol–water also employed previously.[2]

The mercury was taken from stock which is cleaned periodically by a chemical procedure.[25]

General Procedure for Electrochemical Syntheses. The reduction potential which was selected was on the diffusion plateau of the one-electron reduction wave as determined by polarography. For each compound, the appropriate buffer was electrolyzed at the potential to be used until a background current of less than 0.5 mA was obtained. The amount of starting material to be added to the cell was chosen so that its solubility was not exceeded. (**1d** was so insoluble that it was electrolyzed with only partial dissolution. The electrolysis was slow but most of the diketone eventually was reduced.) The quantities chosen ranged from 20 to 750 mg. This amount was then dissolved in 5 cm^3 of hot 95% ethanol and added dropwise with stirring to the cell. About 5 min after the addition of the starting material the electrolysis was begun. Initial currents ranged from 20 to 100 mA and after a period of 1 to 5 h the currents dropped below 10 mA, at which time another equal addition of reactant 1,3-diketone was made. When a total of ~2 g of reactant had been added, the electrolysis was stopped, and the cell contents were removed from the mercury, diluted 1:1 with water (or 0.05 M Na_2CO_3 with **1f** and **1g**), and set aside for 8 h. The insoluble crude product was then removed by vacuum filtration, air-dried for 1–3 h, and then extracted with diethyl ether or chloroform. Table I summarizes the electrochemical preparations reported in this work. The isolation and characterization of products from the various syntheses are described below. Only in the reduction of **1d** was starting material recovered. All of the products could be dehydrated to a dienedione **4** by the method reported earlier.[2] (These could be *Z* or *E* isomers. Isomeric identities were not determined.)

Reduction of 1,3-Diphenyl-1,3-propanedione (1a) in Buffer 1. Extraction of the crude product with ether or chloroform resulted in about 60% dissolution. Evaporation of the extract gave a yellow solid from which various crops of white to yellowish-white crystals of isomers of 2,3,5-trihydroxy-2,3,5-triphenylcyclopentyl phenyl ketone (**6a**). Melting points varied from 197 to 207 °C with ranges of 3 to 0.5 °C. The IR spectra of the samples obtained were identical to that earlier attributed to **2a.**[2] The NMR spectra revealed that each of the various samples contained principally or entirely one of two isomers assigned the structures **6ai** and **6aii,** although the isomers with the benzoyl group cis to the 5-phenyl could not be ruled out (see Results and Discussion). Reproducible conditions for producing one or the other could not be found. The principal evidence for the cyclic structure as opposed to the open-chain pinacol is the number and type of nonaromatic protons, including the fact that three resonances (rather than one) are lost by exchange with D_2O. The two isomers were differentiated on the basis of the larger chemical-shift difference between the methylene protons in **6ai** as opposed to **6aii:** NMR **6ai** δ 2.43, 2.57, 3.85, 4.00 (AB, 2, CH_2, J_{AB} = 14.5 Hz), 2.57 (s, 1, OH), 4.37 (s, 1, OH), 5.31 (s, 1, CH), 6.59 (s, 1, OH), 7.01–7.84 (comp m, 20, arom), singlets at 2.57, 4.37, 6.59 disappear on addition of D_2O; NMR **6aii** δ 2.33 (s, 1, OH), 3.05, 3.22, 3.36, 3.52 (AB, 2, CH_2, J_{AB} = 16.5 Hz), 4.23 (s, 1, OH), 5.40 (s, 1, CH), 5.97 (s, 1, OH), 7.08–7.84 (comp m, 20, arom), singlets at 2.33, 4.23, and 5.97 disappear on addition of D_2O (**3a** and **6aii** have also been found as reduction products of 1a by

Table I. Electrochemical Preparations

Reactant	Cell	Buffer	Potential[a]	Recrystallization solvent	Product	Yield[b] (%)	Comments
1a	1	1	−1.15	C_2H_5OH	*dl*-6a	21–52	3a not obtained in all experiments
				C_6H_6	*meso*-6a	15–42	
				C_2H_5OH	3a	4–5	
1a	2	3	−1.20	C_2H_5OH	3a	13–38	
				C_2H_5OH	*dl*-6a	6–19	
				C_6H_6	*meso*-6a	30	
1b	2	2	−1.24	C_2H_5OH	2b	12–15	3b required 3 recrystallizations
					3b	5	
1c	1	2	−1.16	C_6H_6	2c	20	
1d	1	2	−1.13	C_6H_6	2d	29	
1f	1	2	−1.30	C_2H_5OH	2f	5	
1f	2	3	−1.29	C_2H_5OH	2f		After repeated recrystallizations, only a mixture was obtained
					6f		
4a	1	2	−0.74	C_6H_6	5a	78	

[a] V. vs. SCE. [b] Purified product. Ranges given are for two to five replicate syntheses. Based on starting material.

Juday[26] who employed an acidic medium and diglyme and methoxyethanol as cosolvents).

The gray powder (yield: 15–42%; three experiments) which remains after extraction of the crude electrolysis product was ignored in the earlier work.[2] It was found to have a relatively sharp melting point (239–40 °C) and, though only very slightly soluble in common solvents, it could be recrystallized from benzene, mp 259 °C. On the basis of its spectral and chemical properties, this substance is thought to be a mixture of two isomers of **6a** derived from *meso*-**2a**: IR (KBr) 3559, 3106, 2959, 1656, 1600, 1580 cm^{-1}; mass spectrum no molecular ion, large peaks at *m/e* 225, 120, 105, 77; 270-MHz NMR (benzene-d_6 saturated solution) δ 1.36 (br s, several protons, exchangeable with D_2O), 2.58, 2.62, 2.76, 2.80 (AB, CH_2, J_{AB} = 11.6 Hz), 2.77, 2.84, 4.43, 4.49 (AB, CH_2, J_{AB} = 17.5 Hz), 5.93 (S, CH), 6.80–8.05 (comp m, arom). Anal. Calcd for $C_{30}H_{26}O_4$: C, 79.98; H, 5.82. Found: C, 79.78; H, 5.85 (average of two analyses).

Reduction of 1a in Buffer 2. In this synthesis the anolyte was aqueous 1 M KNO_3. Again, part of the crude product (isomers of **6a** derived from *meso*-**2a**, contaminated with mercury) remained undissolved after extraction. The extract was evaporated giving a solid which upon recrystallization gave 0.2 g (13%) of **1,3,5,7-tetraphenyl-2,4,6-trioxatricyclo[3.3.0.1]nonane (3a):** mp 239–244 °C; IR showed no OH or carbonyl; mass spectrum *m/e* 432 (M^+), 312, 225, 105, 77; NMR δ 2.61 (AB, 4, CH_2, J_{AB} = 11.8 Hz), 7.05 (br s, 10, arom), 7.38–7.89 (m, 10, arom). Anal. Calcd for $C_{30}H_{24}O_3$: C, 83.31; H, 5.59. Found: C, 83.40; H, 5.52. Some **6a** derived from *dl*-**2a** was obtained in later crops during recrystallization.

Preparation of 3a from *dl*-6a. Identification of the lower melting, more soluble isomers of **6a** as being derived from *dl*-**2a** is based on their conversion to the tricyclic **3a**, a reaction which is impossible for *meso*-**2a**. *dl*-**6a** (**54 mg**) was added to 40 mL of buffer 2. The suspension was stirred for 24 h, diluted 4 to 1 with 20% aqueous NaCl, and extracted with three 50-mL portions of $CHCl_3$. The solid obtained after evaporation was recrystallized from ethanol–water, giving 19 mg (36%) of **3a**, mp 233–5 °C. Similar treatment of *meso*-**6a** for 4 days caused no change.

Reduction of 1,3-Bis(*p*-fluorophenyl)-1,3-propanedione (1b) in Buffer 2. Almost all of the crude product dissolved in chloroform. The chloroform-soluble material was recrystallized from ethanol–water, giving several crops of crystals. The first crop was a diastereomer of **1,3,4,6-tetrakis(*p*-fluorophenyl)-3,4-dihydroxy-1,6-hexanedione (2b):** mp 227 °C; IR (KBr) 3552, 3080, 2926, 1646, 1584, 1229, 1213 cm^{-1}; NMR δ 2.40, 2.67, 4.12, 4.29 (AB, 4, CH_2, J = 17.5 Hz), 5.30 (s, 2, OH), 6.82–7.84 (m, 16, arom). Singlet at δ 5.30 disappears on addition of D_2O. Anal. Calcd for $C_{30}H_{22}F_4O_4$: C, 68.96; H, 4.24; F, 14.54. Found: C, 68.92; H, 4.46; F, 14.74.

The second crop was difficult to purify. The highest melting sample (5% yield) had mp 200–203 °C. This substance was identified as **1,3,5,7-tetrakis(*p*-fluorophenyl)-2,4,6-trioxatricyclo[3.3.0.1]-nonane (3b):** IR (KBr) showed no OH or carbonyl; NMR δ 2.57, 2.71, 2.73, 2.84 (AB, 4, CH_2, J = 11.6 Hz), 6.72–7.78 (m, 16, arom). Anal. Calcd for $C_{30}H_{20}F_4O_3$: C, 71.42; H, 4.00; F, 15.06. Found: C, 71.31, H, 4.07; F, 14.85.

Preparation of 1,3,4,6-Tetrakis(*p*-fluorophenyl)-2,4-hexadiene-1,6-dione (4b). 2b (35 mg) was dehydrated, giving 67% recrystallized (CH_2Cl_2–CH_3OH) **4b:** mp 220–1 °C; IR (KBr) 3115, 2985, 1637, 1592, 1550 cm^{-1}; NMR δ 6.84–7.84 (comp m). Similarly, 19.0 mg of **3b** was dehydrated giving 67% **4b.**

Preparation of 1,3,4,6-Tetrakis(*p*-chlorophenyl)-3,4-dihydroxy-1,6-hexanedione (2c). The crude product was recrystallized from benzene, giving 21% of **2c:** mp 227–230 °C; IR (KBr) 3591, 3119, 2961, 1660, 1591, 1573, 1482 cm^{-1}; NMR δ 2.55, 2.73, 4.20, 4.28 (AB, 4, CH_2, J = 17 Hz) 5.33 (s, 2, OH), 7.24–7.78 (m, 16, arom). Anal. Calcd for $C_{30}H_{22}Cl_4O_4$: C, 61.25; H, 3.55; Cl, 24.10. Found: C, 61.23; H, 3.84; Cl, 24.14.

Preparation of 1,3,4,6-Tetrakis(*p*-chlorophenyl)-2,4-hexadiene-1,6-dione (4c). 2c (44 mg) was dehydrated in the same way as **2a**, giving 54% **4c:** mp 223–5 °C (CH_2Cl_2–CH_3OH); IR (KBr) 1639, 1585, 1570 cm^{-1}; NMR: δ 7.20–7.80 (comp m). Anal. Calcd for $C_{30}H_{18}O_2Cl_4$: C, 65.24; H, 3.28; Cl, 25.68. Found: C, 65.22; H, 3.37; Cl, 25.58.

Preparation of 1,3,4,6-Tetrakis(*p*-bromophenyl)-3,4-dihydroxy-1,6-hexanedione (2d). The crude product (yield: 96%) recrystallized from benzene, giving a first crop with a broad melting range, and after three recrystallizations TLC showed two components. The second crop of crystals (yield: 29%) melted sharply (231–232.5 °C), and TLC showed one component, **2d:** IR (KBr) 3509, 2947, 1661, 1583, 1558, 1476. 1201, 1064, 995 cm^{-1}; NMR δ 2.43, 2.61, 4.07, 4.24 (AB, 4, CH_2, J = 17.5 Hz), 5.21 (s, 2, OH), 7.20–7.60 (m, 16, arom). Singlet at δ 5.21 disappears on addition of D_2O. Anal. Calcd for $C_{30}H_{22}Br_4O_4$: C, 47.03; H, 2.90; Br, 41.72. Found: C, 47.11; H, 2.98; Br, 41.58.

Preparation of 1,3,4,6-Tetrakis(*p*-bromophenyl)-2,4-hexadiene-1,6-dione (4d). 2d (41 mg) was dehydrated as above, giving 58% **4d:** mp 233–5 °C (CH_2Cl_2–CH_3OH); IR (KBr) 1645, 1575, 1553 cm^{-1}; NMR δ 7.42–7.73 (comp m). Anal. Calcd for $C_{30}H_{18}Br_4O_2$: C, 49.35; H, 2.48; Br, 43.78. Found: C, 49.48; H, 2.57; Br, 43.82.

Preparation of 1,3,4,6-Tetrakis(*p*-tolyl)-3,4-dihydroxy-1,6-hexanedione (2f). No extraction solvent was used. The crude product was recrystallized from 300 mL of 95% ethanol, giving 96.3 mg (5% yield) of slightly yellow crystals of **2f,** mp 215.5 °C. A second recrystallization from ethanol gave white crystals: mp 230–232 °C; IR (KBr) 3527, 3071, 2961, 1655, 1609. 1513 cm^{-1}; NMR: δ 2.22 (s, 6, CH_3), 2.31 (s, 6, CH_3), 2.47, 2.66, 4.19, 4.37 (AB, 4, CH_2, J_{AB} = 18.5 Hz), 5.23 (s, 2, OH), 6.97–7.20, 7.57–7.67 (m, 16, arom). The singlet at δ 5.23 disappears on addition of D_2O. Anal. Calcd for $C_{34}H_{34}O_4$, C, 80.59; H, 6.78. Found: C, 80.59; H, 6.79.

Preparation of 1,3,4,6-Tetrakis(*p*-tolyl)-2,4-hexadiene-1,6-dione (4f). 2f (28 mg) was dehydrated, giving 72.4% **4f:** mp 168 °C (C_2H_5OH); IR (KBr) 3060, 2951, 1633, 1601, 1546 cm^{-1}; NMR δ 2.26 (br s, 12 H, CH_3), 6.96, 7.03, (d, J = 8 Hz, 8 H, protons ortho to methyl), 7.23, (s, 2 H, olefinic), 7.36, 7.43 (J = 8 Hz, 4 H, protons meta to methyl, aryl groups), 7.59, 7.66 (d, J = 8 Hz, 4 H, protons meta to methyl, aroyl groups). Anal. Calcd for $C_{34}H_{30}O_2$: C, 86.76; H, 6.44. Found: C, 86.58; H, 6.42.

Preparation of 2,3,5-Tris(*p*-tolyl)-2,3,5-trihydroxycyclopentyl

p-Tolyl Ketone (6f). Again, no extraction step was employed. Ninety milligrams of small white crystals was collected as a crude product (46%) which gave the same R_f on silica-gel TLC plates as **2f**. This was recrystallized with difficulty from about 30 mL of 95% ethanol. After a number of recrystallizations, a small amount of product, mp 205–210 °C, was obtained. This was identified as a mixture of **2f** and an isomer of **6f**: NMR of mixture δ 2.00 (s, OH), 2.21 (s, CH_3), 2.26 (s, CH_3), 2.36 (s, CH_3), 2.40 (s, CH_3), 2.52, 2.70, 4.22, 4.41 (AB, CH_2 (open chain), J_{AB} = 18.5 Hz), 3.01, 3.17, 3.29, 3.44 [AB, CH_2 (cyclized), J_{AB} = 15.5], 4.26 (s, OH), 5.27, (s, CH), 5.33, (s, OH), 6.03 (s, OH), 6.83–7.32, 7.50–7.92 (m, arom). The singlets at δ 2.00, 4.26, 5.33, and 6.03 disappear on addition of D_2O.

Reduction of 1,3,4,6-Tetraphenyl-2,4-hexadiene-1,6-dione (4a). A white precipitate was collected and was recrystallized from benzene, giving two crops of white crystals: mp 210 and 225 °C, respectively; TLC, NMR, and IR indicated these two crops were identical. A second recrystallization from benzene yielded colorless needles of 1,3,4,6-tetraphenyl-3-hexene-1,6-dione: mp 232 °C; IR 3065, 2912, 1680, 1591, 1568, 1478, 1421, 1318, 1200, 748, 703 cm^{-1}; NMR (saturated) δ 3.98 (s, CH_2) 7.06–7.76 (m, arom). Anal. Calcd for $C_{30}H_{24}O_2$: C, 86.50; H, 5.82. Found: C, 86.56; H, 5.78.

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Registry No.—**1a,** 1704-15-0; **1b,** 62375-96-6; **1c,** 62375-97-7; **1d,** 6909-81-5; **1f,** 62375-98-8; *meso*-**2a,** 62375-99-9; **2b,** 62376-00-5; **2c,** 62376-01-6; **2d,** 62376-02-7; **2f,** 62376-03-8; **3a,** 62376-04-9; **3b,** 62376-05-0; **4a,** 10562-16-0; **4b,** 62376-06-1; **4c,** 62376-07-2; **4d,** 62376-08-3; **4f,** 62376-09-4; **5a,** 62376-10-7; **6a,** 62376-11-8; **6ai,** 62445-07-2; **6aii,** 62445-08-3; **6f,** 62376-12-9; 1,3,4,6-tetraphenyl-3-hexene-1,6-dione, 62376-10-7.

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Hashish.[1] Synthesis of (±)-Δ^1- and Δ^6-3,4-*cis*-Cannabidiols and Their Isomerization by Acid Catalysis

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The total synthesis of (±)-Δ^1- and Δ^6-3,4-*cis*-cannabidiols (CBD, **5a** and **5b**) by two independent routes is described. The starting materials for these new cannabinoids were the lactones **1a** and **7**. High-pressure liquid chromatography was used to separate the mixture of Δ^1- and Δ^6-CBD diacetates obtained in the final step of each route. The acid-catalyzed (*p*-TSA) transformation products of *cis*-CBDs (**5a** and **5b**) were isolated and identified as the ring closed *cis*-cannabinoids **12–15**. The rate of the reaction and the relative proportions of products were found to be dependent on the acid concentration.

(−)-Cannabidiol (CBD), which occurs naturally in marijuana (*Cannabis sativa*) and is the precursor in some of the syntheses of Δ^1- and Δ^6-tetrahydrocannabinols (THC),[2] has a 3,4-trans ring junction and a double bond in the Δ^1 position. The Δ^6-trans isomer and the corresponding Δ^1- and Δ^6-CBDs with a 3,4-cis junction are not known in the literature.[3-5] This article describes the first syntheses of (±)-Δ^6- and Δ^1-3,4-*cis*-CBDs and the transformations they undergo under the influence of an acid catalyst.

In an earlier article[6] Razdan and Zitko described the acid-catalyzed (*p*-toluenesulfonic acid, *p*-TSA) interconversion of Δ^1-3,4-*cis*-tetrahydrocannabinol (THC) and the isotetrahydrocannabinols (iso-THCs) by way of citrylidene-cannabis as a short-lived intermediate. We have found that both Δ^1- and Δ^6-*cis*-CBD undergo a similar conversion, the extent of which is strongly dependent on the concentration of the acid catalyst.

A total synthesis of (±)-Δ^6-*cis*-cannabidiol (**5a**) was achieved by two different routes from the lactones **1a** and **7** (Schemes I and II). (±)-Δ^1-*cis*-CBD (**5b**) was obtained from a mixture of lactones (**1a** and **1b**), produced by acid-catalyzed equilibration, with subsequent separation of the mixed CBDs.

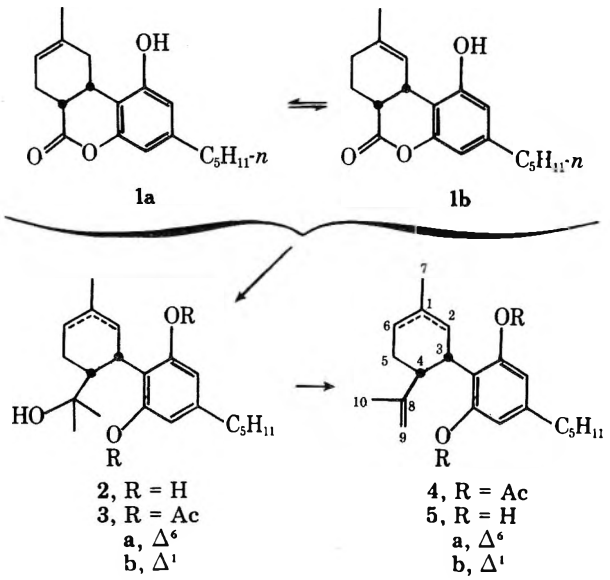
Lactone **1a** was prepared from isoprene and 3-carboxy-5-hydroxy-7-*n*-pentylcoumarin by a Diels–Alder reaction accompanied by decarboxylation. Taylor and Strojny[7] developed this procedure to prepare similar lactones, demonstrating that isoprene adds to the coumarin to give a cis ring fusion and a methyl substituent at C-1, as shown in **1a**. The NMR of **1a** (Table I) is in complete agreement with the assigned structure. The benzylic proton at C-3 appears as two triplets with coupling constants of 6, 6, and 11 Hz, which is consistent with 3,4-cis ring fusion and the double bond at C-6. Hively[8] also prepared **1a** and arrived at similar conclusions

Table I. NMR of (±)-*cis*-Cannabidiols and Precursors[a]

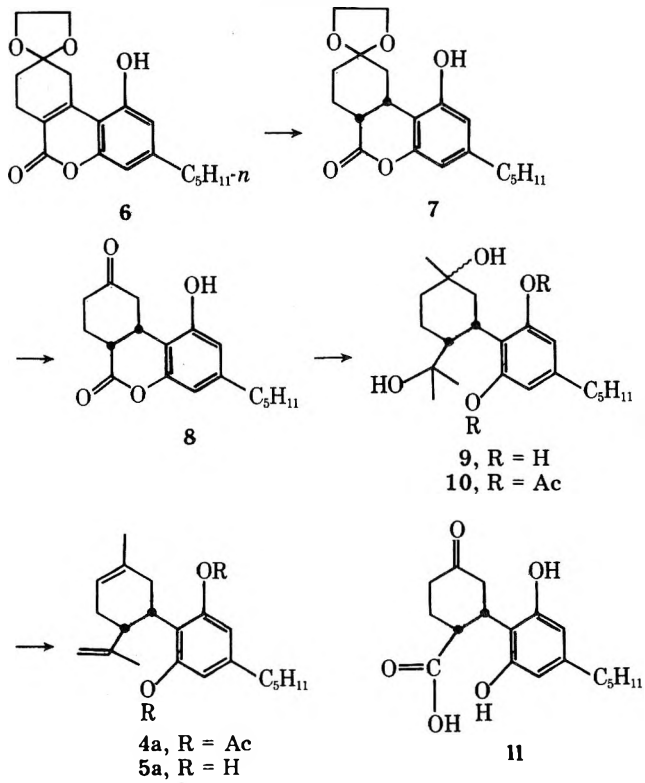
Type of proton	1a	1b	4a	4b	5a	5b
ω-CH_3	0.88 (t)	0.88 (t)	0.88 (t)	0.87 (t)	0.87 (t)	0.88 (t)
C-8 CH_3			1.40 (s)	1.27 (s)	1.73 (s)	1.87 (s)
C-1 CH_3	1.63 (s)[b]	1.63 (s)[b]	1.67 (s)	1.70 (s)	1.63 (s)	1.45 (s)
Acetyl CH_3			2.18 (s)	2.10 (s)		
C-3 benzylic	3.50 (dt)	3.92 (br m)	3.33 (m)	3.80 (m)	3.87 (br m)	4.02 (br m)
C-8 $=CH_2$			4.60 (br d)	4.52 (s)	4.77 (br m)	4.75 (s)
Vinylic	5.47	5.32	5.40 (br)	5.32 (br d)	5.77 (br)	5.87 (br d)
OH	5.83 (s)				5.60 (s)	5.70 (br)
Aromatic	6.48 (s)	6.48 (s)	6.65 (s)	6.62 (s)	6.13 (s)	6.17 (s)

[a] All spectra were determined on a Varian A-60 spectrometer; δ values are given in $CDCl_3$ for 1a and 1b and in CCl_4 for 4a,b and 5a,b, relative to Me_4Si as internal standard. [b] C-9 CH_3, in the numbering system used for the dibenzopyranones.

Scheme I



Scheme II



on the basis of degradation and NMR studies. Reaction of **1a** with CH_3MgI gave the triol **2a**; its diacetate **3a** was dehydrated with thionyl chloride in pyridine to give Δ⁶-3,4-*cis*-CBD diacetate (**4a**).

When the lactone **1a** was heated in solution with *p*-toluenesulfonic acid (*p*-TSA), a 1:1 equilibrium mixture with its isomer **1b** was formed after about 1 h. This mixture was carried through the same transformations as for the pure Δ⁶-cis isomer to give a mixture of the Δ⁶- and Δ¹-*cis*-CBD diacetates (**4a** and **4b**). These were quite different in both their GLC and NMR characteristics, and they were easily separated by high-pressure liquid chromatography (HPLC).

The corresponding diols (**5a** and **5b**) were obtained by hydrolysis in CH_3OH with 5% KOH at ambient temperature. When the hydrolysis of **4b** was interrupted after 20 min, its monoacetate was isolated, indicating that the rate of removal of the second acetate was considerably slower than the first. A difference in rates of silylation was also observed in gas chromatographic studies with both CBDs **5a** and **5b**.

Differences in the NMR (CCl_4) of **5a** and **5b** are noteworthy (Table I): (a) C-1 and C-8 methyl protons in **5a** appear at δ 1.63 and 1.73, whereas in **5b** the corresponding signals are at δ 1.45 and 1.87; (b) the vinylic proton is a broad single peak at δ 5.77 in Δ⁶-*cis*-CBD (**5a**), but is a broad doublet at 5.87 in Δ¹-*cis*-CBD (**5b**); (c) the terminal methylene protons appear as a broad multiplet at δ 4.77 for **5a**, but as a singlet at δ 4.75 for

Scheme III

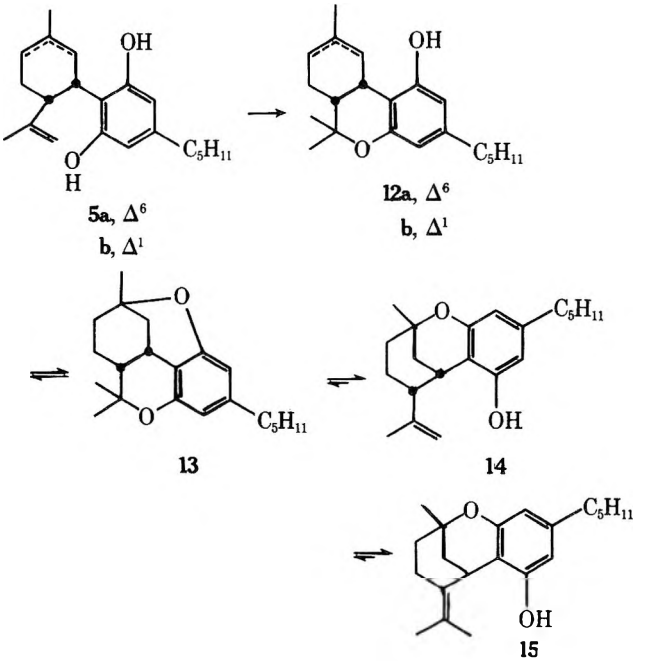


Table II. Effect of Acid on *cis*-Cannabinoids

Reactants	Expt 1	2	3	4	5	6
Vol benzene, mL	22	25	25	1.5	1.7	1.5
Wt cannabinoid, mg	26.2[a]	13.6[b]	16[c]	1.06[d]	1.08[e]	1.27[d]
Concn, g/100 mL	0.12	0.05	0.06	0.07	0.06	0.08
Wt *p*-TSA·H_2O, mg	1.4	10.2	50	2.87	2.5	0.05
Concn, g/100 mL	0.006	0.04	0.20	0.19	0.15	0.003
Products[f]	%, by GLC					
Δ^6-*cis*-CBD	12	0	0	0	0	10
Δ^1-*cis*-CBD	7	0	0	0	0	0
Δ^6-*cis*-THC	50	28	8	22	17	51
Δ^1-*cis*-THC	4	67	31	16	40	12
Δ^8-*cis*-Iso-THC	24	1	15	10	7	17
$\Delta^{4(8)}$-Iso-THC	0	4	44	52	36	10
Cannabicitran[g]	2	Tr	2			

[a] Synthesis; Δ^6-*cis*-CBD, >95% assay by GLC. [b] Fraction by high-pressure liquid chromatography of product from expt 1; Δ^6-*cis*-THC (84%), Δ^1-*cis*-THC (5%), Δ^1- + Δ^6-*cis*-CBD (11%), by GLC. [c] Product from expt 2; Δ^6-*cis*-THC (28%), Δ^1-*cis*-THC (67%), Δ^8-*cis*-iso-THC (1%), $\Delta^{4(8)}$-iso-THC (4%) by GLC. [d] Synthesis; Δ^6-*cis*-CBD (88%), Δ^8-*cis*-iso-THC (12%). [e] Synthesis; Δ^1-*cis*-CBD (>95%). [f] At 30 min for expt 1; all others at 60 min. [g] Also called tetracyclic ether (TCE) and citrylidene-cannabis.[6]

Table III. Products from Experiment 1 (Table II) Separated by High-Pressure Liquid Chromatography[a]

	Analysis by GLC		
		Rel retention time[b]	
	%	Silylated (230 °C)	Not silylated (260 °C)
Fraction 1 (k' = 1.1; 0.9 mg)			
cannabicitran[c]	88	0.96	0.52
Fraction 2 (k' = 2.6; 2.8 mg)			
Δ^8-*cis*-iso-THC[d]	95	0.74	0.63
$\Delta^{4(8)}$-iso-THC	4	1.06	0.82
Fraction 3 (k' = 3.6; 0.9 mg)			
Δ^1-*cis*-CBD	63	0.66	0.85
Δ^8-*cis*-iso-THC	10	0.74	0.63
$\Delta^{4(8)}$-iso-THC	25	1.06	0.81
Fraction 4 (k' = 4.4; 17.4 mg)			
Δ^1-*cis*- + Δ^6-*cis*-CBD	11	0.69	
Δ^6-*cis*-THC[e]	84	0.98	1.0
Δ^1-*cis*-THC	5	1.08	

[a] μPorasil, eluent 2% Et_2O/isooctane. [b] 3% OV-17, Δ^6-*trans*-THC as reference = 1.00, time silylated (230 °C) 5.50 min, not silylated (260 °C) 3.84 min. [c] Not affected by silylation. [d] NMR (CCl_4) δ 6.08, 6.18 (2, 2 d, aromatic), 4.88, 4.67 (2, 2 m, C8 CH_2), 3.30 (1, m, C3 H), 1.82 (s, C8 CH_3), 1.37 (s, C1 CH_3), 0.95 (3, t, ω-CH_3), 4.47 (1, exchangeable OH). [e] NMR (CCl_4) δ 6.15, 5.95 (2, 2 d, aromatic), 5.37 (1, br, C6 olefinic), 3.17 (1, m, C2α), 1.65 (s, C1 CH_3), 1.36, 1.25 (2 s, *gem*-diMe), 0.89 (t, ω-CH_3).

5b. In comparison, signals for the equivalent protons in Δ^1-*trans*-CBD, the natural isomer, are δ 1.63 and 1.80 for the methyl protons, δ 5.57 (br, s) for the vinylic proton, and δ 4.53 (m) for the terminal methylene protons.

The second synthesis of Δ^6-*cis*-CBD (Scheme II) started with the lactone (**6**).[9] Reduction with Raney nickel at high pressure gave the lactone **7**, which Fahrenholtz et al.[9] have shown to be cis at C-3–C-4. Homogeneous acid hydrolysis of ketal **7** in dioxane produced the keto lactone **8**, along with a significant amount of the acid **11**. The latter was readily recyclized to lactone **8**.

Reaction of methyl Grignard with this keto lactone gave two major products, which were separated by high-pressure liquid chromatography. One of them was identified as the desired tetrol **9**. Its acetate (**10**) was dehydrated ($SOCl_2$/pyridine), to give Δ^6-*cis*-CBD diacetate (**4a**) exclusively. Hydrolysis of the diacetate gave Δ^6-*cis*-CBD (**5a**), which was identical in all respects (NMR, GLC, TLC) with the compound synthesized by Scheme I. As a practical matter, the mixture of polyols after Grignard reaction was carried through the acetylation and dehydration steps, and the CBD diacetate **4a** was separated from the mixture by HPLC.

Treatment of *cis*-CBDs with Acids. The *cis*-CBDs under the influence of a strong acid catalyst (*p*-TSA) were readily converted to ring closed compounds (Scheme III); the extent of reaction was strongly dependent on the concentration of catalyst.

With low acid concentration, as previously used in the interconversion of Δ^1-*cis*-THC and iso-THCs[6] (0.006 g of *p*-TSA/100 mL of solution, expt 1, Table II), solutions of Δ^6-*cis*-CBD in benzene at reflux for 30 min produced a mixture containing mainly Δ^6-*cis*-THC (**5a**, 50%) and Δ^8-*cis*-iso-THC (**14**, 24%), with lesser amounts of Δ^1-*cis*-CBD (**5b**), Δ^1-*cis*-THC (**12b**), cannabicitran (**13**),[6] and unchanged Δ^6-*cis*-CBD (Table II). These products were separated by HPLC and identified by NMR and GLC analyses (Table III), as well as by comparison with authentic samples from other sources.

When the reaction at low acid concentration (0.003 g/100

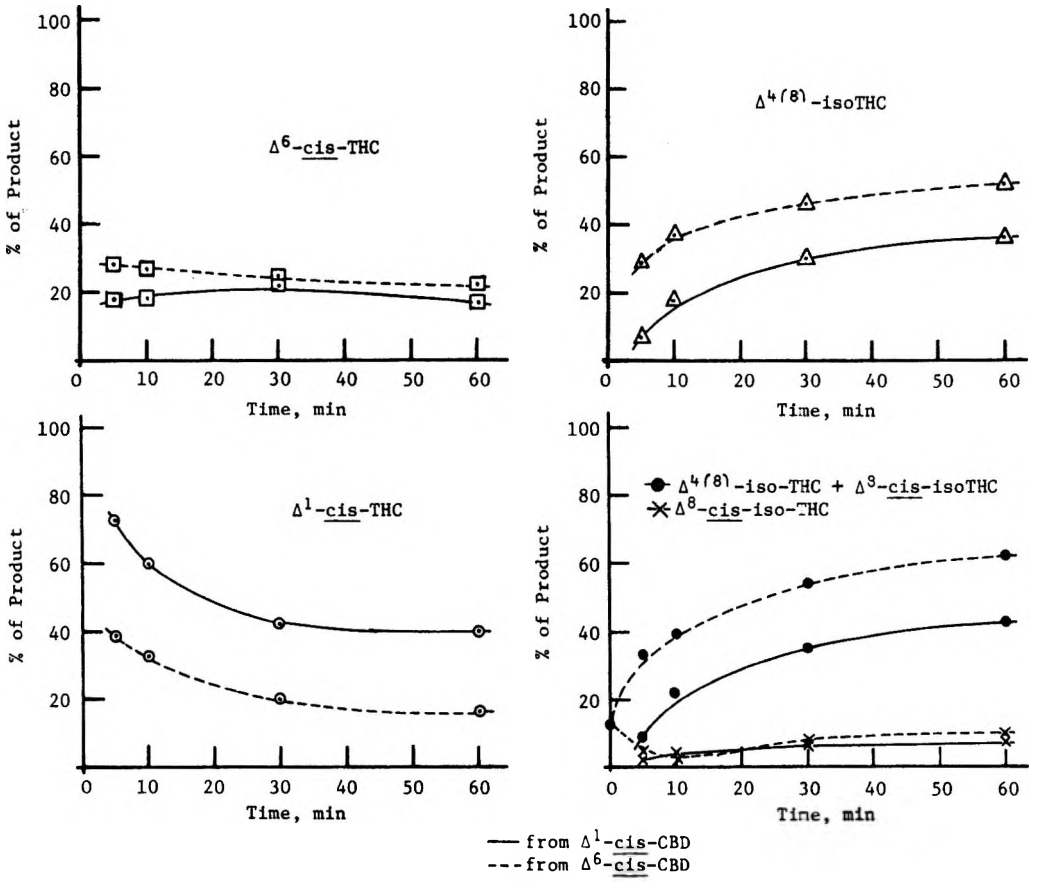


Figure 1. Rate of product formation in strong acid catalyzed ring closure of *cis*-cannabidiols.

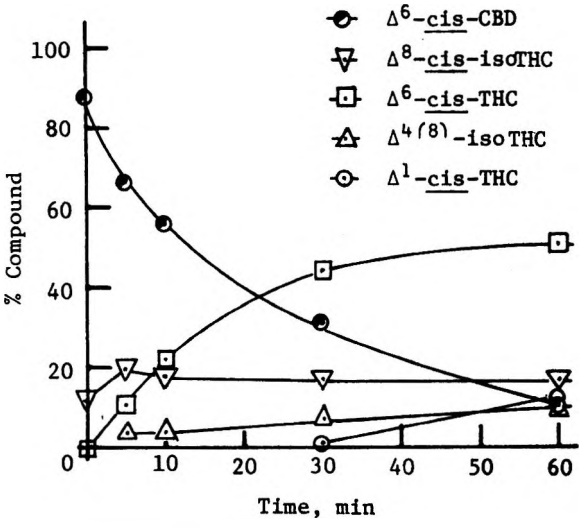


Figure 2. Reaction products from Δ6-*cis*-CBD with low acid concentration.

mL; expt 6, Table II) was followed by sampling at regular intervals, a steady state appeared to be reached in about 60 min, with Δ6-*cis*-THC (**12a**) being the major component (Figure 1).

Similarly, at high acid concentration (0.15–0.19 g of *p*-TSA/100 mL of solution; expt 4 and 5, Table II) a steady state was approached after 60 min for both Δ1- and Δ6-*cis*-CBD (Figure 2). Interestingly, Δ6-*cis*-CBD (**5a**) gave more iso-THCs (7 and 8) than did Δ1-*cis*-CBD (**5b**). The THC/iso-THC ratio after 5 min was 2:1 from the Δ6 isomer and 10:1 from the Δ1 isomer, and 0.6:1 and 1.3:1, respectively, at the end of 1 h.

The ratio of the THCs to iso-THCs in the products from the *cis*-CBDs (**5a** and **5b**) depends on the relative rates of cyclization at the Δ8 and Δ6 (or Δ1) double bonds, respectively. Because Δ1-CBD gave less iso-THC than did Δ6-CBD (Figure 1), and because the rate of reaction at the Δ8 double bond should be similar for both CBDs, it is likely that steric hindrance by the proximal hydroxy group deactivates the Δ1 double bond of **5b** relative to the Δ6 double bond of **5a**.

The fact that acid concentration has a pronounced effect on the rate of reaction but not necessarily on the distribution of products is demonstrated by a comparison of two similar experiments. The total products formed after 17 h at low acid concentration (continuation of expt 6, Table II) were the same as after 15 min with high acid concentration (expt 4, Table II) (% from expt 6 vs. from expt 4: Δ6-*cis*-CBD, 3, 0; Δ6-*cis*-THC, 29, 26; Δ1-*cis*-THC, 26, 28; Δ8-*cis*-iso-THC, 3, 3; Δ4(8)-iso-THC, 39, 39).

These results prompted a reinvestigation of the reaction of Δ1- and Δ6-*cis*-THCs (**12a,b**) with higher concentrations of *p*-TSA (expt 2 and 3, Table II).[6] The composition of the resulting mixture as shown by GLC was confirmed by NMR. As with the *cis*-CBDs, the major products were *cis*-THCs[10,11] at low acid concentrations (expt 2) and iso-THCs at higher acid concentrations (expt 3).

The present results are in agreement with our previous studies on acid transformations of cis compounds.[6,11] Furthermore, a comparison of the acid-catalyzed reactions of *cis*- and *trans*-CBDs shows that Δ1-*cis*-CBD gives much more iso-THC than does Δ1-*trans*-CBD.[12]

Experimental Section

All compounds are (±) racemic mixtures. Melting points were determined in a Thomas-Hoover melting point apparatus and are uncorrected. The IR spectra were recorded on a Perkin-Elmer Model 700 instrument and the NMR spectra were measured on a Varian T-60

spectrometer. The high-pressure liquid chromatographic separations were made with a Waters Associates ALC-202 chromatograph equipped with a Model 6000 solvent delivery system. Preparative separations were made on a 7 ft × 0.375 in. i.d. column packed with Porasil C. Analytical separations were made on a 1 ft × 0.25 in. o.d. column packed with μ Porasil. The analyses by gas chromatography were made on a Varian Aerograph Model 1440, equipped with a 6 ft × 0.125 in. i.d. stainless steel column packed with 2% OV-17 on 100/200 mesh Supelcoport, and a flame ionization detector.

***cis*-6a,10a-1-Hydroxy-9-methyl-3-pentyl-6a,7,10,10a-tetrahydro-6*H*-dibenzo[*b,d*]pyrone (1a).**[8a] 2,6-Dimethoxy-4-pentylbenzaldehyde[13a,b] was demethylated with $AlBr_3$ in CS_2, according to a procedure[13c] used for 2-resorcylaldehyde. 2,6-Dihydroxy-4-pentylbenzaldehyde was obtained in 38% yield as a solid melting at 69–71 °C: NMR ($CDCl_3$) δ 10.35 (1, s, CHO), 9.25 (2, br, OH), 6.18 (2, s, aromatics), 2.52 (2, t, J = 8 Hz, benzylic), 0.88 (3, t, ω-CH_3). Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.75. Found: C, 69.18; H, 7.82. Further evidence for the structure of this aldehyde was provided by the subsequent reactions that led to a cannabidiol (**5a**) identical with that prepared by another route (see below) and whose structure was unequivocal.[14] The aldehyde was allowed to react with malonic acid in the presence of aniline and pyridine by a literature procedure[13c] to give an 81% yield of the known 3-carboxy-5-hydroxy-7-pentylcoumarin as a solid melting at 192–193 °C (lit.[8a] 198–199 °C). A Diels–Alder reaction of this coumarin with isoprene gave pyrone **1a**. The reaction was carried out in an autoclave at 180 °C for 18 h, according to the literature procedure.[8a,13c] The product was a solid melting at 115–117 °C (lit.[8a] 123–125 °C): NMR ($CDCl_3$) δ 6.48 (2, s, aromatics), 5.83 (1, s, OH), exchangeable), 5.47 (1, br, C8 H, vinylic), 3.50 (1, dt, J = 11, 6, 6 Hz, C10a H), 1.63 (3, s, C9 CH_3), 0.88 (3, t, ω-CH_3).

2-[3,4-*cis*-1-Methyl-3-(5-pentyl-2-resorcinyl)cyclohex-6-en-4-yl]-2-propanol (2a). A solution of 0.30 g (0.001 mol) of **1a** in 10 mL of dry benzene was added to the Grignard reagent prepared from 0.24 g (0.010 mol) of Mg turnings and 0.65 mL of CH_3I in 6 mL of anhydrous ether. The reaction mixture was then heated at reflux for 1.5 h under N_2. It was decomposed by the addition of saturated NH_4Cl solution. The organic layer was separated, washed once with saturated NH_4Cl solution followed by brine, and dried. Solvent was removed in vacuo to give 0.32 g (98%) of **2a** as a sticky semisolid. It showed a single spot on TLC (1:4 ethyl acetate/hexane).

On treatment with 0.5 mL of Ac_2O in 5 mL of pyridine (3.5 h at ambient temperature) it formed the diacetate **3a** in 89% yield: IR (neat) 3550 (OH), 1765 cm^{-1} (ester C=O). It was used in the subsequent step without further purification.

Δ^6-*cis*-Cannabidiol Diacetate (4a). A solution of 45 mg (0.11 mmol) of **3a** in 1 mL of dry pyridine was cooled in ice and 2 drops of $SOCl_2$ was added. After 30 min at 24 °C the dark yellow solution was diluted with brine and extracted with ether. The ether extract was washed several times with water and once with very dilute HCl followed by water until neutral, dried, and concentrated in a rotary evaporator. The residue was 28 mg (65%) of **4a** as a colorless gum: NMR (see Table I); IR (CCl_4) 1770 (ester C=O), 900 cm^{-1} (=CH_2); mass spectrum m/e 398.2454 (M^+·) (calcd for $C_{25}H_{34}O_4$, 398.2457). Anal. Calcd for $C_{25}H_{34}O_4$: C, 75.34; H, 8.60. Found: C, 74.98; H, 9.0.

(±)-Δ^6-3,4-*cis*-Cannabidiol (5a). A solution of 144 mg (0.36 mmol) of **4a** in 3 mL of MeOH and 1.0 mL of 5% KOH in MeOH was allowed to stand in ice for 20 min under N_2. An additional 2.0 mL of 5% KOH in MeOH was added and the reaction mixture was allowed to stand at 22 °C for 1.5 h. The resultant dark solution was poured into a water/ether mixture and made acidic with 1:1 dilute HCl and the organic layer was separated. It was washed with saturated brine until neutral, dried, and evaporated to leave 105 mg (93%) of crude **5a**. It was easily purified by chromatography on 5 g of Florisil and eluted with 40:60 benzene/petroleum ether mixture to give 54 mg of **5a** as a colorless gum: NMR (see Table I); IR (CCl_4) 3450 (OH), 1615, 1570, 1450, 1220, 1165, 1010, 905 cm^{-1} (=CH_2); mass spectrum m/e 314 (M^+·), 231 (base).

Δ^1-*cis*-Cannabidiol Diacetate (4b). A solution of 0.709 g (2.36 mmol) of **1a** and 0.133 g (0.7 mmol) of p-TSA·H_2O in 50 mL of dry C_6H_6 was heated at reflux for 1.5 h under N_2. The cooled solution was stirred well with 3 g of Na_2CO_3·H_2O and filtered. The filtrate was concentrated in vacuo to give a 1:1 mixture of **1a** and **1b** (based on NMR integration of vinylic proton) as a glassy gum.

This mixture of lactones **1a** and **1b** was converted to a mixture of the diacetates **4a** and **4b** following the same sequence of reactions as in the preparation of **4a**. The two *cis*-CBD diacetates **4a** and **4b** were readily distinguished by GLC; the retention times (column 260 °C) were 3.30 min for **4a** and 3.56 min for **4b**.

The two diacetates were separated by high-pressure liquid chromatography with 5:95 ether/isooctane as solvent. The capacity factor (k') was 0.68 for **4a** and 1.32 for **4b**, giving a separation factor (α) of 1.94. In a typical run a 100-mg charge was separated in a single pass. Thus 0.24 g of **4a** and 0.15 g of **4b** were collected in an overall yield of 26 and 16%, respectively, from the starting lactones **1**.

The Δ^1-diacetate **4b** was obtained as a colorless gum: NMR (see Table I); IR (CCl_4) 1770 (ester C=O), 900 cm^{-1} (=CH_2), indistinguishable from that of **4a**; mass spectrum m/e 398.2465 (M^+·) (calcd for $C_{25}H_{34}O_4$, 398.2457). Anal. Calcd for $C_{25}H_{34}O_4$: C, 75.34; H, 8.60. Found: C, 75.08; H, 9.03.

(±)-Δ^1-3,4-*cis*-Cannabidiol (5b). Compound **4b** was hydrolyzed as with **4a** to give **5b** as a colorless gum: NMR (see Table I); IR (CCl_4) was the same as for **5a** except for a weak absorption peak at 1070 cm^{-1}; mass spectrum m/e 314 (M^+·), 231 (base). Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.20; H, 9.62. Found: C, 80.44; H, 9.65.

When the hydrolysis of **4b** was stopped after 20 min, the product obtained was mostly the monoacetate, which showed hydroxyl and acetyl groups by IR (CCl_4) 3330 (OH), 1760 cm^{-1} (ester C=O), and by NMR (CCl_4) δ 6.35, 6.47 (2, aromatic), 6.47 (1, s, OH, exchangeable), 5.75 (m, olefinic, C2 H), 4.60 (br, C8 CH_2), 2.15 (3, s, $OCOCH_3$), 1.38 (s, C1 CH_3), 0.92 (t, ω-CH_3).

6aβ,7,8,9,10,10aβ-Hexahydro-1-hydroxy-3-pentylspiro[6*H*-dibenzo[*b,d*]pyran-9,2′-[1′,3′]dioxolan]-6-one (7). By a published procedure,[9] 5.00 g (0.0145 mol) of 1-hydroxy-3-pentyl-7,8,9,10-tetrahydrospiro[6*H*-dibenzo[*b,d*]pyran-9,2′-[1′,3′]dioxolan]-6-one (**6**)[9] was hydrogenated with W-2 Raney nickel as a catalyst to give 4 g of **7** as a colorless solid: mp 142–144 °C (81%) (lit. 142.5–143.5 °C);[9] NMR ($CDCl_3$) δ 6.50 (2, s, aromatic), 4.02 (4, s, methylene of ketal), 3.61 (1, dt, C10a H), 0.88 (3, t, ω-CH_3), 6.27 (OH, exchangeable); IR ($CDCl_3$) ν 3350 (OH), 1750 cm^{-1} (C=O); TLC, R_f (silica, 80:20 Et_2O/petroleum ether) 0.61.

6aβ,7,8,9,10,10aβ-Hexahydro-1-hydroxy-3-pentyl-6*H*-dibenzo[*b,d*]pyran-6,9-dione (8). The ketal **7** (3.5 g, 0.01 mol) was hydrolyzed in dioxane (50 mL) by the slow addition of 40 mL of 3 N HCl. After being stirred at room temperature for nearly 4 h, the yellowing solution was drowned in water and stirred until crystallization was complete. The colorless solid, collected by filtration, washing, and drying, amounted to 2.25 g (75%) of the dione **8**, mp 194–198 °C. The analytical sample, mp 197–198 °C, was obtained by recrystallization from diethyl ether/petroleum ether. Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.48; H, 7.35. NMR ($CDCl_3$) δ 6.52 (2, s, aromatic), 3.75 (1, dt, C10a H), 0.88 (ω-CH_3), 7.25 (OH, exchangeable); IR ($CDCl_3$) ν 3280 (OH), 1750 (C=O, ester), 1700 cm^{-1} (C=O, keto); TLC, R_f (silica, 80:20 Et_2O/petroleum ether) 0.68.

Another product of the hydrolysis, extracted from mother liquors by benzene as a yellow solid of broad melting point, soluble in $NaHCO_3$ (purple solution), was the acid **11** (R_f, silica, 80:20 Et_2O/petroleum ether, 0.14): NMR ($CDCl_3$) δ 6.28 (2, aromatic), 6.93 (3, exchangeable OH); IR ($CDCl_3$) ν 3350 (OH), 1700 (C=O, keto), 1690 cm^{-1} (C=O, acid). It was converted to the lactone **8** by heating in benzene at reflux for 2 h with p-TSA as catalyst, and a Dean-Stark trap to remove water. The product isolated was identical (melting point, TLC) with authentic dione **8**. The overall yield of **8** was thus raised to 91% of theory.

Heating at reflux or a longer reaction time at room temperature increased the proportion of acid during the hydrolysis.

2-[3,4-*cis*-1-Hydroxy-1-methyl-3-(5-pentyl-2-resorcinyl)-4-cyclohexyl]-2-propanol (9). A solution of 2.0 g (0.0066 mol) of **8** in 120 mL of anhydrous diethyl ether (a saturated solution) was added rapidly to a refluxing solution of the Grignard reagent made from 2.57 g (0.105 mol) of magnesium turnings and 7.0 mL (16.0 g, 0.112 mol) of methyl iodide in 40 mL of anhydrous ether. The dione was rinsed in with 50 mL of anhydrous tetrahydrofuran. After 1 h of refluxing the excess Grignard reagent was destroyed by addition of ethyl acetate, followed by saturated aqueous NH_4Cl. The layers were separated, the aqueous layer was extracted with Et_2O, and the combined organic layers were washed with saturated NH_4Cl, dried, and concentrated. After all solvents had been removed, the crude tetrol **9** was obtained (2.47 g) as a light-colored foam. This product melted over a wide range (56–113 °C), was very soluble in Et_2O and insoluble in CCl_4, and showed two spots on TLC in a variety of solvents (R_f, silica, 0.65 and 0.53 in 2:1 EtOAc/benzene; 0.57 and 0.41 in Et_2O). Elemental analysis and NMR indicated that it was a mixture of nonisomeric compounds. Without further purification it was used for the subsequent steps to cannabidiol diacetate.

In a small experiment the products from the Grignard reaction were separated by high-pressure liquid chromatography (μPorasil, 80:20 Et_2O/isooctane as eluent); the k' for the compound moving faster on TLC was 1.6, and for the slower moving compound it was 5.1. The latter compound, a foamy solid, could not be made to crystallize from solution, but it gave an acceptable analysis for the tetrol **9**. Anal. Calcd

for $C_{21}H_{34}O_4$: C, 71.96; H, 9.77. Found: C, 71.68; H, 9.73.

2-(4,5-*cis*-*p*-Mentha-1,8-dien-5-yl)-5-pentylresorcinol Acetate (4a). A solution of 1.46 g (0.0041 mol) of the crude tetrol **9**, from the preceding experiment, 8 mL of dry pyridine, and 1.6 mL of Ac_2O in 20 mL of anhydrous ether was allowed to stand at 20 °C for 4.75 h. Then, 3.3 mL of a solution made from 0.9 mL of $SOCl_2$ and 3.0 mL of anhydrous ether was added during 15 min to the ice-cooled acetate solution. The nearly colorless solution and white precipitate were stirred for 10 min longer. Saturated NaCl solution (8 mL) and 20 mL of petroleum ether were added, and the layers were separated. The aqueous layer was extracted with 1:1 Et_2O/petroleum ether, the pyridine was removed from the organic layer by washing with water and dilute HCl, and the acid was removed by washing with water and $NaHCO_3$. The organic solution was dried and concentrated, leaving 1.44 g of a pale amber resin. NMR indicated that this product was about 50% CBD diacetate (**4a**).

Column chromatography of the diacetate (Florisil, 2:1 benzene/hexane, then 100% benzene) separated impure (about 70% by NMR) *cis*-CBD diacetate (0.27 g).

The final purification was accomplished with HPLC (Porasil, 5% diethyl ether/isooctane). At this point, the *cis*-CBD diacetate (144 mg) showed a single spot on TLC in both 1:4 EtOAc/hexane (R_f 0.58) and 2:1 benzene/hexane, and by GLC it had >90% purity.

Δ^6-*cis*-CBD (5a). The Δ^6-*cis*-CBD diacetate (**4a**) obtained above was hydrolyzed to **5a** with dilute alcoholic KOH as described above in the alternative synthesis, and finally purified by HPLC on μPorasil with eluent 3% Et_2O/isooctane (k' = 3.1) or 2% Et_2O/isooctane (k' = 5.6). The material (60 mg) was identical in all respects (NMR, GLC, TLC) with **5a** prepared earlier. There was no evidence by either GLC or NMR for the presence of Δ^1-*cis*-CBD (**5b**).

Reaction of *cis*-CBDs and *cis*-THCs with *p*-TSA (Table II). General Procedure. The solution of the cannabinoid in dry benzene was mixed with a solution of *p*-toluenesulfonic acid in benzene, made anhydrous from the acid monohydrate by azeotropic distillation of the water, and heated at reflux (oil bath) under nitrogen, with gentle magnetic stirring. Samples for GLC were taken at regular intervals in expt 4, 5, and 6, and added to a slurry of Na_2CO_3·H_2O and CH_2Cl_2 in order to quench the reaction. At the end of the time period, the catalyst was neutralized by the addition of solid Na_2CO_3·H_2O and the solution was filtered. Samples were taken from the filtrate for analysis by GLC, and for the NMR spectra. The cannabinoid products were identified by comparison with authentic specimens from other sources, both unsilylated and silylated analyses being required in the GLC because of overlapping retention times.

Products from expt 1 were separated by high-pressure liquid chromatography and their identities were confirmed by NMR spectra (Table III). The first fraction from HPLC was cannabicitran (**13**) (also called citrylidene-cannabis),[6] identified by its retention time on GLC compared to an authentic sample, and by the fact that this retention time was unchanged by attempted silylation. Δ^8-*cis*-Iso-THC constituted the next fraction eluted from the column; although the compound was identified earlier,[17] its NMR spectrum (Table III) has not been reported. (±)-Δ^6-*cis*-THC was eluted last from the column, and had an NMR spectrum identical with that given by Uliss et al.[11]

Δ^6-*cis*-THC, upon treatment with 0.04 g of *p*-TSA/100 mL (expt 2 of Table II), reached an equilibrium with Δ^1-*cis*-THC (30:70, respectively, GLC) after 60 min. This ratio is similar to that observed by Uliss et al.[11] The NMR spectrum (CCl_4) supported the composition shown by GLC. Olefinic protons for both a Δ^6-THC (**12a**) (δ 5.35, C6 H) and a Δ^1-THC (**12b**) (δ 6.27, C2 H) were evident, and the *gem*-dimethyl protons (δ 1.37, 1.27) were typical for a cis configuration at the C3–C4 ring junction. The absorption at δ 3.17 (m) attributed to the 2α proton of Δ^6-*cis*-THC was partially replaced by a multiplet at δ 3.50, corresponding to the C-3 proton of Δ^1-*cis*-THC.[9]

At a still higher acid concentration (0.2 g/100 mL; expt 3, Table II) this mixture gave a product containing a large proportion (44% by GLC) of $\Delta^{4(8)}$-iso-THC [characteristic NMR absorption peaks ($CDCl_3$) at δ 4.18 and 1.93 corresponding to the protons at C-3 and C-9, respectively[18]]. The olefinic protons for Δ^1- and Δ^6-*cis*-THCs (31% by GLC) were still visible (δ 6.30 and 5.27, respectively). The composition was confirmed by GLC analysis (Table II).

Acknowledgment. We wish to thank Professor John C. Sheehan for his encouragement of this work and Dr. Catherine Costello of M.I.T. for mass spectral data (NIH Grant RR-00317).

Registry No.—**1a**, 62461-63-6; **1b**, 62461-64-7; **2a**, 62461-65-8; **3a**, 62461-66-9; **4a**, 62461-67-0; **4b**, 62504-25-0; **4b** monoacetate, 62461-68-1; **5a**, 62461-69-2; **5b**, 7663-52-7; **6**, 6469-57-4; **7**, 27279-31-8; **8**, 62461-70-5; **9**, 62461-71-6; **11**, 62461-72-7; **12a**, 6216-87-1; **12b**, 6087-73-6; **13**, 62504-22-7; **14**, 62504-23-8; **15**, 62504-24-9; 2,6-dimethoxy-4-pentylbenzaldehyde, 3410-84-2; 2,6-dihydroxy-4-pentylbenzaldehyde, 24237-04-5.

References and Notes

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(3) Petrzilka has noted[4] that the compound he called "*cis*-cannabidiol" in a preliminary communication[5] was in fact the trans position isomer 4-(*p*-mentha-1,8-dien-3-yl)olivetol. For this reason, a reaction ascribed to *cis*-CBD[6] has been amended (ref 2a, footnote, p 93).
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(9) K. E. Fahrenholtz, M. Lurie, and R. W. Kierstead, *J. Am. Chem. Soc.*, **89**, 5934 (1967).
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(14) Hively[8a] reported the use of 2,6-dihydroxy-4-pentylbenzaldehyde as his starting material for synthesizing lactone **1a**, but he did not describe its synthesis, source, or physical properties. Jen et al.[15] claimed the preparation of 2,6-dihydroxy-4-pentylbenzaldehyde, mp 53–56 °C from olivetol, $Zn(CN)_2$, and HCl. Upon repeating Jen's synthesis, we obtained an aldehyde [mp 58–60 °C; NMR ($CDCl_3$) δ 10.83 (1, s, –OH, exchangeable), 10.07 (1, s, –CHO), 7.40 (1, br, –OH, exchangeable), 6.30 (2, s, aromatics), 2.82 (2, t, J = 8 Hz, benzylic), 0.88 (3, t, ω-CH_3)], which we believe to be the 2,4-dihydroxy-6-pentyl isomer.[16]
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Studies on the Total Synthesis of Triptolide. 1

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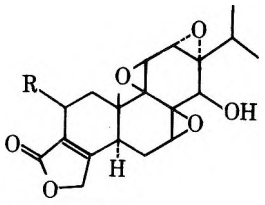
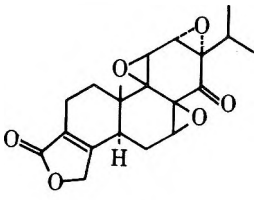
A convenient sequence for the conversion of 6-methoxy-1-tetralone (5) to 16 in nine steps is described. Robinson annelation of 16 affords 17 in overall yield of 33% from 5. Tricyclic enone 17 is converted in five steps to 22 that on oxidation with periodate affords 23 and thus provides a convenient entry to the stereospecific synthesis of the C-ring functionality in triptolide (1).

The isolation of triptolide (1), tripdiolide (2), and triptonide (3) by Kupchan and co-workers provided the first recognized diterpenoid triepoxides.[1] More recently a related diterpenoid bisepoxide, stemolide (4), has been isolated.[2] Of particular interest is the antileukemic activity of 1 and 2 and



1, R = H
2, R = OH



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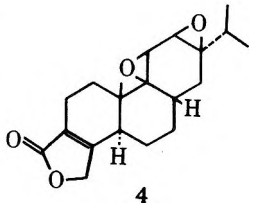

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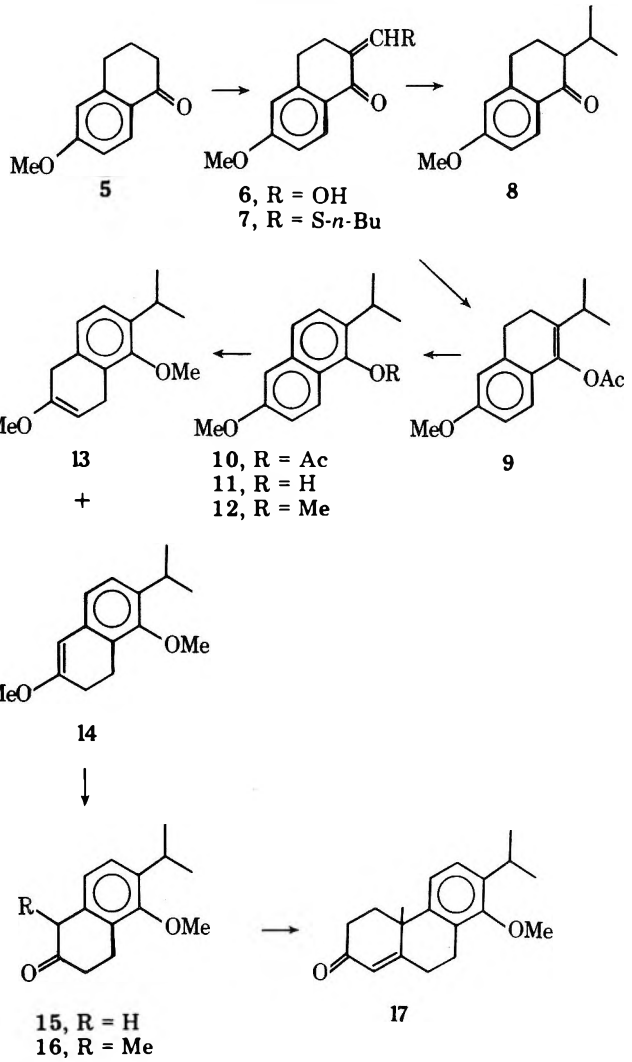
the hypothesis that the hydroxyl-assisted addition of nucleophiles to the 9,11-epoxide of 1 and 2 may mimic the mechanism by which they exert their antileukemic activity.[1]

In connection with efforts toward the total synthesis of 1, a convenient synthesis of 6-isopropyl-5-methoxy-1-methyl-3,4-dihydro-2(*H*)-naphthalenone (16) was desired to provide a starting material that could be obtained in reasonable quantity for an annelation reaction (such as 16 → 17) as an entry to an appropriately substituted tricyclic skeleton. In addition it was desired to convert 17 to 22 to determine whether the model system 22 followed the usual reaction course of substituted *o*-hydroxymethylphenols with periodate[3] to afford the corresponding epoxy cyclohexadienone (23) as an entry to the C-ring functionality in 1.

A convenient starting material for the synthesis of 16 (Scheme I) was 6-methoxy-1-tetralone (5). Although monoalkylation of 5 to afford 8 was effected to an extent of 55% on treatment with 1 equiv of lithium diisopropylamide in 1,2-dimethoxyethane in the presence of excess isopropyl iodide at 50 °C for 23 h, no further conversion was effected by prolonged heating; and, although alkylation with 2 equiv of base increased the conversion to 65%, it resulted in substantially more side products. Since separation of 8 from unalkylated 5 required a tedious distillation that resulted in reduced yields, a more satisfactory preparation of pure 8 was developed. Formylation of 5 with excess ethyl formate and base at room temperature afforded 6[4,5] in nearly quantitative yield, and subsequent reaction of 6 with *n*-butanethiol in the presence of *p*-toluenesulfonic acid catalyst with removal of water according to the general procedure of Ireland and Marshall[6] gave crystalline 7 in 72% yield. Application of the Coate's procedure[7] for bis-conjugative alkylation of *n*-butylthio-

Scheme I



methylene ketones with lithium dimethylcuprate afforded, after aqueous workup, tetralone 8 in 93% yield from 7.

Attempts to dehydrogenate 8 to the corresponding naphthol with quinone reagents were not successful.[8,9] Consequently the enolate generated in the reaction of 7 with lithium dimethyl cuprate was quenched with acetic anhydride to give 9 (92%). Dehydrogenation of 9 with sulfur at 250 °C afforded 10 in 68% yield. Acetate 10 was hydrolyzed to naphthol 11 in quantitative yield with 10% aqueous sulfuric acid in methanol at reflux, and 11 smoothly underwent quantitative methylation with dimethyl sulfate and barium hydroxide in dimethylformamide to afford 12.

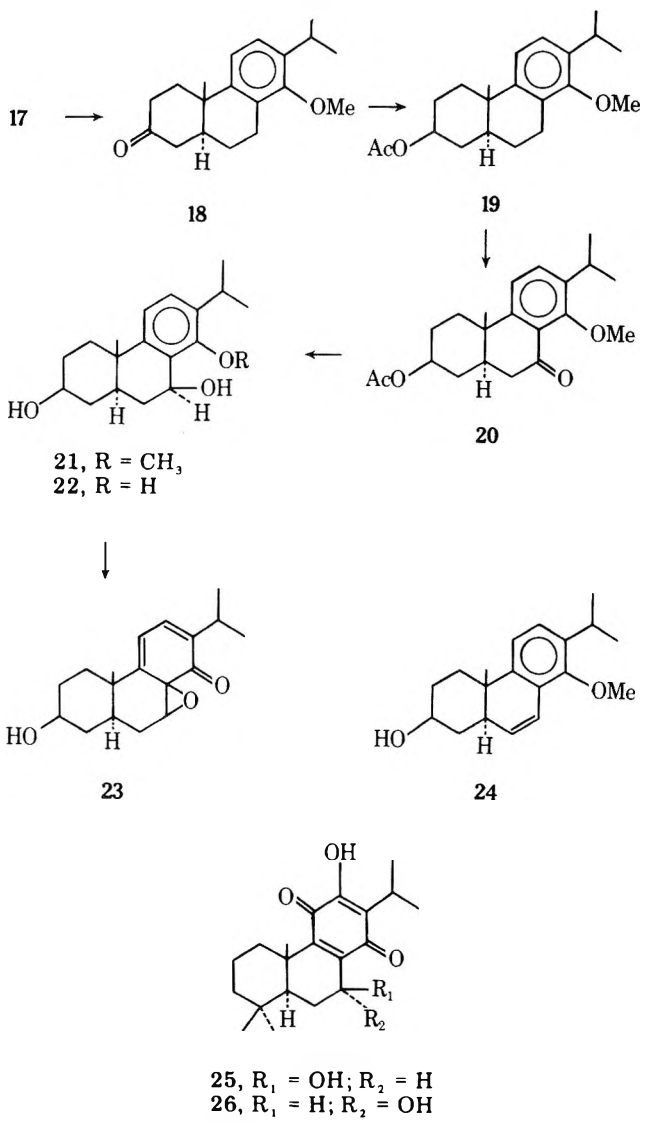
Under Birch conditions (Na/NH_3/THF/EtOH) 12 gave enol ether 13 as the sole product (94%). Reduction of 12 with sodium in ethanol under reflux according to the general procedure of Conforth and Robinson[10] proved to be preparatively

superior and afforded in nearly quantitative yield a 2:1 mixture of **13** and **14** (see Experimetal Section). The enol ether mixture was hydrolyzed with oxalic acid in aqueous methanol under reflux to give tetralone **15** (92%) that was conveniently isolated and purified as the air-stable bisulfite adduct.

Mild conversion of **15** to the pyrrolidine enamine was effected by stirring a benzene solution of **15** with pyrrolidine over 3A molecular sieves at room temperature, and methylation of the enamine with excess methyl iodide in refluxing dioxane afforded, after hydrolysis, **16** in 98% yield from **15**.[11] Robinson annelation of **16** with methyl vinyl ketone in aqueous methanolic potassium hydroxide gave tricyclic enone **17** in 81% yield; the overall yield of **17** from **5** is 33%.

Reduction of **17** (Scheme II) with lithium in ammonia[12] provided trans-fused ring ketone **18** that was obtained in 81%

Scheme II



yield on small scale after purification by column chromatography on alumina and on large scale could be isolated by recrystallization in 66% yield. Conversion of **18** to the 3β-acetoxy derivative **19** in 78% yield was accomplished by lithium tri-*tert*-butoxyaluminum hydride reduction to the 3β alcohol, according to the known stereochemical course of reductions of 3-keto steroids,[13] followed by acetylation with acetic anhydride in pyridine.

Attempts to effect benzylic oxidation of **19** with selenium dioxide in refluxing acetic acid or with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone[14] in refluxing methanol were not successful, but chromium trioxide oxidation in aqueous acetic acid afforded ketone **20** in 42% yield after dry column chromatography on alumina. Reduction of the ketone function of **20** with sodium borohydride followed by workup with aqueous acid effected stereoselective reduction of the ketone function to the β alcohol with cleavage of the acetoxy group to afford **21** in 94% yield. The NMR spectrum of the product indicated that it was 97% β alcohol and 3% α alcohol. As expected, reduction of ketone **20** with lithium tri-*tert*-butoxyaluminum hydride gave slightly more α alcohol (94% β:6% α), and reduction with potassium tri-*sec*-butylborohydride (K-Selectride), the reagent of choice for selective reduction of cyclohexanones to axial alcohols,[15] gave considerably more α alcohol (60% β:40% α). Further support for the stereochemical assignment in **21** is obtained from the NMR spectrum where the α benzylic carbinol hydrogen appears at δ 5.16 as a triplet with an apparent coupling constant of 8 Hz and a half-band width of 15 Hz as expected for the coupling of this axial proton with the adjacent methylene group. A similar pattern is observed for the axial 7α hydrogen in the NMR spectrum of taxoquinone (**25**), which appears as a broad triplet with an apparent coupling constant of 7 Hz, whereas the corresponding absorption for the 7β hydrogen in horminone (**26**) is a broad signal with a half-band width of 8 Hz as expected for an equatorial β hydrogen.[16]

Cleavage of the *O*-methyl ether of **21** was effected with boron tribromide in methylene chloride at room temperature but always resulted in substantial dehydration of the benzylic alcohol to olefin **24**. Quantitative demethylation of **21** to **22** was effected with sodium *n*-propanethiolate in dimethylformamide at 40 °C for 30 h. At 100 °C considerable dehydration of the benzylic alcohol was observed.

Reaction of **22** with sodium metaperiodate in aqueous methanol afforded **23** in 66% yield as a pale yellow solid, the spectral data of which allow unambiguous assignment of structure (see Experimental Section). The periodate reaction with *o*-hydroxymethylphenols thus appears to be a convenient entry to an attractive intermediate for the stereospecific construction of the C-ring functionality in triptolide and related substances.

Experimental Section

General. Melting points were determined on a Thomas-Hoover Uni-Melt apparatus and are corrected. Boiling points are uncorrected. Infrared spectra were determined either with a Perkin-Elmer Model 237-B or Model 567 grating spectrophotometer. ^{1}H NMR spectra were determined with either a 60-MHz Varian Model T-60 spectrometer or, where noted, with a 90-MHz Hitachi Model R-22 spectrometer. Chemical shift data are reported in parts per million downfield from tetramethylsilane as internal standard. Mass spectra were determined with a Hitachi Perkin-Elmer RMU-6E spectrometer with an ionizing potential of 70 eV and are expressed in percent relative to the most intense peak. Except for the high-mass region only the *m/e*'s of greater than 20% relative intensity are listed. High-resolution mass spectra were run on a CEC-21-110B spectrometer.[17] Ultraviolet spectra were determined with a Cary Model 14 recording spectrophotometer. Gas chromatographic analyses and isolation of compounds were performed on a Varian Aerograph Series 2100 (flame ionization) chromatograph with 6 ft × 2 or 3.5 mm i.d. glass columns packed with specified liquid phase and inert support (glass injection port and glass effluent splitter). Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

2-Hydroxymethylene-6-methoxy-3,4-dihydro-1(2*H*)-naphthalenone (6). The procedures of Akhrem and Zavel'skaya[4] and of Banerjee, Chatterjee, Pillai, and Bhatt[5] were modified as follows. To a stirred mixture of 105 mL (96.9 g, 1.314 mol) of ethyl formate, 43.2 g (0.801 mol) of sodium methoxide, and 450 mL of reagent benzene in a three-neck 2-L round-bottom flask under nitrogen at 0 °C was added dropwise over a 45-min period a solution of 75.0 g (0.426 mol) of **5** (Aldrich) in 300 mL of reagent benzene. The ice bath was removed, and stirring was continued for an additional 1.75 h. The mixture was quenched, with cooling, with 600 mL of 5% aqueous sulfuric acid. The benzene layer was washed with two portions of water and with saturated brine, dried (Na_2SO_4), and evaporated in vacuo

to give 86.5 g (100%) of **6** as a tan solid (>95% pure by NMR and GLC), mp 63–68 °C (lit.[4] mp 66.5–67.5 °C, lit.[5] mp 67–68 °C).

2-*n*-Butylthiomethylene-6-methoxy-3,4-dihydro-1(2*H*)-naphthalenone (7). A solution of 57.10 g (0.280 mol) of **6**, 35 mL (0.325 mol) of *n*-butanethiol, 48 mg (0.25 mmol) of *p*-toluenesulfonic acid monohydrate, and 200 mL of reagent benzene was stirred under reflux in a nitrogen atmosphere for 21 h with removal of water in a Dean-Stark trap (4.25 mL, 85% theory). The mixture was cooled to room temperature and quenched with 150 mL of saturated sodium bicarbonate solution. The benzene layer was washed with saturated brine, dried (Na_2SO_4), and evaporated in vacuo to give a dark oil which crystallized after trituration with petroleum ether (30–60 °C). The crude material was recrystallized from 700 mL of hexanes. In the initial stages of crystallization the filtrate was decanted from an oil and dark solid which had formed, and the recrystallization was allowed to continue to give 55.72 g (72%) of **7** as tan prisms, mp 60–64 °C. An analytically pure sample was prepared by recrystallization from pentane to give large, pale green-yellow prisms: mp 63.5–64.5 °C; IR (CCl_4) 2960, 2940, 1655, 1600, 1560, 1555, and 880 cm^{-1}; NMR ($CDCl_3$) δ 0.77–1.13 (3 H, m), 1.20–1.93 (4 H, m), 2.60–3.04 (6 H, m), 3.87 (3 H, s), 6.60 (1 H, m, obscured by other aromatic proton absorption), 6.74 (1 H, d of d, J = 8, 2 Hz), 7.65 (1 H, br s), and 7.97 ppm (1 H, d, J = 8 Hz); MS *m/e* (rel intensity) 277 (3), 276 (M^+, 13), 243 (12), 219 (60).

Anal. Calcd for $C_{16}H_{20}O_2S$: C, 69.52; H, 7.29; S, 11.60. Found: C, 69.59; H, 7.33; S, 11.61.

2-Isopropyl-6-methoxy-3,4-dihydro-1(2*H*)-naphthalenone (8). A dry three-neck 1-L round-bottom flask equipped with nitrogen inlet and magnetic stirring bar was charged with 40.00 g (0.210 mol) of purified cuprous iodide and, under nitrogen, with 100 mL of dry ethyl ether. To the mixture at 0 °C under nitrogen was added over a 15-min period 247 mL (0.420 mol) of 1.7 M methyllithium in ether (Alfa). Solid **7** (27.60 g, 0.100 mol) was added to the cooled mixture in small portions over a 30-min period from an Erlenmeyer flask through Gooch tubing. The mixture was stirred in the cold for 30 min and then quenched at 0 °C with a slow dropwise addition of 20 mL of water. The mixture was diluted with an additional 50 mL of water and filtered through a medium pore sintered-glass funnel. The copper salts were washed with ethyl ether. The combined ethereal extracts were washed with water and with saturated brine, dried (Na_2SO_4), and evaporated in vacuo to give 20.16 g (93%) of **8** as an amber liquid. The product (>95% pure by NMR and GLC) was used without further purification but could be distilled at 120–123 °C (0.35 Torr) to give a pale yellow oil. An analytically pure sample was prepared by preparative GLC (10% SE-30 on Chromosorb W, 180 °C) to give a colorless oil: IR (CCl_4) 2960, 2940, 1760, 1600, 1490, 1465, 1370, 1350, 1270, 1260, 1250, and 1230 cm^{-1}; NMR ($CDCl_3$) δ 0.97 (3 H, d, J = 7 Hz), 1.07 (3 H, d, J = 7 Hz), 1.7–3.1 (6 H, m), 3.85 (3 H, s), 6.65 (1 H, m, obscured by other aromatic proton absorption), 6.76 (1 H, d of d, J = 8, 2 Hz), and 7.98 ppm (1 H, d, J = 8 Hz); MS *m/e* (rel intensity) 218 (M^+, 7), 203 (11), 176 (7), 175 (100).

Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.87; H, 8.25.

1-Acetoxy-2-isopropyl-6-methoxy-3,4-dihydronaphthalene (9). To a 5-L three-neck round-bottom flask, equipped with a mechanical stirrer and attached with Gooch tubing to an Erlenmeyer flask containing starting material **7**, was charged with 285.66 g (1.50 mol) of reagent cuprous iodide and, under nitrogen, with 600 mL of dry ethyl ether. The system was flushed thoroughly with nitrogen and cooled to −20 °C (dry ice/CCl_4). The contents of three 1-mol bottles of 1.8 M methyllithium in ether (Alfa) were added via cannula at a rapid rate over a 20-min period to the stirred mixture followed by the addition of 198 g (0.718 mol) of solid **7** over a 30-min period. During the addition the temperature of the bath was maintained below −5 °C. Stirring was continued at the cold temperature for an additional 30 min followed by the slow addition of 375 mL of acetic anhydride via syringe. (Caution! exothermic. Bath temperature was maintained below −10 °C.) The mixture was stirred at room temperature for 3 h and then carefully quenched with 225 mL of water via syringe. The ethereal layer was decanted from the precipitate which was washed with an additional 400 mL of ethyl ether. Concentration of the combined ethereal solutions gave some wet solid product. The precipitate in the flask was washed with 800 mL of chloroform. The suspension was transferred to a medium pore sintered-glass funnel and filtered under suction. The salts were washed with an additional 800 and 600 mL of chloroform. The combined solution of crude product and chloroform filtrates was filtered through Celite in a medium pore sintered-glass funnel, washed with saturated brine, dried (Na_2SO_4), filtered again through Celite, and evaporated in vacuo to give a wet solid. Volatiles were removed under high vacuum to give a solid which was washed with several portions of pentane totaling 500 mL to give, after air drying, 171.6 g (92%) of **9** as a pale yellow, crystalline solid, mp 112–120 °C. The product (≫95% pure by NMR and GLC) was used without further purification. A 0.479-mol scale gave 93% yield of **9**. An analytically pure sample was prepared by three recrystallizations from pentane to give very pale yellow, fine plates: mp 122.5–123 °C; IR (CCl_4) 2960, 2940, 2840, 1770, 1610, 1465, 1430, 1370, 1310, 1280, 1255, 1230, 1215, 1135, 1125, 1075, 1050, and 1040 cm^{-1}; NMR ($CDCl_3$) δ 1.02 (6 H, d, J = 7 Hz), 2.07–3.08 (5 H, m), 2.28 (3 H, s), 3.75 (3 H, s), and 6.47–7.00 ppm (3 H, m; br s at 6.67, d at 6.92, J = 9 Hz); MS *m/e* (rel intensity) 261 (4), 260 (M^+, 19), 258 (3), 219 (6), 218 (35), 203 (70), 43 (100).

Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.81; H, 7.74. Found: C, 73.78; H, 7.84.

1-Acetoxy-2-isopropyl-6-methoxynaphthalene (10). A 500-mL Claisen flask was charged with a mixture of 52.0 g (0.20 mol) of **9** and 6.40 g (0.20 mol) of sulfur (Merck sublimed). While nitrogen was swept through the system and through a trap containing 200 mL of 2 N sodium hydroxide, the flask was immersed in a silicone oil bath preheated to 230 °C. After 5 min a vigorous exothermic reaction ensued. Oil-bath temperature was maintained at 250 °C for an additional 75 min. Trituration of cooled crude product with three 100-mL portions of pentane left a dark solid which was sublimed (100 °C, 0.05 Torr) to initially give a yellow, oily impurity which was rinsed from the cold finger. Further sublimation gave 35.2 g (68%) of **10** as pale yellow prisms, mp 123–127 °C. A 0.352-mol scale reaction afforded 64% yield of sublimed material. An analytically pure sample was obtained by an additional sublimation (115–120 °C, 0.05 Torr) to give pale yellow prisms: mp 126.5–128 °C; IR (CCl_4) 2965, 1770, 1610, 1485, 1420, 1370, 1270, 1240, 1205, 1175, 1170, 1035, 850 cm^{-1}; NMR ($CDCl_3$) δ 1.27 (6 H, d, J = 7 Hz), 2.44 (3 H, s), 3.14 (1 H, septet, J = 7 Hz), 3.80 (3 H, s), and 6.95–7.73 ppm (5 H, m); MS *m/e* (rel intensity) 259 (4), 258 (M^+, 20), 216 (78), 201 (84), 43 (100).

Anal. Calcd for $C_{16}H_{18}O_3$: C, 74.39; H, 7.02. Found: C, 74.50; H, 7.01.

2-Isopropyl-6-methoxy-1-naphthol (11). A mixture of 52.25 g (0.202 mol) of **10**, 400 mL of reagent methanol, and 100 mL of 10% aqueous sulfuric acid was deoxygenated with nitrogen and stirred under reflux in the dark for 43 h. Most of the methanol was evaporated in vacuo, and product was extracted with two portions (500 and 100 mL) of ethyl ether. The ether solution was washed with three 200-mL portions of water and with saturated brine, dried (Na_2SO_4), and evaporated in vacuo to give 42.88 g (98%) of **11** as a pale yellow solid, mp (sublimed 67 °C) 75–83 °C. The air-sensitive product was usually used immediately in the next reaction, but can be stored safely under nitrogen in a refrigerator. The reaction was successfully run on a 0.55-mol scale to give 100% yield of **11**. An analytically pure sample was prepared by two recrystallizations from petroleum ether (bp 30–60 °C) to give colorless needles: mp 85–86.5 °C; IR ($CHCl_3$) 3600, 3370, 2960, 2940, 1630, 1605, 1580, 1480, 1460, 1425, 1390, 1380, 1370, 1340, 1280, 1265, 1255, 1185, 1165, 1155, 1140, 1075, 1030, 850 cm^{-1}; NMR ($CDCl_3$) δ 1.31 (6 H, d, J = 7 Hz), 3.22 (1 H, septet, J = 7 Hz), 3.86 (3 H, s), 5.17 (1 H, s, exchanges with D_2O), 7.06–7.30 (4 H, m), and 8.00 ppm (1 H, m); MS *m/e* (rel intensity) 217 (9), 216 (M^+, 58), 201 (100).

Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.74; H, 7.46. Found: C, 77.74; H, 7.41.

1,6-Dimethoxy-2-isopropylnaphthalene (12). In a 2-L three-neck round-bottom flask a solution of 42.88 g (0.187 mol) of **11** in 500 mL of reagent DMF was thoroughly deoxygenated with nitrogen and cooled under a nitrogen atmosphere with an ice-bath. The system was opened to the atmosphere just long enough to add 78.7 g (0.249 mol) of barium hydroxide octahydrate to the stirred solution. After 5 min 55 mL (73.1 g, 0.58 mol) of dimethyl sulfate (Aldrich) was added at a moderately rapid rate to the cooled mixture via addition funnel. Stirring was continued at room temperature under nitrogen overnight. Sodium hydroxide (500 mL, 2 N) was added followed by stirring for an additional 1 h. The mixture was extracted with two portions (500 and 200 mL) of chloroform. The chloroform solution was washed with three 500-mL portions of water and with 300 mL of saturated brine, dried (Na_2SO_4), and evaporated in vacuo to give an oil. Residual DMF was removed under high vacuum to give 45.57 g (100%) of **12** as an almost colorless solid, mp 84–86 °C. The product was sufficiently pure to use directly in the next reaction. The reaction was successfully run on a 0.547-mol scale to give 99% yield of **12**. An analytically pure sample was prepared by two recrystallizations from pentane to give fine, colorless plates: mp 85–86 °C; IR (CCl_4) 2960, 2940, 1630, 1605, 1485, 1460, 1445, 1410, 1370, 1340, 1315, 1265, 1245, 1235, 1195, 1165, 1160, 1085, 1035, 995, 850 cm^{-1}; NMR ($CDCl_3$) δ 1.30 (6 H, d, J = 7 Hz), 3.54 (1 H, septet, J = 7 Hz), 3.85 (3 H, s), 3.88 (3 H, s), 7.05–7.55

(4 H, m), and 7.89–8.05 ppm (1 H, m); MS *m/e* (rel intensity) 231 (14), 230 (M^+, 88), 215 (100), 128 (34), 115 (30).

Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.22; H, 7.88. Found: C, 78.18; H, 7.93.

2,5-Dimethoxy-6-isopropyl-1,4-dihydronaphthalene (13) and 2,5-Dimethoxy-6-isopropyl-3,4-dihydronaphthalene (14) by Sodium–Ethanol Reduction of 12. A 2-L three-neck round-bottom flask equipped with mechanical stirrer and two condensers was charged with 80.5 g (0.35 mol) of **12** and 600 mL of absolute ethanol. One wide-diameter condenser for sodium addition was attached to a nitrogen inlet tube, while the other was attached to an outlet tube leading to a bubbler. The mixture was heated under a slow nitrogen flow to near reflux. When all solid had dissolved, 58.9 g (2.56 mol) of sodium was added in thin pieces over a 90-min period causing gentle refluxing of the mixture. Reflux was maintained until all of the sodium had reacted. The solution was diluted with 100 mL of absolute ethanol, allowed to cool to room temperature, and then diluted cautiously with 300 mL of water. Evaporation of ethanol in vacuo was followed by extraction with two portions (500 and 200 mL) of ethyl ether. The ether solution was washed with two 200-mL portions of water and with two portions of saturated brine, dried (Na_2SO_4), and evaporated in vacuo to give 80.9 g (100%) of **13** and **14** as a somewhat air-sensitive oil which was used without further purification. The product can be safely stored under nitrogen in a refrigerator. The NMR spectrum indicated a 64:36 mixture of enol ethers **13** and **14**, respectively, according to integration of the corresponding vinyl absorptions: 4.79 ppm (m) for **13** and 5.50 ppm (s) for **14**. A sample of pure 1,4-dihydro compound **13** was prepared by Birch reduction as described in the following experiment.

2,5-Dimethoxy-6-isopropyl-1,4-dihydronaphthalene (13) by Sodium-Ammonia Reduction. Ammonia (30 mL) was condensed into a solution of 1.15 g (5 mmol) of **12**, 15 mL of dry THF, and 1.17 mL (20 mmol) of absolute ethanol at −65 °C. Sodium (0.46 g, 20 mmol) was added. After 10 min of stirring under nitrogen 0.4 mL of ethanol was added, and stirring was continued for an additional 30 min. After 1 mL of water was carefully added, the ammonia was allowed to evaporate. The mixture was partitioned between water (10 mL) and ethyl ether (50 mL). The ether solution was washed with saturated brine, dried (Na_2SO_4), and evaporated in vacuo to give 1.09 g (94%) of **13** as an almost colorless oil which darkened upon prolonged exposure to the atmosphere. An analytically pure sample was prepared by preparative GLC (10% SE-30 on Chromosorb W, 175 °C) to give a colorless solid: mp (sublimed 52 °C) 55–61 °C dec; IR (CCl_4) 2960, 2940, 1645, 1485, 1465, 1450, 1420, 1385, 1325, 1265, 1200, 1180, 1160, 1150, 1080, 1035, and 835 cm^{-1}; NMR ($CDCl_3$) δ 1.23 (6 H, d, J = 7 Hz), 3.2–3.6 (5 H, m), 3.54 (3 H, s), 3.72 (3 H, s), 4.79 (1 H, m), 6.83 (1 H, d, J = 8 Hz), and 7.07 ppm (1 H, d, J = 8 Hz); MS *m/e* (rel intensity) 234 (3), 233 (19), 232 (M^+, 99), 217 (100).

Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.54; H, 8.68. Found: C, 77.32; H, 8.80.

6-Isopropyl-5-methoxy-3,4-dihydro-2(1*H*)-naphthalenone (15). A thoroughly deoxygenated mixture of 80.94 g (0.348 mol) of crude enol ether mixture **13** and **14** in 1200 mL of MeOH/H_2O (85:15) was stirred under reflux with 44.20 g (0.35 mol) of oxalic acid dihydrate under nitrogen in the dark for 21 h. After evaporation of the methanol in vacuo, product was extracted with 500 mL of ethyl ether. The ether solution was washed successively with 100 mL of water, 200 mL of saturated sodium bicarbonate solution, 100 mL of water, and saturated brine, dried (Na_2SO_4), and evaporated in vacuo to give an oil which was dissolved in 100 mL of 95% ethanol and shaken in a 2-L Erlenmeyer flask with a solution of 120 g (1.15 mol) of sodium bisulfite in 500 mL of water. The mixture was shaken thoroughly until a solid adduct had completely formed, placed in a refrigerator overnight with occasional shaking, and filtered. The solid was washed with 75 mL of absolute ethanol and with four 50-mL portions of ethyl ether and air dried to give a white solid adduct. Regeneration of oily air-sensitive tetralone **15** from a hot saturated solution of the bisulfite adduct with sodium carbonate followed by ether extraction and usual workup aforded a 92% yield of **15** from the enol ether mixture. An analytically pure sample was prepared by preparative GLC (10% SE-30 on Chromosorb W, 175 °C) to give a colorless oil: IR (CCl_4) 2965, 2940, 2910, 2870, 1725, 1485, 1450, 1445, 1420, 1330, 1305, 1260, 1210, 1170, 1070, 1055 cm^{-1}; NMR δ ($CDCl_3$) 1.25 (6 H, d, J = 7 Hz), 2.35–2.67 (2 H, m), 2.97–3.7 (5 H, m), 3.53 (2 H, s), 3.77 (3 H, s), 6.85 (1 H, d, J = 8 Hz), and 7.13 ppm (1 H, d, J = 8 Hz); MS *m/e* (rel intensity) 219 (17), 218 (M^+, 100), 203 (88), 176 (34), 175 (60), 161 (28), 131 (24), 128 (20), 117 (21), 115 (26), and 91 (29).

Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.75; H, 8.47.

6-Isopropyl-5-methoxy-1-methyl-3,4-dihydro-2(1*H*)-naphthalenone (16). Molecular sieves (3A, predried at 300 °C) (78 g) were added to a solution of 83.08 g (0.381 mol) of **15** in 560 mL of reagent benzene. The solution was thoroughly deoxygenated with nitrogen, cooled briefly with an ice bath, and treated with 36.7 mL (31.3 g, 0.44 mol) of pyrrolidine (Aldrich, 99%) added via syringe at a moderate rate. The ice bath was removed, and stirring was continued at room temperature under nitrogen for 4.5 h. Volatile solvents were evaporated in vacuo to give after high vacuum overnight tan solid enamine which was stored under nitrogen.

Dioxane (670 mL) was passed through 100 mL of neutral activated alumina (Woelm) directly into the flask containing the enamine through a no-air stopper while nitrogen was swept through the system. Methyl iodide (556 g) was added, and the solution was stirred under reflux for 48 h during which time a precipitate formed. The mixture was then stirred under reflux with 280 mL of 5% aqueous hydrochloric acid for 3 h and extracted with three portions (600, 300, and 300 mL) of ethyl ether. The combined ethereal extracts were washed with two portions of water and with saturated brine, dried (Na_2SO_4), and evaporated in vacuo to give after high vacuum overnight 86.99 g (98% from **15**) of **16** as an oil. The product was sufficiently pure to use directly in the next reaction. The reaction was successfully carried out on a 0.686-mol scale. A small sample was purified by distillation at 103 °C (0.08 Torr) to give an almost colorless oil. An analytically pure sample was prepared by preparative GLC to give an almost colorless oil: IR (CCl_4) 2964, 2940, 2870, 1720, 1485, 1450, 1420, 1330, 1260, and 1040 cm^{-1}; NMR ($CDCl_3$) δ 1.25 (6 H, d, J = 7 Hz), 1.45 (3 H, d, J = 7 Hz), 2.33–2.67 (2 H, m), 2.77–3.64 (4 H, m), 3.75 (3 H, s), 6.95 (1 H, d, J = 8 Hz), and 7.20 ppm (1 H, d, J = 8 Hz); MS *m/e* (rel intensity) 213 (5), 186 (52), 110 (100), 52 (21).

Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.54; H, 8.68. Found: C, 77.43; H, 8.53.

7-Isopropyl-8-methoxy-4a-methyl-4,4a,9,10-tetrahydro-2(3*H*)-phenanthrenone (17). To a deoxygenated solution of 43.20 g (0.655 mol) of 85% potassium hydroxide in 88 mL of water diluted with 1 L of reagent methanol and cooled to 0 °C was added under a nitrogen atmosphere a solution of 132.40 g (0.570 mol) of **16** in 200 mL of reagent methanol. The rapidly stirred solution was cooled to −20° C (dry ice/CCl_4), and 4.7 mL (41 g, 0.577 mol) of 98.5% methyl vinyl ketone (Aldrich) was added slowly over a 15-min period under nitrogen. After 1 h the cooling bath was removed and stirring was continued overnight at room temperature. The mixture was stirred under reflux for 3 h, cooled with an ice bath, and quenched with a solution of 65 mL of concentrated hydrochloric acid which had been diluted to a volume of 250 mL with water. The mixture was diluted with 500 mL of water and extracted with three 1-L portions of ethyl ether. The ether solution was washed with two 1-L portions of water and with saturated brine, dried (Na_2SO_4), and evaporated in vacuo to give a yellow solid which was dissolved in 250 mL of hot absolute ethanol and refrigerator cooled to give 130.8 g (81%) of **17** as pale yellow needles, mp (sublimed 94 °C) 100–106 °C. The product was sufficiently pure to use in the next reaction. An analytically pure sample was prepared by two recrystallizations from ethanol to give almost colorless prisms: mp 106–108.5 °C (partially resolidifies and remelts at 116–116.5 °C); IR ($CHCl_3$) 3000, 2970, 2870, 1660, 1625, 1485, 1445, 1410, 1355, 1330, 1260, 1245, and 1030 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.23 (3 H, d, J = 7 Hz), 1.26 (3 H, d, J = 7 Hz), 1.57 (3 H, s), 1.78–3.55 (9 H, m), 3.69 (3 H, s), 5.89 (1 H, s), 7.04 (1 H, d, J = 8 Hz), and 7.15 ppm (1 H, d, J = 8 Hz); MS *m/e* (rel intensity) 285 (10), 284 (M^+, 46), 270 (20), 269 (100), 227 (16).

Anal. Calcd for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.50; H, 8.36.

7-Isopropyl-8-methoxy-4aβ-methyl-3,4,4a,9,10,10aα-hexahydro-2(1*H*)-phenanthrenone (18). The reduction was run in a nitrogen atmosphere under anhydrous conditions with the usual precautions. Into a 2-L three-neck round-bottom flask equipped with dry ice condenser and mechanical stirrer was condensed 500 mL of liquid ammonia. The system was briefly opened to introduce 1.03 g (148 mmol) of lithium wire in about six pieces. After 5 min a solution of 20.0 g (70.5 mmol) of **17** in 500 mL of dry THF was added to the stirring solution via cannula. The dry ice bath was removed, and after stirring for 30 min 0.12 g (17 mmol) of lithium wire was added. After stirring for an additional 1 h 10 mL of water was slowly added via syringe, and the ammonia was allowed to evaporate. The mixture was diluted with 350 mL of water and extracted with two 500-mL portions of ethyl ether. The ether solution was washed with two 250-mL portions of water and with saturated brine, dried (Na_2SO_4), and evaporated in vacuo to give an oil which solidified upon pentane trituration to give 19.82 g of a pale yellow solid containing 10–15% of starting material. The crude product was recrystallized from absolute ethanol to give 13.18 g (66%) of **18** as an almost colorless solid, mp 107–111 °C.

An NMR spectrum indicated about 5% contamination by starting material. On smaller scale crude product was purified by dry column chromatography on alumina (CH_2Cl_2) to give 81% yield of pure **18**. An analytically pure sample was prepared from chromatographed material by recrystallization from pentane to give clusters of very fine colorless needles and thin plates: mp 113.5–115 °C; IR (CCl_4) 2960, 2940, 2870, 1715, 1410, and 1035 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.23 (6 H, d, J = 7 Hz), 1.30 (3 H, s), 1.4–3.2 (11 H, m), 3.29 (1 H, septet, J = 7 Hz), 3.69 (3 H, s), and 7.06 ppm (2 H, s); MS *m/e* (rel intensity) 287 (21), 286 (M^+, 100), 272 (19), 271 (96), 229 (47), and 55 (33).

Anal. Calcd for $C_{19}H_{26}O_2$: C, 79.67; H, 9.15. Found: C, 79.80; H, 9.20.

2β-Acetoxy-7-isopropyl-8-methoxy-4aβ-methyl-1,2,3,4,4a,-9,10,10aα-octahydrophenanthrene (19). To a solution of 47.62 g (0.182 mol) of lithium tri-*tert*-butoxyaluminum hydride (Alfa) in 500 mL of dry THF cooled to −15 to −20 °C (dry ice/CCl_4) under a nitrogen atmosphere was added via cannula a solution of 40.33 g (0.141 mol) of **18** in 250 mL of dry THF. After 20 min the cooling bath was removed, and stirring was continued at room temperature for 4 h. With ice-bath cooling 200 mL of 10% aqueous hydrochloric acid was added (with caution at first via syringe). The mixture was filtered, and the salts were washed with 100 mL of THF and with 400 mL of ethyl ether. The combined filtrate and washes were diluted with 250 mL of water and extracted with two 500-mL portions of ethyl ether. The ether solution was washed with two 500-mL portions of water and with saturated brine, dried (Na_2SO_4), and concentrated to give a viscous oil which was stirred with 500 mL of acetic anhydride and 30 mL of pyridine at room temperature overnight. The volatiles were removed under high vacuum to give a wet solid which was recrystallized from 200 mL of methanol to give from three crops 36.43 g (78%) of **19** as colorless needles, mp 90–95 °C. An analytically pure sample was prepared by two recrystallizations from methanol to give clusters of beautiful, colorless needles: mp 94.5–96 °C; IR (CCl_4) 2960, 2940, 2870, 1730, 1410, 1360, 1245, and 1035 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.12 (3 H, s), 1.23 (6 H, d, J = 7 Hz), 1.3–2.4 (9 H, m), 2.03 (3 H, s), 2.6–3.1 (2 H, m), 3.28 (1 H, septet, J = 7 Hz), 3.69 (3 H, s), 4.75 (1 H, br m), and 7.04 ppm (2 H, s); MS *m/e* (rel intensity) 331 (12), 330 (M^+, 48), 256 (21), 255 (100), and 43 (63).

Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.16; H, 9.20.

2β-Acetoxy-7-isopropyl-8-methoxy-4aβ-methyl-2,3,4,4a,10,-10aα-hexahydro-9(1*H*)-phenanthrenone (20). A solution of 13.00 g (130 mmol) of chromium trioxide in 100 mL of acetic acid/water (90:10) was added over a 20-min period to a water bath cooled solution of 21.52 g (65.2 mmol) of **19** in 80 mL of glacial acetic acid. After stirring for 2 h at room temperature an additional 13.00 g (130 mmol) of chromium trioxide in 100 mL of acetic acid/water (90:10) was added. After stirring for an additional 2 h at room temperature 9.80 g (98 mmol) of chromium trioxide in 65 mL of acetic acid/water (90:10) was added following by stirring for 2 h. The solution was then diluted with an equal volume of water and extracted with two 500-mL portions of chloroform. The chloroform solution was washed with two 500-mL portions of water, 250 mL of saturated sodium bicarbonate solution, 500 mL of water, and with two portions of saturated brine, dried ($MgSO_4$), and evaporated in vacuo to give a semisolid. Dry column chromatography of the crude product on alumina ($CHCl_3$, two 2-in. diameter × 30 in. length columns, R_f 0.4) afforded 16.05 g (42%) of **20** as a pale yellow solid, mp 142–147 °C. An analytically pure sample of **20** was obtained by two recrystallizations of chromatographed material from hexanes to give fine, colorless needles: mp 159.5–161.5 °C; IR (CCl_4) 2960, 2930, 2870, 1735, 1685, 1470, 1385, 1365, 1235, and 1030 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.18 (3 H, s), 1.22 (3 H, d, J = 7 Hz), 1.25 (3 H, d, J = 7 Hz), 1.4–2.8 (9 H, m), 2.06 (3 H, s), 3.41 (1 H, septet, J = 7 Hz), 3.79 (3 H, s), 4.73 (1 H, br m), 7.13 (1 H, d, J = 8 Hz), and 7.43 ppm (1 H, d, J = 8 Hz); MS *m/e* (rel intensity) 345 (9), 344 (M^+, 33), 330 (25), 329 (100), and 43 (49).

Anal. Calcd for $C_{21}H_{28}O_4$: C, 73.22; H, 8.19. Found: C, 73.14; H, 8.30.

7-Isopropyl-8-methoxy-4aβ-methyl-1,2,3,4,4a,9,10,10aα-octahydro-2β,9β-phenanthrenediol (21). A mixture of 5.16 g (15 mmol) of **20** in 150 mL of 95% ethanol was warmed until complete solution was obtained, cooled with an ice bath, and treated with 1.13 g (30 mmol) of solid sodium borohydride. The solution was stirred at room temperature for 47 h, cooled, and neutralized with 25% aqueous hydrochloric acid. The mixture was diluted with water and extracted with two portions (350 and 200 mL) of ethyl ether. The ether solution was washed with two 200-mL portions of water, one portion of saturated sodium bicarbonate solution, and with saturated brine, dried (Na_2SO_4), and evaporated in vacuo to give after high vacuum overnight 4.27 g (94%) of **21** as an almost colorless solid, mp 123–128 °C. Integration of a minor methoxy singlet at 3.86 ppm showed about 3% contamination by the α isomer. An analytical sample of **21** was prepared by two recrystallizations from hot ethyl ether with refrigerator cooling to give clusters of very fine, colorless needles: mp 135–136 °C; IR ($CHCl_3$) 3000, 2965, 2940, 2870, 1335, 1070, 1055, 1025, and 1005 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.20 (3 H, s), 1.21 (3 H, d, J = 7 Hz), 1.28 (3 H, d, J = 7 Hz), 1.3–2.3 (9 H, m), 1.80 (1 H, s, exchanges with D_2O), 3.29 (1 H, septet, J = 7 Hz), 3.66 (1 H, br m), 3.82 (3 H, s), 4.39 (1 H, s, exchanges with D_2O), 5.16 (1 H, br t, J = 8 Hz, half-band width 15 Hz), 7.07 (1 H, d, J = 8 Hz), and 7.18 ppm (1 H, d, J = 8 Hz); MS *m/e* (rel intensity) 306 (3), 305 (22), 304 (M^+, 100), 303 (24), 262 (27), 253 (65), 192 (78), 185 (20), and 177 (78).

Anal. Calcd for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 74.80; H, 9.24.

7-Isopropyl-4aβ-methyl-1,2,3,4,4a,9,10,10aα-octahydro-2β,8,-9β-phenanthrenetriol (22). In a 100-mL round-bottom flask under a nitrogen atmosphere 768 mg (16 mmol) of sodium hydride (50% oil dispersion) was washed with pentane. The pentane was removed via syringe, and 21 mL of dry DMF was added. To the ice-bath cooled mixture was slowly added dropwise via syringe 1.47 mL (16.2 mmol) of propanethiol. After completion of the addition the ice bath was removed, and a solution of 0.96 g (3.16 mmol) of **21** in 16 mL of dry DMF was added. The solution was stirred at 40 °C for 30 h under a nitrogen atmosphere. The cooled solution was then poured into 100 mL of cold 10% ammonium chloride solution and extracted with two 150-mL portions of ethyl ether. The ether solution was washed with water and with saturated brine, dried (Na_2SO_4), and evaporated in vacuo to give 0.99 g of **22** as a very pale yellow solid. Trituration of the crude product with benzene left 0.52 g (57%) of **22** as a white solid, mp 82–84 °C (to a wax which liquefied at 140 °C with decomposition). Evaporation of the benzene triturate gave 0.41 g (45%) of crude **22** (about 80% pure). An analytically pure sample was prepared by preparative layer chromatography on silica gel GF (Et_2O, R_f 0.5) to give a white solid which was recrystallized from benzene to give long, fine, colorless needles: mp 83–85 °C (to a waxy solid which liquefies up to 140 °C with decomposition): IR (KBr) 3320, 2950, 2930, 2860, 1450, 1420, 1380, 1335, 1275, 1250, 1105, 1030, 985, and 955 cm^{-1}; NMR (acetone-d_6, 90 MHz) δ 1.15 (3 H, s), 1.20 (3 H, d, J = 7 Hz), 1.22 (3 H, d, J = 7 Hz), 1.3–2.35 (9 H, m), 2.96 (1 H, br s, exchanges with D_2O), 3.31 (1 H, septet, J = 7 Hz), 3.45–3.8 (1 H, br m), 3.72 (1 H, br m, exchanges with D_2O), 5.07 (1 H, br t, half-band width 15 Hz), 5.35 (0.4 H, br m, exchanges with D_2O), 6.79 (1 H, d, J = 8 Hz), 7.06 (1 H, d, J = 8 Hz), and 10.07 ppm (0.6 H, br s, exchanges with D_2O); MS *m/e* (rel intensity) 186 (3), 110 (4), 78 (100), 77 (16), 52 (23), and 51 (21).

Anal. Calcd for $C_{18}H_{26}O_3$: C, 74.44; H, 9.03. Found: 74.34; H, 8.89.

8a,9-Epoxy-2β-hydroxy-7-isopropyl-4aβ-methyl-1,2,3,4,4a,-10aα-hexahydro-8(10*H*)-phenanthrenone (23). To a stirred solution of 146 mg (0.504 mmol) of **22** in 3 mL of methanol was added a solution of 120 mg (0.561 mmol) of sodium metaperiodate in 0.75 mL of water. A precipitate formed after 30 s. After being stirred for 5 h at room temperature, the mixture was filtered and partitioned between chloroform and water. The chloroform solution was washed with saturated brine, dried (Na_2SO_4), and evaporated in vacuo to give a yellow oil. Preparative layer chromatography on silica gel GF (Et_2O, two developments, R_f after second development ⅔) afforded 96.2 mg (66%) of **23** as a pale yellow solid: mp (sublimed 40°C) 45–48 °C; IR (CCl_4) 3600 (m), 3450 (br), 2960, 2930, 2870, 1660, 1635, and 1040 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.10 (6 H, d, J = 7 Hz), 1.21 (3 H, s), 1.2–2.1 (9 H, m), 1.87 (1 H, s, exchanges with D_2O), 2.92 (1 H, br septet, J = 7 Hz), 3.56 (1 H, br m), 3.96 (1 H, m), 6.33 (1 H, d, J = 7 Hz), and 6.97 ppm (1 H, br d, J = 7 Hz); MS *m/e* (rel intensity) 290 (3), 289 (13), 288 (M^+, 57), 274 (20), 273 (100), 239 (18), 213 (20), 161 (30), 128 (28), 115 (32), 91 (36), 77 (31), 65 (21), 57 (37), 55 (45), 53 (27), 51 (20), 44 (25), 43 (79), 41 (95), 39 (42); UV (95% EtOH) 347.5 nm (ε 5600).

High-resolution mass spectrum calcd for $C_{18}H_{24}O_3$: 288.17254. Found: 288.17467 (allowed tolerance: 0.00244).

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Registry No.—**1**, 38748-32-2; **5**, 1078-19-9; **6**, 16252-53-2; **7**, 62416-05-1; **8**, 62416-06-2; **9**, 62416-07-3; **10**, 62416-08-4; **11**, 62416-09-5; **12**, 62416-10-8; **13**, 62416-11-9; **14**, 62416-12-0; **15**, 62416-13-1; **16**, 62460-42-8; **17**, 62416-14-2; **18**, 62416-15-3; **19**, 62416-16-4; **20**, 62416-17-5; **21**, 62416-18-6; **22**, 62416-19-7; **23**, 62416-20-0; ethyl formate, 109-94-4; butanethiol, 109-79-5.

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Base-Catalyzed Reactions of 1,3-Disubstituted Uracils[1]

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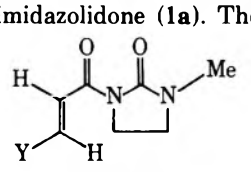
The first step in the base-catalyzed hydrolysis of 1,3-dialkyluracils (**2**) in both aqueous and Me_2SO solutions involves Michael addition to C-6 followed by ring opening between N-1 and C-6 to an enolate (**5**). From aqueous solution, with 1,3-dimethyluracil (**2a**) as substrate, formylacetic acid (**4'**) and *N,N'*-dimethylurea (**3a**) were isolated, but **5** was not observed. On the other hand, in Me_2SO evidence for the very rapid formation of the intermediate enolate was obtained. This enolate, however, was not the stable end product. In the reaction mixture it underwent a complex series of transformations leading finally to the formation of three products. Using **2a** as the disubstituted uracil, these were *N,N'*-dimethylurea (**3a**) and two *pyridine* derivatives: 1-methyl-5-(methylcarbamyl)-2-pyridone (**12a**) and 1-methyl-3-(methylaminomethylene)-2,6-pyridinedione (**13a**). 1-Ethyl-3-methyluracil (**2b**), 3-ethyl-1-methyluracil (**2c**), and 1,3-diethyluracil (**2d**) also yielded analogous, stable end products under the same conditions. A scheme is proposed to rationalize the conversion of **2** to **3**, **12**, and **13** by means of tetramethylammonium hydroxide in Me_2SO solution. The elaboration of this scheme was based on a body of data which included the isolation and characterization of an intermediate, 1,3-dimethyl-5-(methylaminomethylene)-6-(methylcarbamylmethyl)-5,6-dihydrouracil (**10a**), from the reaction of **2a** with TMAH in Me_2SO. It was found that the ethylmethyluracils, **2b** and **2c**, underwent an isomerization reaction in basic Me_2SO in which the positions of the alkyl groups were interchanged. This reaction, as well as the conversion of **2d** to **2a** by means of *N,N'*-dimethylurea in the same medium, provides additional evidence for the reversibility of the transformation of uracil, **2**, to enolate, **5**. The results obtained in this investigation provide alternative mechanisms for H-5 exchange in uracil derivatives and for a number of enzymatic C-methylation reactions. They also suggest a pathway for the biosynthesis of nudiflorine, a naturally occurring 2-pyridone, other than that previously reported.

Although the fact that 1,3-disubstituted uracils are unstable in alkaline solution has been known for more than two decades,[2] it is only recently that an aldehyde has been postulated as an intermediate in the degradation of such compounds.[3] An analogous aldehyde has been postulated as an intermediate in reactions of various substituted 6-hydroxy-5,6-dihydrouracils.[4]

During the course of a study of the reactions of 3-(β-methanesulfonyloxyethyl)-1-methyluracil with bases,[5] an aldehyde was obtained and was identified as N^1-(formylacetyl)-N^3-methylimidazolidone (**1a**). The UV absorption



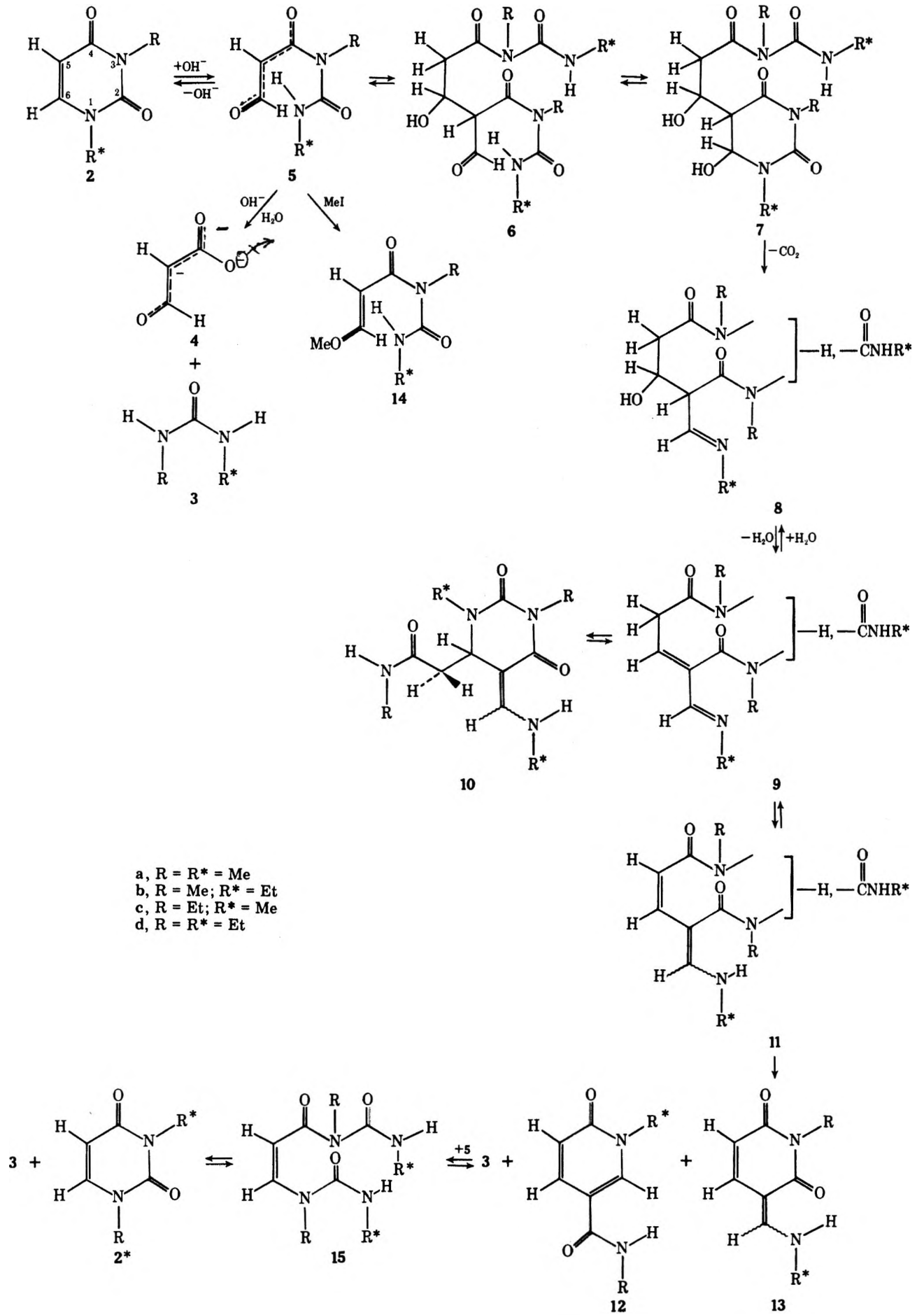
1a, Y = OH
b, Y = Me_2CHNH

characteristics of Shugar's intermediate[4b] were the same as those of **1a**. Our present experiments elucidate, in detail, the base-catalyzed reactions of 1,3-dialkyluracils in both water and dimethyl sulfoxide (Me_2SO).

The reaction of 1,3-dimethyluracil (**2a**) with sodium hydroxide or tetramethylammonium hydroxide pentahydrate (TMAH) in aqueous solution was followed by means of both UV and ^1H NMR spectroscopy. The spectroscopic changes which were observed corresponded to the formation of 1,3-dimethylurea (**3a**) and the enolate of formyl acetate (**4**) (Scheme I). Unreacted **2a**, **3a**, and anion **4**, as its parent acid (**4'**),[6] were recovered from a reaction mixture by ion exchange chromatography. No intermediates were observed in this degradation even when the reaction conditions were modified. The spectroscopic properties of **4** support the structure assigned to it. The identity of **4'** was confirmed by conversion to its oxime.[7]

The behavior of **2a** in Me_2SO solution containing TMAH was much more complex than in aqueous solution. Scheme I is a representation that is in good agreement with our experimental observations. Compound **2a** was dissolved in Me_2SO containing TMAH. The changes which took place were followed by spectrophotometric observation of the reaction mixture. With a solution 0.1 M in both reactants, it was found that **2a** disappeared and a single new chromophore with λ_{max} 296 nm (**5a**) was produced. The rapidity with which this

Scheme I[a]



[a] In general, no attempt has been made to represent the actual charged species taking part in the various reactions.

Table I. Reactions of 1,3-Dialkyluracils with TMAH in Me_2SO

1,3-Dialkyluracil		Products[a]		
Substrate[b]	% recovered	3, %	12, %	13, %
2a	5	58	27	39
2a (excess base)	0		0	25
2b	9	45	13	25
2c	12	44	6	3
2d	19	40	2	1

[a] These yields are based on the conversion of 2 mol of 2 to 1 mol of 3 and 1 mol of 12 or 13. [b] The reaction mixtures were ca. 0.06 M in 2 and 0.07 M in TMAH, except in the second reaction with 2a. In this case, 2a was ca. 0.03 M and the base 0.10 M.

chromophore reached its maximum absorbance (less than 3–4 min) was striking. As the reaction proceeded, λ_{max} 296 nm was replaced by a transitory peak at λ_{max} 320 nm (e.g., **10a**). Finally, after about 6–7 days, two stable chromophores appeared which had absorption maxima at ca. 260 (**12a**) and 365 nm (**13a**). It is to be emphasized that the precise spectrophotometric changes which are observed, and the products which are isolated from a reaction mixture, are very dependent on reaction conditions.[8] For example, if reactions are run at ten times the usual dilution, the absorption at λ_{max} 296 nm slowly disappears and there occurs a net loss of UV-absorbing compounds.

Four compounds were isolated from a 0.1 M reaction mixture in Me_2SO after it reached the stage where it was not undergoing further change. These were **2a**, **3a**, and two compounds which proved to be *pyridine* derivatives. One of these was shown to be 1-methyl-5-(methylcarbamyl)-2-pyridone (**12a**). This assignment of structure is based on a comparison of its properties with those of nudiflorine, 5-cyano-*N*-methyl-2-pyridone, and the corresponding carboxylic acid and methyl ester.[9] The other pyridine derivative was shown to be 1-methyl-3-(methylaminomethylene)-2,6-pyridinedione (**13a**) on the basis of its molecular formula, a comparison of its UV spectrum with that of **1b**,[10] and its other spectroscopic properties.

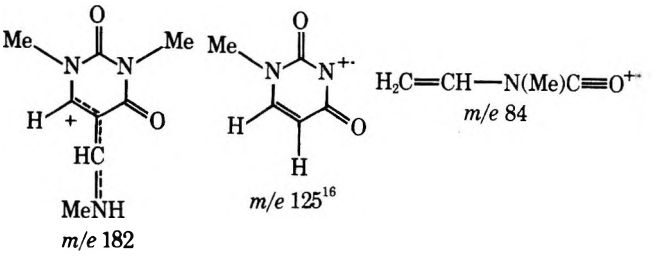
Additional significant information concerning the final reaction products was obtained in an experiment in which 1-ethyl-3-methyluracil (**2b**) was treated with TMAH in Me_2SO solution. The products were unequivocally shown to be *N*-ethyl-*N'*-methylurea (**3b**), **12b** in which the ethyl group is on the ring nitrogen, and **13b** in which the ethyl group is on the enamine nitrogen. These facts require an enamine structure to be formed prior to a ring closure step leading to **12b**.

When the reaction was run with 3-ethyl-1-methyluracil (**2c**) and 1,3-diethyluracil (**2d**), it was found by means of UV spectrophotometry that **5** was formed readily from these two compounds also. Since the stable end products, **12** and **13**, were obtained in poor yields (Table I), it is obvious that subsequent reactions of **5c** and **5d**, other than those indicated in Scheme I, predominated.

Having firmly established the end products of the reactions of **2a** and **2b** in Me_2SO containing TMAH, further evidence was sought for the nature of the intermediates. A crystalline precipitate was deposited within a few minutes after the reaction mixture containing **2a** and TMAH in Me_2SO was prepared. When attempts were made to purify the solid, the first intermediate observed, it underwent rapid chemical change. It appears to be the tetramethylammonium salt of the enolate, **5a**. Although it was not possible to purify **5a** owing to its instability, chemical and physical evidence support the assignment of structure. For example, dilution of a Me_2SO solution of **5a** with 0.1 N HCl or NaOH brings about ring closure to **2a**.[4b] With the 0.1 N NaOH, however, partial hydrolysis of **5a** to **4** also takes place. This conversion is supported by the fact that a hypsochromic shift is observed upon hydrolysis of the acyl ureido group of **5a** to a carboxyl group.[11]

Finally, **5a** was trapped as its enol ether, [(*E*)-3-methoxypropenoyl)]-*N,N'*-dimethylurea (**14a**), by addition of methyl iodide to a reaction mixture containing only **5a** (UV). The yield was 2%. In addition, 49% of **2a** and 22% of 1,3-dimethylthymine were isolated from the reaction mixture. The **2a** which was isolated after the methylation reaction was formed by ring closure.[4b] The 1,3-dimethylthymine apparently arises from methylation of **5a**[12] at C-5,[13] again followed by re-formation of the pyrimidine[4b] ring. This pathway for the formation of 1,3-dimethylthymine is reasonable. When base is added to a mixture of **2a** plus methyl iodide, the base is consumed by reaction with the latter but no 1,3-dimethylthymine is formed. Furthermore, anion formation at C-6, not C-5, of the pyrimidine ring[14] occurs under the conditions used in this experiment.

A second intermediate, which was isolated as a pure, crystalline compound, is 1,3-dimethyl-5-(methylaminomethylene)-6-(methylcarbamylmethyl)-5,6-dihydrouracil (**10a**, Scheme I). This assignment of structure is in agreement with its molecular formula and its spectroscopic[15] and chemical properties. Although the parent ion peak in the mass spectrum (*m/e* 254) is small, peaks are present which correspond to the structures



When **10a** was dissolved in a solution of TMAH in Me_2SO, 67% of **12a** and 12% of **13a** were formed after 18 h at room temperature. This ratio of **12a** to **13a** is quite different from the 2:3 ratio observed (Table I) when **12a** and **13a** are formed directly from **2a**, and may indicate that **10a** is not the compound with λ_{max} (Me_2SO) 320 nm observed spectrophotometrically in the reaction mixture, but rather an artifact of the workup. Pathways for product formation which are dependent on the position of the carbamyl group in a species such as **8** could give rise to different ratios of **12** to **13**.

The transformation of **2** to **5** in Me_2SO solution is analogous to reactions which have been described previously.[5] The first step is a Michael addition of hydroxide ion to C-6 of **2** followed by ring opening in the resulting adduct by cleavage of the N^1–C^6 bond to give **5**. The reaction of **2** with aqueous hydroxide apparently proceeds by the same pathway to give **4**, but **5** is not observed. Instead, it appears that the hydrolysis of **5** is more rapid than its formation.

The various other transformations in Scheme I involve well-known reactions, with the exception of the conversion of **7** to **8**. This mechanism, similar to that first described by Thurber and Townsend,[17] involves attack of hydroxide ion on C-2 of a dihydropyrimidine nucleus and ring opening, followed by elimination of CO_2 from the resulting carbamyl moiety. This sequence results in enamine formation at C-6 of the dihydropyrimidine ring. The conversion of **5** to **6** is an aldol condensation. The interconversion of **8** and **9** is a Michael addition and its reversal. Other transformations in this scheme involve transfer of an *N*-alkylcarbamyl group from one amido nitrogen atom to another in **8**, **9**, and **11**. The final

products are obtained by elimination of a molecule of urea only.

Further experiments with **2b** and **2c** yielded additional information of interest. When **2c** was subjected to the action of TMAH in Me_2SO solution, the 1,3-dialkyluracil which was recovered was found to be a mixture of 34% **2b** and 66% **2c**. If, instead, the experiment was carried out using **2b**, the 1,3-dialkyluracil recovered was 77% **2b** and 23% **2c**. A study of the rate of isomerization demonstrated that the reaction was slow initially and reached a plateau in approximately 24 h. Since the rate of exchange is fast by comparison[14c] with the rate of isomerization, the two reactions cannot have a common intermediate, e.g., the symmetrical species proposed by Wechter for the base-catalyzed deuterium exchange at C-6 of pyrimidines.[14b]

One explanation for the isomerization reaction is that an aldehyde intermediate, **5**, reacts with a free molecule of urea produced during the course of the final series of reactions (**11** → **3**) to give **15** (Scheme I). This compound could now undergo ring closure to an isomer of **2** (**2***). The conversion of **15** to **2*** resembles the formation of **12** and **13** from **11**. Evidence in agreement with this pathway was obtained by subjecting **2d** to the action of TMAH in Me_2SO solution in the presence of **3a**. Using approximately equimolar amounts of **2d** and **3a**, a 47% yield of **2** was recovered after a reaction time of 1 h. Its composition was 60% **2a** and 40% **2d**. The yields were independent of whether the urea was present from the beginning or whether it was added after the formation of the compound with λ_{max} 296 nm (**5d**). The result of this experiment also can be explained, however, by assuming nucleophilic attack of a molecule of urea directly on **2** either at C-4 or C-6. The synthetic applicability of this type of reaction remains to be investigated.

The results obtained in this study suggest several interesting possibilities. The fact that there can be a rapid interconversion of a cyclic pyrimidine structure, **2**, and an acyclic enolate, **5**, affords another mechanistic pathway for C-5 exchange in pyrimidines.[14] Furthermore, this rapid interconversion, and the fact that 1,3-dimethylthymine was obtained as one of the products in the experiment described above on the methylation of **5**, suggest an alternative mechanism for biological C-alkylations, e.g., those catalyzed by enzymes such as thymidylate synthetase[14a,18] and deoxycytidine 5′-phosphate and deoxyuridine 5′-phosphate hydroxymethylases.[19] It is interesting to speculate also on the possibility that the biosynthesis of nudiflorine[9] may proceed by a pathway analogous to that followed in the conversion of **2** to **12**.

Experimental Section

^1H NMR spectra were obtained on a Varian A-60A spectrometer at room temperature using tetramethylsilane or sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) as internal standards. A Cary 14 and a Perkin-Elmer 457 grating infrared spectrophotometer were used to obtain UV and IR spectra, respectively. UV spectra were measured in cells (Precision Cells, Inc., Hicksville, N.Y.) of 0.1 mm, 1 mm, and 1 cm path lengths. Mass spectra were obtained on a Varian M-66 mass spectrometer at an ionizing potential of 70 eV, an ionizing current of 30 μA, a resolution of ca. 2200, and with perfluorokerosene as a standard.

Thin layer chromatography was performed on Analtech silica gel G thin layer plates containing fluorescent indicator (Analtech, Inc., Newark, Del.). In all reactions involving solutions of TMAH in Me_2SO, a preliminary separation of salts from Me_2SO and organic products was achieved by pouring the reaction mixture on to silica gel Woelm (ICN, Cleveland, Ohio), 1 g for each mL, and allowing the Me_2SO to filter through the column. This was followed with a wash of approximately twice the volume of AcOEt. Evaporation gave a salt-free mixture suitable for further chromatography. Preparative chromatography (dry column) was performed on the silica gel as obtained or after activation at 100 °C for 15 h. The progress of such chromatography was monitored by TLC. When more than one eluting solvent is indicated, solvent polarity was increased by the use of a gradient after each component or group of components was eluted from the column. High-pressure liquid chromatography (HPLC) was performed using Waters ALC 202 and ALC 100 liquid chromatographs. Analytical work was done on Corasil I (4 ft × 0.125 in.) and preparative separations on Porasil A (8 ft × 0.375 in.) (Waters Associates, Inc., Framingham, Mass.).

Analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Melting points are uncorrected.

1,3-Dimethyluracil (2a) and 1,3-Diethyluracil (2d). Compound **2a** was synthesized by the method of Davidson and Baudisch.[20] Compound **2d** was synthesized from either uracil[20] or 2,4-diethoxypyrimidine.[21]

3-Ethyl-1-methyluracil (2c). This was synthesized by the method of Hilbert and Johnson,[21b] mp 56–58.5 °C (lit.[21b] mp 60–61 °C).

1-Ethyl-3-methyluracil (2b). This compound was prepared from 1-ethyluracil[22] by methylation with $(CH_3)_2SO_4$.[20] An analytical sample was obtained from AcOEt/petroleum ether: mp 73.5–75.5 °C; UV (95% EtOH) λ_{max} 266 nm (ε 8800) and 207 (8050); UV (0.1 N HCl) λ_{max} 266 nm (ε 8850); UV (0.1 N NaOH) λ_{max} 266 nm (ε 9000); ^1H NMR ($CDCl_3$) δ 1.32 (t, 3, J_{Et} = 7 Hz, CH_3CH_2), 3.33 (s, 3, CH_3N), 3.81 (q, 2, J_{Et} = 7 Hz, CH_3CH_2), 5.72 (d, 1, $J_{5,6}$ = 8 Hz, H-5), and 7.11 ppm (d, 1, $J_{5,6}$ = 8 Hz, H-6); $M^+ \cdot$ *m/e* 154 (100).

Anal. Calcd for $C_7H_{10}N_2O_2$: C, 54.54; H, 6.54; N, 18.17. Found: C, 54.44; H, 6.49; N, 18.03.

Isolation of Formylacetic Acid (4′). Two hundred milligrams (1.43 mmol) of **2a** was dissolved in 3 mL (3.33 mmol) of 1.1 N aqueous TMAH solution. Samples were removed for ^1H NMR and UV spectra. The resonances for **2a** slowly decreased and a singlet at 2.59 ppm due to **3a** and a doublet at 8.09 ppm (J = 11 Hz) due to **4** appeared. After 22 h, the ^1H NMR spectrum showed 22% **2a**, 78% **3a**, 54% of formylacetate (**4**), and 7% of an unidentified component with a resonance at 8.30 ppm. The reaction mixture was diluted to 10 mL with water. Aliquots in 0.1 N NaOH and 0.1 N HCl showed ca. 20% unreacted **2a** and two pH-dependent λ_{max} at 260 and at 325 nm. An estimate of ε for **4**, derived from combined UV and ^1H NMR data, is 18 000. Ion exchange chromatography [Rexyn RG 50 (H^+), Fischer Scientific Co.], using H_2O as eluent, afforded 50 mg of a yellow oil, **4′** [λ_{max} (0.1 N NaOH) 259 nm; ^1H NMR (CD_3CN) δ 3.40 (d, 2, J = 2.5 Hz, CH_2), 7.55 (broad, carboxyl proton[23]), and 9.67 ppm (t, 1, J = 2.5 Hz, CH=O), plus resonances due to some **2a**]; 16 mg of pure **2a** (8%); and 79 mg of **3a** (63%).

Repetition of the reaction with NaOH gave similar results.

Preparation of the Oxime of Formylacetic Acid. One gram (7.15 mmol) of **2a** was dissolved in 16 mL (17.6 mmol) of 1.1 N aqueous TMAH solution. After 13 h at room temperature, a sample was removed for ^1H NMR. The reaction mixture contained 27% **2a**, 73% **3a**, and 55% of formylacetate, **4**. The reaction mixture was cooled in ice and 940 mg (13.5 mmol) of hydroxylamine hydrochloride was added. After 90 min the reaction mixture was extracted with $CHCl_3$. The aqueous layer was acidified to pH 3 with 3 N H_2SO_4 (4.4 mL) and extracted with Et_2O. The Et_2O extracts were dried ($CaCl_2$) and evaporated in vacuo. The crude weight of oxime was 255 mg (63%). A small portion of Et_2O was added to the crude material and 120 mg of crystalline material was collected: mp 111–112 °C;[7] ^1H NMR (Me_2SO-d_6)[24] δ 3.15 (25%) and 3.27 (75%) (d, 2, J = 6.5 and 5.0 Hz, CH_2), 6.87 (75%) and 7.37 (25%) (t, 1, J = 6.5 and 5.0 Hz, CHNOH), and 10.37 ppm (broad, 2, NOH and COOH). All protons exchange in D_2O.

Anal. Calcd for $C_3H_5NO_3$: C, 34.96; H, 4.89; N, 13.59. Found: C, 35.10; H, 4.92; N, 13.53.

UV Spectral Studies of Reaction of 2a with TMAH in Me_2SO. Standard Reaction Conditions. Compound **2a** (116.6 mg, 0.833 mmol) was placed in a 10-mL volumetric flask and diluted to the mark with a 0.1 N solution of TMAH in Me_2SO.[25] The solid dissolved within 3 min and the solution was transferred to a 0.1-mm cell. A crystalline precipitate separated after ca. 5 min. The UV spectrum was obtained using calibrated screens in the reference path to compensate for the high concentration. The initial spectrum had a sharp λ_{max} at 296 nm. This λ_{max} disappeared and was replaced (1 h) by two maxima at 320 and 276 nm. These maxima did not persist. During the course of the next 18 h, other transient maxima were observed, but by 68 h three maxima were present at 265, 315, and 365 nm. These were still present after 7 days. An estimate of the extinction coefficient for **5a** from this experiment gives 6300.[26]

UV Spectral Studies of Reaction of 2a with TMAH in Me_2SO. Dilute Solutions. Compound **2a** (9.90 mg, 7.07×10^{-2} mmol) was dissolved in 2 mL of Me_2SO and 9 mL of a 9.05×10^{-2} N solution of TMAH (0.815 mmol) in Me_2SO was added. The UV spectrum was obtained within 4 min of mixing. A sharp maximum was observed at

296 nm (A = 1.47, corresponding to ϵ 23 000).[26] The absorbance slowly decreased, with ~50% loss in 3 h. After 6 h, a new maximum was evident at 266 nm whose absorbance increased slightly after another day and then remained constant for 7 days at an absorbance of 0.31. It is presumed to be due to 42% of **2a** which was regenerated by ring closure of **5a** as the concentration of base decreased.[4b]

The value of ϵ 23 000 for **5a**, compared to that of 6300 found in the previous experiment, suggests that the crystalline precipitate noted in that experiment possesses the chromophore corresponding to λ_{max} 296 nm, i.e., the precipitate is the tetramethylammonium salt of **5a**. To obtain confirmatory evidence for this explanation, **2a** (22.25 mg, 0.159 mmol) was treated with 10 mL of 0.1 N TMAH in Me_2SO in a centrifuge tube. After the initial solid dissolved, a new solid separated (5 min). The reaction mixture was centrifuged and the resulting precipitate was dissolved in absolute ethanol. The UV spectrum of this solution had maxima at 296 and 270 nm. Within 8 min, the λ_{max} at 296 nm decreased by 30%.

UV Spectral Studies of Reaction of 2a with TMAH in Me_2SO. Dilution of Aliquots with Aqueous Acid and Base. One hundred milligrams (0.715 mmol) of **2a** was placed in a 10-mL volumetric flask and diluted to the mark with a solution of 0.1 N TMAH in Me_2SO. Aliquots of 20 μL were removed periodically and diluted with 0.1 N NaOH and 0.1 N HCl for the measurement of UV spectra. The spectrum in NaOH solution of an aliquot taken after 5 min had λ_{max} 267 nm and a shoulder at 295 nm which rapidly decreased as the former increased. The initial spectrum in acid of an aliquot taken at the same time had λ_{max} 267 nm and an absorbance that was half that in base. Within 1 h the spectrum of an aliquot in basic solution had a maximum at 310 nm, in addition to that at 267 nm. The 310-nm absorption was not present in the corresponding aliquot diluted with acid. After 7 days the spectrum of an aliquot in base had maxima at 265 and 345 nm, while the spectrum in acid had maxima at 260 and 348 nm.

Reaction of 2a with TMAH in Me_2SO. Preparation of 1-Methyl-5-(methylcarbamyl)-2-pyridone (12a) and 1-Methyl-3-(methylaminomethylene)-2,6-pyridinedione (13a). TMAH (3.6 g, 20 mmol) was dissolved in 225 mL of Me_2SO in an atmosphere of dry, oxygen-free nitrogen by warming to 60–70 °C. The solution was then cooled to room temperature. Compound **2a** (2.3 g, 16 mmol) in 50 mL of Me_2SO was added. Aliquots were removed periodically and diluted with 0.1 N NaOH and 0.1 N HCl for measurement of UV spectra. The reaction mixture turned yellow immediately and a crystalline precipitate appeared. These crystals redissolved and within several hours fine white needles separated. This latter precipitate may be tetramethylammonium carbonate, since gas evolution takes place immediately upon dissolving it in dilute acid. In 24 h, the reaction mixture had turned bright red. After 7 days no further change in the UV spectrum was taking place. The reaction mixture was desalted and chromatographed on silica using $CHCl_3$, $CHCl_3$/AcOEt, AcOEt, and AcOEt/EtOH as the developing solvents. Mixtures of **2a**, Me_2SO_2,[27] and **13a** (658 mg), and **3a** and **12a** (940 mg), were obtained. The latter mixture afforded **12a** on crystallization from MeCN: mp 186.5–188 °C; IR (KBr) 3370 and 3320 (NH), 1665 (NC=O), and 1620 cm^{-1} (C=C); UV (95% EtOH) λ_{max} 304 nm (ϵ 4100) and 257 (14 700); UV (0.1 N HCl) λ_{max} 298 nm (ϵ 4800) and 257 (14 400); UV (0.1 N NaOH) λ_{max} 298 nm (ϵ 4800) and 257 (14 700); ^1H NMR (Me_2SO-d_6) δ 2.77 (d, 3, $J_{Me,NH}$ = 4.5 Hz, CH_3NH), 3.51 (s, 3, CH_3N), 6.41 (d, 1, $J_{3,4}$ = 9.5 Hz, H-3), 7.87 (d of d, 1, $J_{3,4}$ = 9.5, $J_{4,6}$ = 3 Hz, H-4), 8.16 (broad, 1, NH), and 8.32 ppm (d, 1, $J_{4,6}$ = 3 Hz, H-6); M^+· m/e 166 (100).

Anal. Calcd for $C_8H_{10}N_2O_2$: C, 57.82; H, 6.07; N, 16.86. Found: C, 58.16; H, 6.18; N, 17.05.

The residue from the above crystallization was sublimed in vacuo at 72 °C (bath temperature) and 1 × 10^{-4} mm to give 315 mg of **3a**: mp 102.5–105.5 °C (lit.[28] mp 105 °C); ^1H NMR ($CDCl_3$) δ 2.75 (d, 3, $J_{Me,NH}$ = 4.5 Hz, CH_3N) and 5.22 ppm (broad, 1, NH); M^+· m/e 88 (100).

The first mixture was rechromatographed on silica gel ($CHCl_3$) to give 35 mg of **2a**; 219 mg of a mixture of **2a**, Me_2SO_2,[27] and **13a** (141 mg by UV); and **13a** (370 mg). The latter was recrystallized twice from n-hexane–$CHCl_3$ to give **13a**, which was pale yellow in color: mp 124.5–126 °C; IR (KBr) 3450 (NH), 1680 (NC=O) and 1600 cm^{-1} (C=C); UV (95% EtOH) λ_{max} 345 nm (ϵ 30 500), 280 (1850), and 240 (8400); UV (0.1 N HCl) λ_{max} 348 nm (ϵ 30 800), 280 (2200), and 237 (9100); UV (0.1 N NaOH) λ_{max} 345 nm (ϵ 20 300) and 275 (6500); ^1H NMR ($CDCl_3$) δ 3.19 (d, 3, $J_{Me,NH}$ = 5 Hz, CH_3NH), 3.30 (s, 3, CH_3N), 5.75 (d, 1, $J_{4,5}$ = 9.5 Hz, H-5), 6.92 (d, 1, $J_{4,5}$ = 9.5 Hz, H-4), 7.25 (d, 1, $J_{CH,NH}$ = 13.5 Hz, NHC**H**=), and 10.30 ppm (broad, 1, NH); M^+· m/e 166 (100).

Anal. Calcd for $C_8H_{10}N_2O_2$: C, 57.82; H, 6.07; H, 16.86. Found: C, 58.04; H, 6.18; N, 16.95.

The overall yields of products follow: **2a**, 5%; **3a**, 58%; **12a**, 27%; and **13a**, 39%.

Repetition of the previous experiment with 26.7 mg (0.176 mmol) of **2a** in 5 mL of 0.1 N TMAH (0.5 mmol) in Me_2SO afforded no **12a**, a 25% yield of **13a**, and another compound with an absorption at λ_{max} 290 nm (pH dependent).

Reaction of 1,3-Diethyluracil (2d) with TMAH in Me_2SO. A solution of 3.05 g of TMAH (16.7 mmol) in 167 mL of Me_2SO was prepared as described above. To this was added 2.3 g (13.7 mmol) of **2d** in 25 mL of Me_2SO plus another 17 mL of Me_2SO. The reaction was followed by UV. After 7 days, the reaction mixture was desalted. Chromatography on silica gel (CH_2Cl_2) afforded a mixture of **2d** and Me_2SO_2[27] (450 mg); several minor components; **3d** (290 mg) [^1H NMR ($CDCl_3$) δ 1.12 (t, 3, J_{Et} = 7.5 Hz, CH_3CH_2), 3.22 (d of q, 2, J_{Et} = 7.5 and $J_{CH_2,NH}$ = 5.5 Hz, CH_3CH_2NH), and 5.75 ppm (broad, 1, NH)]; and a mixture containing mostly **12d** [UV (0.1 N NaOH) λ 290 nm (shoulder) and λ_{max} 257 nm; ^1H NMR ($CDCl_3$) δ 1.22 (t, 3, J_{Et} = 7 Hz, CH_3CH_2NH), 1.36 (t, 3, J_{Et} = 7 Hz, CH_3CH_2N), 3.40 (m, 2, J_{Et} = 7 Hz, CH_3CH_2NH), 4.09 (q, 2, J_{Et} = 7 Hz, CH_3CH_2N), 6.59 (d, 1, $J_{3,4}$ = 9.5 Hz, H-3), 7.67 (broad, 1, NH), 7.97 (d of d, 1, $J_{3,4}$ = 9.5, $J_{4,6}$ = 3 Hz, H-4), and 8.38 ppm (d, 1, $J_{4,6}$ = 3 Hz, H-6); M^+· m/e 194 (100)]. The latter mixture contained 0.256 mmol (2%) of **12d** (UV), assuming ϵ to be the same as for **12a**. The UV assay of the total reaction mixture indicated that 0.8% of 1-ethyl-3-(ethylaminomethylene)-2,6-pyridinedione (**13d**) was present. The yield of **3d** was 40% and 19% of **2d** was recovered.

Reaction of 1-Ethyl-3-methyluracil (2b) with TMAH in Me_2SO. Compound **2b** (2.11 g, 13.5 mmol) in 25 mL of Me_2SO was added to a solution, prepared as described previously, of TMAH (3.05 g, 16.8 mmol) in 184 mL of Me_2SO. The reaction was followed by UV. After 7 days, the reaction mixture was desalted. Chromatography on silica gel (CH_2Cl_2) afforded the following fractions: a mixture (275 mg) of Me_2SO_2,[27] **2b** and **2c** (HPLC, see below), and **13b**; **13b** and an unidentified component (350 mg); and a mixture of **3b** and **12b**. Rechromatography ($CHCl_3$) of the second mixture gave 70 mg of the dialkyluracils, **2b** and **2c** (HPLC), and pure **13b** (166 mg). The latter was sublimed in vacuo at ~100 °C (bath temperature) and 1 × 10^{-4} mm to give 100 mg of pale yellow 1-methyl-3-(ethylaminomethylene)-2,6-pyridinedione (**13b**), which turned pink after standing for several days at room temperature: mp 50.5–55.5 °C; IR (KBr) 3450 (NH), 1675 (NC=O), and 1600 cm^{-1} (C=C); UV (95% EtOH) λ_{max} 347 nm (ϵ 30 800), λ_{sh} 280 nm (ϵ 2250), and λ_{max} 241 nm (ϵ 9000); UV (0.1 N HCl) λ_{max} 349 nm (ϵ 32 000), 280 (2350), and 237 (9500); UV (0.1 N NaOH) λ_{max} 345 nm (ϵ 21 200) and 272 (7300); ^1H NMR ($CDCl_3$) δ 1.34 (t, 3, J_{Et} = 7.5 Hz, CH_3CH_2), 3.32 (s, 3, CH_3N), 3.54 (d of q, 2, J_{Et} = 7.5 Hz, $J_{CH_2,NH}$ = 13.5 Hz, CH_2NH), 5.77 (d, 1, $J_{4,5}$ = 9.5 Hz, H-5), 6.99 (d, 1, $J_{4,5}$ = 9.5 Hz, H-4), 7.35 (d, 1, $J_{CH,NH}$ = 13.5 Hz, NHC**H**=), and 10.21 ppm (broad, 1, NH); M^+· m/e 180 (100).

Anal. Calcd for $C_9H_{12}N_2O_2$: C, 59.99; H, 6.71; N, 15.54. Found: C, 59.79; H, 6.59; N, 15.43.

The mixture of **3b** and 12b was sublimed below 100 °C (bath temperature) at 1 × 10^{-4} nm to give 110 mg of **3b**: ^1H NMR ($CDCl_3$) δ 1.10 (t, 3, J_{Et} = 7 Hz, CH_3CH_2), 2.72 (s, 3, CH_3), 3.16 (q, 2, J_{Et} = 7 Hz, CH_3CH_2), and 5.22 (broad, 2, NH). Sublimation at a temperature above 100 °C at 1 × 10^{-4} mm gave 1-ethyl-5-(methylcarbamyl)-2-pyridone (**12b**). A sample for analysis was recrystallized from n-hexane–$CHCl_3$: mp 157.5–158.5 °C; IR (KBr) 3320 (NH), 1680 (NC=O), and 1635 cm^{-1} (C=C); UV (95% EtOH) λ_{max} 305 nm (ϵ 4500) and 259 (15 700); UV (0.1 N HCl) λ_{max} 300 (ϵ 4800) and 257 (14 900); UV (0.1 N NaOH) λ_{max} 299 nm (ϵ 5080) and 257 (15 600); ^1H NMR ($CDCl_3$) δ 1.35 (t, 3, J_{Et} = 7 Hz, CH_3CH_2), 2.91 (d, 3, $J_{Me,NH}$ = 4.5 Hz, CH_3NH), 3.99 (q, 2, J_{Et} = 7 Hz, CH_3CH_2), 6.42 (d, 1, $J_{3,4}$ = 9.5 Hz, H-3), 7.30 (broad, 1, NH), 7.78 (d of d, 1, $J_{3,4}$ = 9.5, $J_{4,6}$ = 3 Hz, H-4), and 8.13 ppm (d, 1, $J_{4,6}$ = 3 Hz, H-6); M^+· m/e 180 (100).

Anal. Calcd for $C_9H_{12}N_2O_2$: C, 59.99; H, 6.71; N, 15.54. Found: C, 60.17; H, 6.75; N, 15.71.

The overall yield of products was 45% of **3b**, 13% of **12b**, and 25% of **13b**. Nine percent of **2** was recovered.

The mixture of **2b** and **2c** was separated by preparative HPLC using 7.5% EtOH in n-hexane as solvent. Compound **2b** had κ' = 4.06 and **2c** had κ' = 6.25. The two compounds, 77 and 23%, respectively, were identified by comparison of ^1H NMR spectra with those of authentic samples.

Reaction of 3-Ethyl-1-methyluracil (2c) with TMAH in Me_2SO. Compound **2c** (2.11 g, 13.7 mmol) in 25 mL of Me_2SO was added to a solution, prepared as described above, of TMAH (3.05 g, 16.8 mmol) in 184 mL of Me_2SO. The progress of the reaction was followed as usual. After 7 days the reaction mixture was desalted. Chromatography on silica gel (CH_2Cl_2) yielded several fractions. These were a mixture (265 mg) of Me_2SO_2,[27] **2b** and **2c** (HPLC; see

below); an unidentified component and 1-ethyl-3-(methylaminomethylene)-2,6-pyridinedione (**13c**) (2.7% by UV) [^{1}H NMR ($CDCl_3$) δ 1.28 (t, 3, J_{Et} = 7 Hz, CH_3CH_2), 3.26 (d, 3, $J_{Me,NH}$ = 5 Hz, CH_3NH), 4.07 (q, 2, J_{Et} = 7 Hz, CH_3CH_2N), 5.82 (d, 1, $J_{4,5}$ = 9.5 Hz, H-5), 7.11 (d, 1, $J_{4,5}$ = 9.5 Hz, H-4), 7.52 (d, 1, $J_{CH,NH}$ = 13.5 Hz, NHC**H**=), and 10.50 ppm (broad, 1, NH)]; a 50:50 mixture (85 mg) of **13c** and **3b**; and **3b** plus 1-methyl(5-ethylcarbamyl)-2-pyridone (**12c**) (5.5% by UV) [^{1}H NMR ($CDCl_3$) δ 1.22 (t, 3, J_{Et} = 7 Hz, CH_3CH_2), 3.64 (s, 3, CH_3N), 6.56 (d, 1, $J_{3,4}$ = 9.5 Hz, H-3), 8.09 (d of d, 1, $J_{3,4}$ = 9.5, $J_{4,5}$ = 3 Hz, H-4), 8.27 (broad, 1, NH), and 9.29 ppm (d, 1, $J_{4,6}$ = 3 Hz, H-6)]. In this last spectrum, the resonance corresponding to the methylene moiety of the ethyl group was presumed to be under the resonance due to the methylene protons of the **3b** present in the sample.

The mixture of **2b** and **2c** was identified by means of analytical HPLC using *n*-hexane/5% EtOH as the developing solvent: κ' for **2b** (34%) = 1.62, κ' for **2c** (66%) = 2.28.

Reaction of 5a with Methyl Iodide. [(*E*)-3-Methoxypropenoyl]-*N,N'*-dimethylurea (14a) and 1,3-Dimethylthymine. A mixture of **2a** (1.29 g, 9.2 mmol) and TMAH (1.77 g, 9.7 mmol) in 100 mL of Me_2SO was shaken for 17 min. Methyl iodide (1 mL, 16 mmol) was added. The solution became neutral within 6 min. It was evaporated in vacuo at 45 °C and the residue, chromatographed on activated silica gel (AcOEt), afforded a mixture of a new compound of molecular weight 172 and 1,3-dimethylthymine (130 mg); a 1:1 mixture of **2a** and 1,3-dimethylthymine (438 mg); and **2a** (420 mg). The new compound (30 mg), κ' = 2.15, and 1,3-dimethylthymine[29] (67 mg), κ' = 4.55, were separated by means of preparative HPLC (7.5% EtOH/*n*-hexane). The new component was recrystallized from *n*-hexane to give 10 mg of analytically pure [(*E*)-3-methoxypropenoyl]-*N,N'*-dimethylurea (**14a**): mp 74.5–77.5 °C; IR (Nujol) 3300 (NH), 1700, 1630, and 1600 cm^{-1} (C=C and C=O); UV (95% EtOH) λ_{max} 247 nm (ϵ 12 800); UV (0.1 N HCl) λ_{max} 250 nm (ϵ 12 000); UV (0.1 N NaOH)[30] λ_{max} 265 nm (ϵ 5300); ^{1}H NMR ($CDCl_3$) δ 2.85 (d, 3, $J_{Me,NH}$ = 4.5 Hz, CH_3NH), 3.30 (s, 3, CH_3N), 3.75 (s, 3, CH_3O), 5.63 (d, 1, $J_{2,3}$ = 12 Hz, H-2), 7.61 (d, 1, $J_{2,3}$ = 12 Hz, H-3), and 9.15 ppm (broad, 1, NH); $M^+\cdot$ *m/e* 172 (72).

Anal. Calcd for $C_7H_{12}N_2O_3$: C, 48.83; H, 7.02; N, 16.07. Found: C, 48.88; H, 6.98; N, 16.17.

The total yields of the various products were 22% 1,3-dimethylthymine, 49% **2a**, and 2% **14a**.

Isolation of 1,3-Dimethyl-6-(*N*-methylcarbamylmethyl)-5-(methylaminomethylene)-5,6-dihydrouracil (10a). Compound **2a** (2.03 g, 14.5 mmol) was added to 190 mL of 0.09 N TMAH (17.1 mmol) in Me_2SO. Three minutes after the initial solid dissolved, another solid separated. The reaction was followed by UV. After 4.5 h, when the absorption at 320 nm had reached a maximum, glacial acetic acid (1 mL, 17.6 mmol) was added to stop further reaction. The mixture was chromatographed to remove salts. The residue obtained was dissolved in 25 mL of absolute EtOH and an aliquot was analyzed by HPLC (5% EtOH in *n*-hexane). Four components were present: **2a**; a compound with λ_{max} 310 nm (κ' = 6.15); and two others. A 29% yield (UV) of the component with λ_{max} 310 nm was present. Chromatography (AcOEt and 3:1 AcOEt/EtOH) of the main portion of the residue, after evaporation of the EtOH, afforded 390 mg (19%) of **2a**; a mixture (140 mg) of **2a** (5%, UV) and **13a** (2.5%, UV); **13a** (300 mg; 2%, UV); and two other components (1.103 g), one of which was **10a**. The latter mixture afforded a white solid, mp 158–164 °C, on addition of 1,2-dichloroethane. Recrystallization from $CHCl_3$/1,2-dichloroethane afforded 80 mg of pure **10a**: mp 171–173 °C; IR ($CHCl_3$) 3460 and 3310 (NH and OH), 1660, 1651 (NC=O), and 1600 cm^{-1} (C=C); UV (95% EtOH) λ_{max} 310 nm (ϵ 18 200); UV (0.1 N HCl) shoulders on end absorption at 260 nm (ϵ 3800) and 225 (6340); UV (0.1 N NaOH) λ_{max} 309 nm (ϵ 18 900); ^{1}H NMR ($CDCl_3$) δ 2.20 (d of d, 1, $J_{CH_2,6}$ = 9, J_{gem} = 13 Hz, CH_2CH), 2.42 (d of d, $J_{CH_2,6}$ = 5, J_{gem} = 13 Hz, CH_2CH), 2.68 (d, 3, $J_{Me,NH}$ = 4.5 Hz, CH_3NH),[31] 2.88 (d, 3, $J_{Me,NH}$ = 4 Hz, CH_3NH),[31] 2.94 (s, 3, CH_3N),[31] 3.02 (s, 3, CH_3N),[31] 4.12 (d of d, 1, $J_{CH_2,6}$ = 5 and 9 Hz, CH_2CH), 5.83 (broad, 1, NH), 6.55 (d, 1, $J_{CH,NH}$ = 13 Hz, CHNH), and 8.01 ppm (broad, 1, NH); mass spectrum *m/e* (rel intensity) $M^+\cdot$ 254 (1), 182 (100), 125 (12), and 84 (17).

Anal. Calcd for $C_{11}H_{18}N_4O_3$: C, 51.95; H, 7.13; N, 22.03. Found: C, 51.79; H, 7.10; N, 21.66.

Reaction of 10a with TMAH in Me_2SO. Compound **10a** (40 mg, 0.158 mmol) was dissolved in 300 μL of Me_2SO-h_6 and the ^{1}H NMR spectrum was obtained: NH hydrogens at 7.81 and 7.61, vinyl hydrogen at 6.59 (J = 13.5 Hz), CH_2 group at 4.01 (J = 5 and 8 Hz), and methyl groups at ca. 2.82, 2.90, and 2.94 ppm. The remaining proton resonances were obscured by the absorption of the solvent. The solution was removed from the ^{1}H NMR tube and added to 20 mg (0.11 mmol) of TMAH, which did not dissolve completely. The solution turned yellow. It was returned to the ^{1}H NMR tube without transferring solid. The spectrum had a single broad resonance centered at 7.40 ppm and methyl group resonances at 2.92, 2.85, and 2.77 ppm, in addition to solvent, water, and tetramethylammonium resonances. After 18 h, resonances corresponding to **12a** were present. UV analysis in 0.1 N NaOH and 0.1 N HCl indicated the presence of 67% of **12a** and 12% of **13a**.

Degree of Isomerization of 2c as a Function of Time. A sample of **2c** (151 mg, 0.98 mmol) was placed in a 10-mL volumetric flask. A 0.1 N solution of TMAH (1 mmol) in Me_2SO was added to the mark. Aliquots (2 mL) were removed after 2 min, 0.5, 2.5, 6.5, and 24 h. Each aliquot was treated with 50 μL (0.88 mmol) of glacial acetic acid and desalted. The residues were dissolved in 10 mL of absolute EtOH for UV determinations in 0.1 N NaOH and 0.1 N HCl, and HPLC analysis using 5% EtOH in *n*-hexane as developing solvent. The extent of isomerization was 0, 1, 9, 17, and 23%, respectively.

Reaction of 1,3-Diethyluracil (2d) with 1,3-Dimethylurea (3a) in the Presence of TMAH. Compound **2d** (150 mg, 0.89 mmol) and **3a** (80 mg, 0.91 mmol) were placed in a 10-mL volumetric flask and 0.11 N TMAH (1.1 mmol) in Me_2SO was added to the mark. Aliquots (3 mL) of this solution were removed after 1 and 2 h. Each was treated with 200 μL of glacial acetic acid and desalted. The residues obtained were dissolved separately in absolute EtOH. The solutions were subjected to UV analysis and HPLC. By UV it was found that both solutions contained **10** and the chromophore present in **2**. The sample taken at 1 h contained 56% (UV, 0.1 N HCl) of the latter chromophore, while the 2-h sample contained 47%. HPLC analysis (5% EtOH in *n*-hexane) showed that the content of **2** of both samples was made up of 63% of **2a** and 37% of **2d**.

In a similar reaction, after a chromatographic separation on silica gel, **3a** and **3d** were found (^{1}H NMR) to be present in addition to the **2a** and **2d**.

A solution of **2d** (150 mg, 0.89 mmol) and 10 mL of 0.1 N TMAH (1.0 mmol) in Me_2SO was allowed to react for 1.75 h. Then **3a** (80 mg, 0.91 mmol) was added and the solution was allowed to stand for another 2.75 h. At the end of this time, the reaction mixture was worked up as described above. The total yield of **2** by UV was 50%, consisting of 61% **2a** and 39% **2d** (HPLC).

Registry No.—**2a**, 874-14-6; **2b**, 62415-62-7; **2c**, 59495-24-8; **2d**, 22390-04-1; **3a**, 96-31-1; **3b**, 28145-10-0; **3d**, 623-76-7; **4'**, 926-61-4; **4'** oxime, 62415-63-8; **5a**, 62415-64-9; **10a**, 62415-65-0; **12a**, 62415-66-1; **12b**, 62415-67-2; **12c**, 62415-68-3; **12d**, 62415-69-4; **13a**, 62415-70-7; **13b**, 62415-71-8; **13c**, 62415-72-9; **14a**, 62415-73-0; 1-ethyluracil, 6490-42-2; $(CH_3)_2SO_4$, 77-78-1; hydroxylamine HCl, 5470-11-1; methyl iodide, 74-88-4.

References and Notes

(1) The authors are indebted to two anonymous donors for their generosity in providing partial support for this investigation. Additional support was provided by a Biomedical Sciences Support Grant from the General Research Support Branch, Division of Research Resources, Bureau of Health Professions Education and Manpower Training, National Institutes of Health.

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(7) H. von Pechmann [*Justus Liebigs Ann. Chem.*, **264**, 261 (1891)] gives mp 117–118 °C; I. J. Rinkes [*Recl. Trav. Chim. Pays-Bas*, **46**, 268 (1927)] gives mp 114 °C.

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(15) The UV spectrum of **10a**, which varies with pH, is in good agreement with that of **1b**, which has a related chromophore. The only significant difference between the spectra of **10a** and the imidazolidone, **1b**, is in the extinction coefficients. This difference may well be due to a difference in the stereochemistry of the two chromophores. See ref 5.
(16) The species *m/e* 125 may be a radical cation or a cation.
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(23) This area integrates for ca. 3 protons due to the fact that not all water was removed from the original sample by evaporation.
(24) The assignment of the resonances to the syn and anti isomers is arbitrary. These were present in a ratio of 25:75.
(25) Me_2SO was purified by azeotropic distillation with benzene to remove the bulk of the water followed by vacuum distillation from CaH_2.
(26) The value of ϵ given for **5a** is based on 100% conversion of **2a**.
(27) Dimethyl sulfone was a ubiquitous minor component of all of these reactions. A control reaction in which the dialkyluracil was omitted did not produce any sulfone.
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(29) This material was identical with a sample of 1,3-dimethylthymine prepared by the methylation of thymine.[20]
(30) The UV spectra in both 95% EtOH and 0.1 N HCl are reasonable for the structure assigned to **14a**. The initial spectrum of this compound in 0.1 N NaOH showed a shoulder at ~290 nm which disappeared in a short time. The spectrum was invariant after 1 h. The value of λ_{max} 265 nm reported is probably due to **2a** which is formed by a Michael addition of hydroxide ion to the enol ether carbon atom of **14a**, followed by the expulsion of methoxide ion in a reverse Michael addition. The resulting product is **5a** (λ_{max} 296 nm in Me_2SO), which then undergoes ring closure to **2a** (59% yield).
(31) The assignment of these methyl groups cannot be made with certainty.

Nucleophile and Borate Reactivity with Nicotinamide Adenine Dinucleotide and Its Analogues[1]

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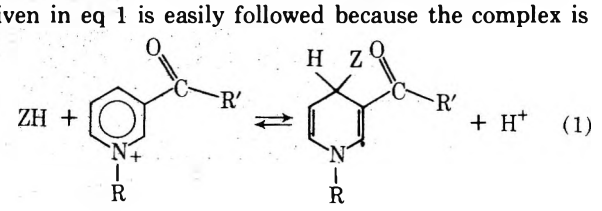
Nucleophilic reactivity for a variety of nucleophiles to the ring addition reaction of pyridine nucleotides has been measured. There is no relationship between rate of reaction and equilibrium affinity for the nucleophile. This situation is similar to the reaction of nucleophiles with the carbonyl carbon or with carbonium ions. The position of equilibrium correlates with γ, the position of equilibrium for nucleophilic reaction with the carbonyl group. However, a better correlation between pyridinium ion addition reactions has been obtained: A new affinity scale for the pyridinium ion, P^+, is defined. Boration of the ribose adjacent to the pyridinium ring reduces the equilibrium constant for nucleophile addition three- to sevenfold, regardless of the structure of the pyridinium moiety.

Nicotinamide adenine dinucleotide (NAD^+)[2] is transformed into ring addition complexes by a variety of agents. Sulfite,[3] hydroxide,[4] cyanide,[5] and enols[6] form favorable complexes. Weaker interactions take place with mercaptans, hydroxylamine, and imidazole.[6,7] A number of stable inhibitory ternary NAD^+–nucleophile–dehydrogenase complexes are formed.[7-11] Though NAD^+ ring addition complexes are formed in the absence of enzyme, complex formation is favored on the enzyme surface when the nucleophile bears a structural resemblance to the natural substrate. Kaplan and Everse[12] have proposed that the ternary complex formed by NAD^+, pyruvate, and lactate dehydrogenase plays a role in metabolite regulation in the living cell.

Borate complexes with the ribose adjacent to the nicotinamide cation in NAD^+ to form NADB, which forms less favorable nucleophilic ring addition complexes at a lower rate, in comparison with NAD^+.[13] The borate complexation with NAD^+ is the cause of the competitive inhibition of a number of dehydrogenases by borate with respect to NAD^+.[14]

In order to understand what chemical properties of the nucleophile favor a stable addition complex, a study of both the rate and equilibrium constants was initiated. This reaction as given in eq 1 is easily followed because the complex is



(1)

chromophoric, absorbing maximally at 310–360 nm (depending upon the nucleophile and the pyridinium ion). Rate and equilibrium constants were obtained as a function of pH, in order to elucidate the overall stoichiometry of the reaction and of the transition state. NAD^+, 3-acetylpyridine adenine dinucleotide ($APAD^+$), and their nucleotide and alkyl analogues were studied. In addition we have measured the boration and phenylboration equilibrium of $APAD^+$, nicotinamide adenine dinucleotide phosphate (NADP), and other analogues of NAD^+, and we have measured the effect of boration on nucleophilic reactivity and affinity. We have compared the scale of reactivity and affinity of nucleophiles to NAD^+ with the reactivity and affinity scales of carbonium ions and carbonyl compounds. A new pyridinium ion affinity scale, P_+, is defined.

Experimental Section

Materials. The pyridine nucleotides were products of Sigma Chemical Co. The concentration of pyridine nucleotide was assayed using horse or yeast alcohol dehydrogenase from Sigma. 1-Benzyl-3-acetylpyridinium chloride ($BzAP^+Cl^-$) was prepared by mixing benzyl chloride with 3-acetylpyridine in benzene at room temperature. Recrystallization from ethanol yielded a white product, mp 189–190 °C (uncorrected). 1-Methyl-3-acetylpyridinium iodide ($MeAP^+I^-$) was prepared by mixing methyl iodide with 3-acetylpyridine at room temperature. Recrystallization from 1-propanol yielded yellow crystals, mp 163–165 °C (uncorrected). 1-Methyl-3-carboxymethylpyridinium iodide ($McCP^+I^-$), *N*-methylnicotinamide iodide ($MeNic^+I^-$), and *N*-methylisonicotinamide iodide ($MeIsonic^+I^-$) were prepared in the same way as $MeAP^+$, using methyl iodide and the corresponding pyridine derivative, mp 258–260, 207–211, and 129–133

°C (all uncorrected), respectively. 1-Benzyl-3-carboxylmethylpyridinium ion ($BzCP^+Cl^-$) was prepared by refluxing methyl nicotinate with benzyl chloride in methanol. After recrystallization from propanol–ether, white crystals were obtained, mp 129–133 °C (uncorrected). 1-Benzylnicotinamide chloride ($BzNic^+Cl^-$) was prepared as above, using nicotinamide as the base, mp 240–242.5 °C (uncorrected). Phenylboronic acid from Sigma was recrystallized from water, vacuum dried, and stored in the desiccator. Fisher reagent grade sodium sulfite and boric acid were used without further purification.

Buffers. To minimize the effect of the slow decomposition of sulfite,[15] fresh sulfite solutions were used for all experiments. Borate buffers were prepared by the neutralization of boric acid with NaOH. The thiol, hydroxylamine, methoxyamine, and hydrazine buffers were prepared just before use, by adding NaOH to the thiol or the amine hydrochloride. Low pH (pH 5–6) sulfite buffers contained acetate/acetic acid to maintain the pH. All the buffer solutions were maintained at constant ionic strength with potassium chloride. Phenylboronic acid buffers were prepared by adding NaOH to phenylboronic acid and filtering. The concentration of phenylboronic acid was determined spectrally at 267 nm.[16] Hydrogen peroxide was determined by titration with $KMnO_4$. The concentration of $KMnO_4$ was standardized by titration with sodium oxalate.

Spectral Measurements. Absorption spectra were obtained with either a Cary Model 14 or a Model 15 recording spectrophotometer, using 1-cm, 3-mL quartz absorption cells. NMR spectra were obtained with a Varian Model T-60 spectrometer. The measurements were made with solutions containing 0.14 M pyridine nucleotide and 0–0.6 M nucleophile in D_2O. The pH was approximately 7–8.

Kinetics. The rate of production of ring addition adducts and their partial decomposition in the presence of borate were measured at 310–360 nm using a Durrum stopped-flow spectrophotometer with an instrument dead time of 2.5 ms. Reactions were performed under pseudo-first-order conditions with nucleophilic concentration in large excess over that of pyridinium ion in a series of Z/ZH buffers of varying total buffer concentration at a constant buffer ratio X. Several buffer ratios were generally used. The transmittance values from the oscilloscope trace were converted to absorbance values; and first-order rate constants, k_{obsd}, were calculated from plots of log $(A_\infty - A_t)$ or log $(A_t - A_\infty)$ against time.[17] All plots were linear to 90% reaction. Second-order rate constants were obtained from the slopes of plots of k_{obsd} against nucleophile concentration. The data were treated using a linear least-squares program on the Olivetti P602 microcomputer.

Equilibrium Constants. A Cary Model 16 or a Beckman DU-2 spectrophotometer, thermostated at 25.0 ± 0.1 °C, was used for equilibrium determinations. The pyridinium salt was introduced with an Eppendorf micropipet into a 1-cm quartz cuvette containing measured amounts of borate buffer solution. The total volume was 3.0 mL and the initial ionic strength was kept constant. Manual measurements were made in the 300–365-nm region, depending upon the substrate and the nucleophile, giving the absorbance value, A, of the cell and its contents, with air as reference. Aliquots of nucleophile were added to the cuvette. The contents of the cuvette were rapidly mixed, and measurements of the absorbance were recorded after each addition of nucleophile. The procedure was repeated for monitoring the pH of the solution before and after addition. The absorbance values were corrected for the volume change due to addition of nucleophile. Double reciprocal plots of absorbance against nucleophile concentrations were made for various concentrations of borate.[18] Assuming that the molar extinction coefficient, ϵ, is the same for the pyridine nucleotide–nucleophile complex and the pyridine nucleotide–nucleophile–borate complex, ϵ was calculated from the average value of the intercepts and the substance concentration, c: $\epsilon = 1/(\text{intercept} \times c)$.[13] The equilibrium constant, K_{app}, was calculated from the slope, substrate concentration, and molar extinction coefficient: $K_{app} = 1/(\text{slope} \times \epsilon \times c)$. For cyanide equilibria which cannot be forced to completion at the cyanide concentrations used, the method of Behme and Cordes[19] was used, where K is the slope of a plot of $A_{obsd}/(CN^-)$ vs. A_{obsd}.

The values of K_{app} and the corresponding values of borate concentration were treated using a nonlinear least-squares curve fitting program on the DEC System-10 computer in order to determine the individual equilibrium constants of Schemes II and III.

pH Determinations. The pHs of the solutions were measured using a Radiometer Type TTT1D pH meter with a Type PHA 630T scale expander. The electrode system employed consisted of a G2222C glass electrode and a K4112 calomel electrode. For the kinetics experiments, the pH of the solutions was measured at the completion of the reactions. For equilibrium studies, the procedure for adding aliquots of nucleophile to a solution of pyridine nucleotide in borate buffer was repeated. The pH was measured before and after each nucleophile addition.

Results

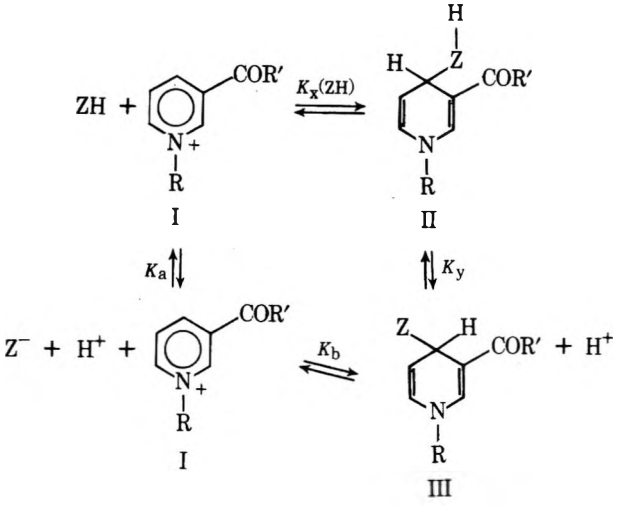
General Treatment. Equilibrium constants were obtained by observing the absorbance of the complex as a function of ZH/Z concentration of constant pH and constant initial concentration of pyridine nucleotide. This process was repeated at a number of pH values. The value of the equilibrium constant K_{tot} is obtained from eq 2, which describes a linear double reciprocal plot of A_{obsd}^{-1} vs. $(Z)_{tot}^{-1}$ for the ring addition of Z. Z_{tot} is [Z + ZH], K_a is the acid dissociation constant of ZH, l is the cell width, ϵ is the extinction coefficient of the complex, C_0 is the initial concentration of pyridinium ion, and A_{obsd} is the observed absorbance. From this plot, ϵ and K_{tot} are both obtained, providing $(Z)_{tot}$ can be varied to concentrations high enough so that the $K_{tot}(Z)_{tot} > 1$. When K_{obsd} is unfavorable, $K_{tot}(Z)_{tot} < 1$ over the entire concentration range of $(Z)_{tot}$, and eq 2 is simplified to eq 3.

$$\frac{lC_0}{A_{obsd}} = \frac{1}{\epsilon}\left(1 + \frac{1}{K_{tot}[Z]_{tot}}\right) \tag{2}$$

$$\frac{A_{obsd}}{l} = K_{tot}\epsilon C_0(Z)_{tot} \tag{3}$$

In this case K_{tot} and ϵ are no longer separable, and only the quantity $K_{tot}\epsilon$ can be obtained by dividing the slope of the A_{obsd} vs. $(Z)_{tot}$ plot at constant C_0 by C_0. Scheme I illustrates

Scheme I



the formation of two complexes, II and III, which are in protonic equilibrium with each other. The value of K_{tot} is given by eq 4, where K_{ab} is K_aK_b, K_{xy} is K_xK_y. Plots of K_{tot} vs. $(H^+)^{-1}$ give K_{xy} as the slope and K_x as the intercept, when $K_a < (H^+)$. If ZH has a measurable ionization constant, K_a, then K_b can be obtained from eq 4.

$$K_{tot} = \frac{K_x[H^+] + K_{ab}}{K_a + [H^+]} = \frac{K_x[H^+] + K_{xy}}{K_a + [H^+]} \tag{4}$$

The equilibrium data for the addition of pyridine nucleotides of sulfite, mercaptide, cyanide, imidazole, hydrazine, and hydroxylamine give K_x values of zero. Only K_{xy} values rather than K_b values can be obtained for most amines, as most amines do not have measurable K_a values. For very weakly interacting systems, ZH, as well as Z, interacts.

Borate buffers were found to profoundly decrease the interaction of nucleophiles with ribose-containing pyridinium compounds, as was found for NAD^+ and nicotinamide adenine mononucleotide (NMN^+) earlier.[13] Scheme II accounts for the effect of borate. The equilibrium constants for boration

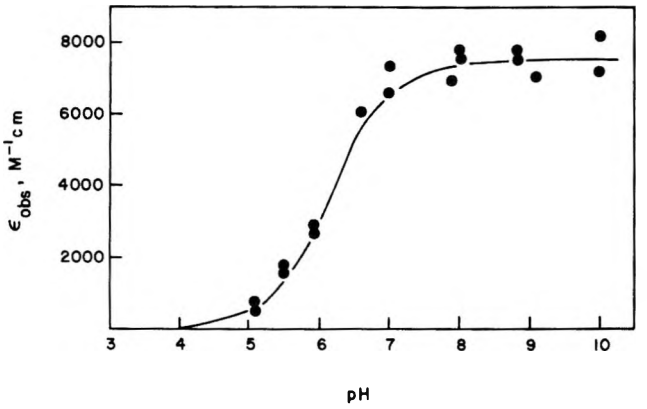


Figure 1. Apparent extinction coefficient for the equilibrium of $[SO_3^{2-} + HSO_3^-]$ with APAD$^+$. Solid line calculated from eq 8 with $\epsilon = 7500\ M^{-1}\ cm^{-1}$, $K_1 = 1590\ M^{-1}$, $K_2' = 240\ M^{-1}$.

Scheme II

$$\begin{array}{ccc} Z^- + NAD^+ & \overset{K_b}{\rightleftharpoons} & NAD\text{-}Z \\ K_I(\text{borate}) \uparrow\downarrow & & \uparrow\downarrow K_{II}(\text{borate}) \\ Z^- + NAD\text{-}B & \overset{K_c}{\rightleftharpoons} & NADZ\text{-}B \end{array}$$

and phenylboration of the nucleotides and nucleotide adducts were obtained from eq 5, which is derived from eq 4.

$$K_{obsd,z} = \frac{K_b + K_I K_c(\text{borate})}{1 + K_I(\text{borate})} \quad (5)$$

$$K_I K_c = K_{II} K_b \quad (6)$$

Sulfite, Cyanide, and Mercaptide Addition. Previous studies on the effect of pH on K_{obsd} have demonstrated that only dianionic SO_3^{2-} and anionic RS^- add to the pyridinium ring.[3,13,20] We now show that in the case of pyridinium rings with aldehyde or acetyl groups in the 3 position, in addition to the pyridinium ring addition equilibrium depending on Z^-, another equilibrium involving the addition of ZH to the carbonyl group is present. The second ZH-dependent equilibrium is apparent from the fact that the apparent equilibrium constant does not follow eq 4, with $K_x = 0$, but falls off more slowly in the acid pH range ($<pK_a$), indicating the presence of a finite K_x term. This is in contrast to the sulfite equilibria with NAD$^+$ and NMN$^+$, where K_x is zero. Another indication of ZH equilibria at the carbonyl group is that ϵ_{obsd} values do not remain constant with pH change, as would be expected for equilibria involving the formation of ring addition products only (Figure 1). The effects of pH on both ϵ and K_{obsd} indicate that at low pH, nonchromophoric HSO_3^- complexes are formed. The complexation reactions of PAAD$^+$ and APAD$^+$ could not be studied at pH values greater than 10, owing to the formation of yellow products, presumably due to the hydroxide ring addition reaction, as in the case of NAD$^+$.[4]

The presence of a second ZH-dependent equilibrium is also manifested by the difference in the number of transients seen in the reaction of sulfite with NAD$^+$ and NMN$^+$ in contrast to APAD$^+$, MeAP$^+$, and BzAP$^+$. Only a single sulfite-dependent transient is observed for NAD$^+$ and other nicotinamide cations at all pH values. This transient is first order in $[SO_3^{2-}]$ and is due to the ring addition reaction.[13] In contrast, for APAD$^+$ and other acetylpyridine cations, at high pH, a single sulfite-dependent transient is seen; and at low pH two transients are seen (Figure 2). The biphasic reaction consists of a rapid sulfite-dependent decrease in transmittance, followed by a slower increase in transmittance (decrease in absorbance), which is independent of sulfite. The second slower reaction has a hyperbolic dependence on sulfite concentration:

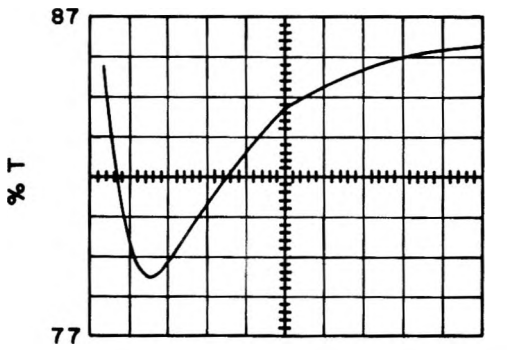


Figure 2. Transmittance vs. time for reaction of APAD$^+$ with 5 mM SO_3^{2-} in a pH 5.1 acetate buffer, $\mu = 0.6$ M. Each horizontal division is 0.2 s.

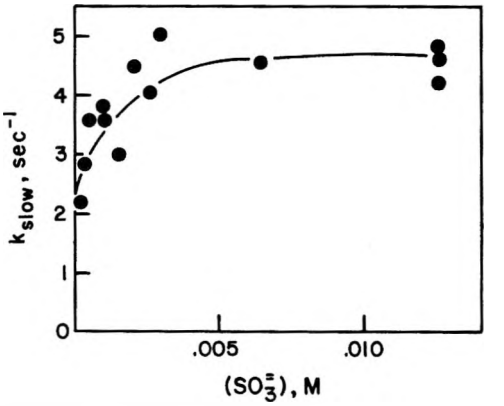
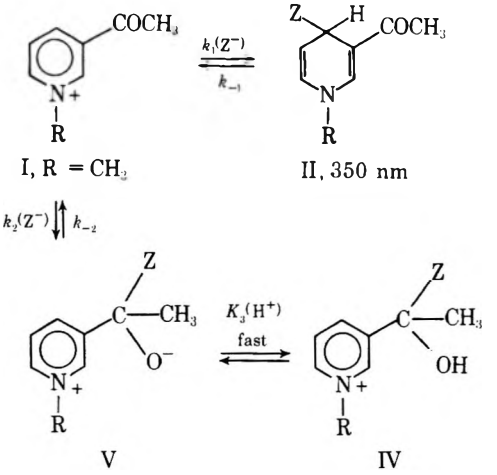


Figure 3. Observed first-order rate constant for the second transient in Figure 2 vs. SO_3^{2-} concentration. The pH range is 4.9–5.3.

at very low sulfite concentrations the rate is sulfite dependent, and at higher sulfite concentrations, the rate becomes sulfite independent (Figure 3). At intermediate pH, 7–9, k_{slow} shows a pH dependence with a 0.7 order in $1/(H^+)$, approximately first order.[22]

Scheme III explains both the rate and equilibrium data. The

Scheme III



pH dependencies for K_{obsd} and ϵ_{obsd} are given by eq 7 and 8

$$K_{obsd,tot} = \frac{[K_a K_b + (H^+)K_2']}{[(H^+) + K_a]} \quad (7)$$

$$\epsilon_{obsd} = \frac{K_a K_I}{[K_a K_b + (H^+)K_2']} \quad (8)$$

where $K_{obsd,tot}$ is the dissociation constant with respect to total Z + ZH, K_2' is the product of K_2 and K_3, K_b is k_1/k_{-1}, and K_2

Table I. Rate and Association Constants for the Interaction of Sulfite with Pyridinium Ions[a]

Registry no.	Pyridinium ion	λ_{max}, nm	ϵ, M^{-1} cm^{-1}	K_b, M^{-1}	K_2', M^{-1}	k_1, M^{-1} s^{-1}	k_2, M^{-1} s^{-1}
	β-NAD+ [p]	320	4500 ± 150	41 ± 1		2050 ± 180	
	β-NAD-B[p]	320	4500 ± 150	8.4 ± 0.7		473 ± 46	
62430-84-6	β-NAD-PhB	320	6134 ± 134	3.1 ± 0.4			
62430-85-7	Deamino-NAD+	320	4095 ± 70	30.5 ± 2.2[o]		1390 ± 30[t]	
62475-99-4	α-NAD+	320	1040 ± 240	15.7 ± 0.8[r]		2200[s]	
62430-86-8	α-NAD-B	320	1040 ± 240	2.7 ± 0.6[r]			
62461-57-8	APAD+	340	6900 ± 200[u]	1500 ± 100[u]			
			7500 ± 100[m]	1410 ± 90[m]	240[m]	12 000 ± 400[n]	~2100[l]
62430-87-9	APAD-B	340	7500 ± 70[u]	220 ± 70[u]		3100[q]	
62430-88-0	Deamino-APAD+	340	6176 ± 400	980 ± 140[d]		10 200[r]	
62430-89-1	Deamino-APAD-B	340	6196 ± 410	300		2400[q]	
62430-90-4	NADP+	320	3170 ± 590	22.5 ± 0.5[r]		1400[s]	
62430-91-5	NADP-B	320	3170 ± 590	6.1 ± 0.4[r]		345[s]	
62430-92-6	BzAP+	340	6840 ± 200	108 ± 12[b]	*b*	4670[j]	~2000[k]
62430-93-7	MeAP+	340	2610 ± 690	19 ± 3[h]	200[h]	1800[i]	~2000[g]
62430-94-8	ThioNAD+	365	4890 ± 180	101 ± 9[f]		2130 ± 180[e]	
62430-95-9	PAAD+	340		2000 ± 130[d]		(26)[c]	
	NMN+[p]	320	4050 ± 13	25 ± 1		1240 ± 50	
	NMN-B[p]	320	4050 ± 13	9.3 ± 0.8		455 ± 30	

[a] Association constants, K, measured at 25.0 ± 0.1 °C, ionic strength 0.6 M; rate constants measured at 25 ± 1 °C, 0.6 M ionic strength. [b] Measured at pH 8.2 and 10.0. The equilibrium constant was not measured in the acid pH range which would allow determination of K_2'. [c] Measured at pH 9.0 and 9.7. The small value represents a rate process other than ring addition. [d] Measured at pH 8.15 and 9.25. The equilibrium constant was not measured in the acid pH range which would allow determination of K_2'. [e] Measured at pH 9.1, 7.2, 6.8, 5.4, and 4.8. [f] Measured at pH 9.1 and 8.0. [g] Measured at pH 6.0–6.5. [h] Measured at pH 6.0, 7.1, 8.1, 8.2, 8.4, 9.1, and 10.1. [i] Measured at pH 8.2, 8.8, and 9.5. [j] Measured at pH 10.1. [k] Measured at pH 4.9–6.5. [l] Measured at pH 4.9–5.3. [m] Measured at pH 5.0–10. [n] Measured at pH 8–10. [o] Measured at pH 7.0, 9.2, and 10.0. [p] From Johnson and Smith.[13] [q] Measured at pH 8.9. [r] Measured at pH 9.1. [s] Measured at pH 9.7–9.8. [t] Measured at pH 7.8, 8.9, and 9.1. [u] Measured in the presence of borate at pH 7.9, and analyzed according to Scheme II. [v] Measured at pH 9.1 and 10.4. [w] Measured by stopped-flow spectrophotometry.

Table II. Association Constants for the Interaction of Mercaptide and Cyanide and Pyridinium Ions[a]

Registry no.	Z^-	Pyridinium ion	μ, M	λ_{max}, nm	ϵ, M^{-1} cm^{-1}	pH	K_b, M^{-1}	K_2', M^{-1}
62430-96-0	ME	β-NAD+	1.0	325	5060	9.5	1.8 ± 0.3[b]	
	ME	β-NAD+	0.5, 50% ethanol	325	6700		9.4 ± 0.5[b]	
62430-97-1	AcCys	β-NAD+	1.0	325	6000	9.0	1.1[b]	
62461-58-9	TG	β-NAD+	1.0	325	8700 ± 2300	9–11[d]	3.56 ± 1.03	
5815-31-6	CN^-	β-NAD+	0.63	325	5270 ± 330	11.4	221 ± 5	
62430-98-2	CN^-	β-NAD-B	0.63	325	5270 ± 330	11.4	41 ± 3	
62430-99-3	TG	APAD	0.63	350	5370 ± 1280	9.1[f]	440 ± 10	
	TG	APAD	1.0	350	5390 ± 1290	5.7–10[e]	171	3
62431-00-9	TG	APAD-B	0.63	350	5370 ±1280	9.1	51 ± 10	
62476-00-0	TG	PAAD	0.63	350	5290 ± 1100	5.7–10[c]	4920 ± 50[a]	88.9 ± 8

[a] Measured at 25.0 ± 0.1 °C unless otherwise noted. [b] Measured at 25 ± 1 °C. [c] Measured at pH 5.7, 6.6, 7.2, 8.0, 8.1, 8.7, 9.7, and 10.0. Fifteen separate measurements were calculated according to eq 7, with $K_a = 2 \times 10^{-10}$ M. [d] Measured at pH 9.0, 10.0, and 11.0. [e] Measured at pH 8.1, 9.0, and 10.0. [f] Measured in the borate system according to Scheme II.

is k_2/k_{-2}. In Scheme III, the HSO_3^--dependent equilibrium is a carbonyl addition reaction, and the SO_3^{2-}-dependent equilibrium is the ring addition reaction. By analogy with sulfite addition to benzaldehyde, the carbonyl addition reaction would be expected to depend on SO_3H^- much more strongly than on SO_3^{2-}. At high pH, only the K_b equilibrium is important, and the only transient seen is due to the k_1 step. At low pH, the K_2' equilibrium becomes more important, but the addition to the pyridinium ring (k_1) is more rapid than the addition to the carbonyl group (k_2). As a result, a metastable K_b equilibrium is established during the fast first transient, resulting in an increase in absorbance as II is formed. The overshoot in the formation of II is then slowly diminished by sulfite addition to the carbonyl group in the k_2 step. As with the rate of sulfite addition to benzaldehyde, the reaction rate depends upon SO_3^{2-} rather than SO_3H^-.[23] According to Scheme III the rate of the low pH second slow step is predicted to be hyperbolic in sulfite, according to eq 9, where K_{OH} is the acid dissociation constant of the OH group.

$$k_{slcw} = \frac{k_2(SO_3^{2-})}{1 + K_b(SO_3^{2-})} + \frac{k_{-2}K_{OH}}{(H^+) + K_{OH}} \quad (9)$$

Table I contains equilibrium and rate data for the addition of sulfite to the pyridinium ring. Table II contains equilibrium data for mercaptide and cyanide addition. For those $APAD^+$, $BzAP^+$, $MeAP^+$, and 3-pyridine aldehyde adenine dinucleotide ($PAAD^+$) systems studied over a wide pH range, data from the additional equilibria and rates due to carbonyl addition, analyzed according to eq 7, 8, and 9, are given. The k_2 values are approximate because of saturation of the rate process at very low sulfite concentrations. Rate data for mercaptide reaction with pyridinium ions are not given in Table II, because the second-order rate constant exceeds 10^4

Table III. Association and Rate Constants for the Interaction of Borate and Phenylborate with Pyridine Nucleotides at 25 °C, μ = 0.6 M[a]

Pyridine nucleotide	pH	$K_{B(OH)_4}$, M^{-1}	k_B, k_{BH}, M^{-1} s^{-1}	System	K_{PhB}, M^{-1}	k_{PhB}, k_{PhBH}, M^{-1} s^{-1}
NAD^+[b]	10.4	1500 ± 400	285, 350	SO_3^{2-}	2500 ± 150	170, 7500[d]
	9.0	1700 ± 300		SO_3^{2-}	3400 ± 190	
	8.75	2000 ± 60		Ethanol[c]		
NAD-CN	11.4	150 ± 20		CN^-		
NAD-SO_3^- [b]	10.4	250 ± 90		SO_3^{2-}	150 ± 20	
	9.0	350 ± 70				
NADH[c]	8.75	130 ± 8				
$APAD^+$	9.1	2050 ± 770		SO_3^{2-}		
	7.9	3100 ± 1300		SO_3^{2-}		
	9.1	1960 ± 240		TG		
APAD-TG	9.1	230 ± 50		TG		
APAD-SO_3^-	9.1	560 ± 240		SO_3^{2-}		
	7.9	450 ± 240		SO_3^{2-}		
α-NAD^+	9.0	2270 ± 580		SO_3^{2-}		
α-NAD-SO_3^-	9.0	400		SO_3^{2-}		
NMN^+ [f]	9.0	1900 ± 800	440, 690	SO_3^{2-}		
NMN-SO_3^-	9.0	720 ± 300		SO_3^{2-}		
$NADP^+$	9.1	900 ± 120	950, 490[e]	SO_3^{2-}		
NADP-SO_3^-	9.1	240 ± 40		SO_3^{2-}		

[a] pH values at which boration constants were measured are in the first column. [b] See Johnson and Smith.[13] [c] Boration of NADH was determined by the perturbation effect borate has on the equilibrium between NAD^+, ethanol and NADH, acetaldehyde, with the attainment of the equilibrium condition facilitated by the addition of alcohol dehydrogenase.[14] [d] Measured at pH 9.8, 10.5, and 10.8. [e] Measured at pH 9.7–9.8. [f] Registry no., 62461-59-0.

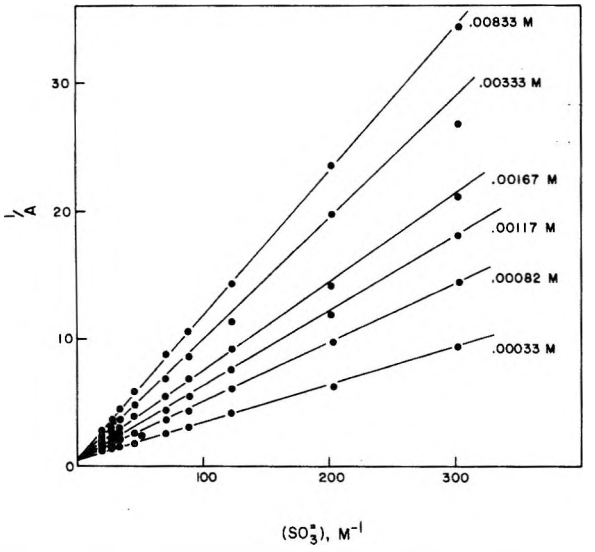


Figure 4. Determination of the perturbation of the equilibrium between sulfite and NAD^+ by phenylboronate. Measurements were made at pH 9.1, μ = 0.63, 25.0 ± 0.1 °C.

M^{-1} s^{-1} in the case of reaction with NAD^+. Using 10^{-3} M NAD^+ and 0.03–0.6 M mercaptide, the reaction was completed within the 2-ms deadtime of the instrument. The unfavorable equilibrium precludes the use of lower concentrations of mercaptide. Therefore only the lower limit of k_1 can be determined. The equilibrium is more favorable with $APAD^+$ and $PAAD^+$, but the kinetics have not been carried out, owing to the multiple equilibria (Scheme III) and the difficulty of identifying the rate constants associated with the multistep process. For example, the second-order rate constant of 26 M^{-1} s^{-1} for the reaction of SO_3^{2-} with $PAAD^+$ (Table I) probably represents a rate of dehydration of the aldehyde or of interaction with carbonyl group, rather than interaction with the ring, because it is so far out of line with the other values of k_1. Weak systems of RSH/RS^-–pyridinium ion interaction will be presented later. That the interaction of RS^- and SO_3^{2-} with pyridine nucleotides represents a covalent reaction is demonstrated by NMR studies of the NAD^+–thioglycolate reaction. Treatment of NAD^+ with increasing concentrations of thioglycolate (TG) buffer results in the progressive broadening of the nicotinamide signals at τ 2.31 (H_2); 2.44 (H_6) doublet, J = 7 Hz; 2.78 (H_4) doublet, J = 8 Hz; 3.48 (H_5) multiplet. The two adenine signals at 3.20 (H_2') and 3.36 (H_8') remain sharp and unperturbed. New signals emerge at τ 4.1, 1 proton (H_2); 5.20 and 5.25, 2 protons (H_5 and H_6); and τ 6.25 (H_4). Treatment of $MeAP^+$ with sulfite results in the progressive broadening of the pyridinium protons τ 0.60 (H_2); 1.05 and 0.09 (H_5 and H_6); and 1.75 (H_4). New broad signals emerge at τ 4.0, 3.0, and 1.85. The NMR spectrum of the product of NAD^+ and SO_3^{2-} has been previously reported.[13]

Borate and Phenylboronate Reactions. The equilibrium of borate and phenylboronate with the nucleotides was studied by the lowering of the apparent nucleophilic association constants in the presence of borate or phenylboronate, as shown in Figure 4. Only the basic forms of borate and phenylboronate are involved in the equilibria. In contrast, both the basic and acidic forms are involved in the rate of reaction with the nucleotides. The rate constants were obtained from the pseudo-first-order rate constants at low borate or phenylboronate concentrations, as before.[13] The rate and equilibrium data are given in Table III.

Weak Nucleophilic Interactions with Pyridinium Ions. The interaction of mercaptans with pyridinium ion is due to the RS^- species only; RSH does not give rise to an absorption band in the 300–360-nm region. Because the interaction is very weak, ϵ and K_{xy} could not be separated; only the product $K_{xy}\epsilon$ could be obtained. The results of RS^- interaction are given in Table IV. The reaction with mercaptans is reversible; lowering the pH reverses the reaction. The solvent effect on the interaction of 2-mercaptoethanol (ME) with $MeNic^+$, changing the solvent from 0 to 50% dioxane, causes a sixfold increase in $K_{xy}\epsilon$ and a dramatic increase in the sharpness of the band (from 130 to 30 nm half-width). In contrast, for

Table IV. Association Constants for Weak Interactions of Pyridinium Ions with Sulfhydryl Anions[a]

Registry no.	RS^-	Pyridine nucleotide	μ, M, and cosolvent[c]	λ, nm	$K_{xy\epsilon} \times 10^{-4}$, $M^{-2}\,cm^{-1}$
62431-01-0	TG	MeNic+	1.0	330	0.0415 ± 0.005[b]
	TG	MeNic+	1.0	340	0.030
62431-02-1	ME	MeNic+	0.94	340	0.026
	ME	MeNic+	0.5	340	0.030
	ME	MeNic+	0.5, 20% EtOH	340	0.040
	ME	MeNic+	0.5, 33% EtOH	340	0.061
	ME	MeNic+	0.5, 50% EtOH	340	0.11
	ME	MeNic+	0.5, 50% dioxane	340	0.18
62521-39-5	ME	MeIsonic+	0.97	340	0.02
	ME	MeIsonic+	0.47	340	0.024
	ME	MeIsonic+	0.47, 47% EtOH	340	0.036 ± 0.001
	ME	MeIsonic+	0.31, 63% EtOH	340	0.051
	ME	MeIsonic+	0.47, 47% dioxane	340	0.045
	ME	MeIsonic+	0.31, 63% dioxane	340	0.072 ± 0.03
62521-40-8	AcCys	MeIsonic+	0.94	340	0.0185 ± 0.0005
62521-41-9	TG	MeIsonic+	0.97	340	0.026 ± 0.002
	TG	MeIsonic+	1.0	330	0.025 ± 0.002[b]

[a] Measured at 25 ± 1 °C unless otherwise stated. [b] Measured at 25.0 ± 0.1 °C. [c] Solvent is water unless otherwise specified.

Table V. Rate and Association Constants for the Interaction of Primary Amines with Pyridinium Ions[a]

Registry no.	Pyridinium ion	Amine	k, $M^{-1}\,s^{-1}$ (pH)	pH range of equilibrium study	λ_{max}, nm	μ, M	K_{xy}	K_x, M^{-1}	$K_{xy}\epsilon$, $M^{-1}\,cm^{-1}$	$K_x\epsilon$, $M^{-2}\,cm^{-1}$
62430-69-7	NAD^+	NH_2OH	220 (11.1) 110 (10.2)[b]	9.2–11.5	315	2.5	1.7×10^{-11}	0	1.66×10^{-7}	0
62430-70-0		$MeONH_2$		10.8	310	0.5			6.2×10^{-8}	
62430-71-1		NH_2NH_2		8.4–10.5	310	1.0			1.5×10^{-8}	0
62430-72-2		Butylamine		10.8–11.7	300	0.63				310[c]
62430-73-3		Glycine		10.6	300	0.9				380
62430-74-4	NMN^+	NH_2OH		9.1–10.7	313	2.5	1.7×10^{-11}	0	1.6×10^{-7}	0
62430-75-5	$APAD^+$	NH_2OH	73 (8.7)	8.7–9.8	325	2.5	2.1×10^{-9}	3.0	1.9×10^{-5}	0
62430-76-6		NH_2NH_2		8.3–9.4	330	1.0	1.2×10^{-9}	b	5.0×10^{-7}	17 000
62430-77-7	$BzAP^+$	NH_2OH		9.0–10.8	333	2.5	5.7×10^{-10}	0.3	3.7×10^{-7}	0

[a] Equilibrium determinations were made at 25.0 ± 0.1 °C. Rate determinations were made at 25 ± 1 °C at ionic strength 1.25. [b] At pH 9.5 the equilibrium constant could be determined separately as 3.9 ± 1.1. K_{xy} is calculated as $K_{obsd}[H^+]$. [c] Corrected for the ionization of NAD^+ (ref 4).

MeIsonic+ (changing the solvent from 0 to 50% dioxane) causes only a 1.9-fold increase in $K_{xy\epsilon}$ and no change in bandwidth (130-nm half-width).

The reaction of primary amines with pyridinium ions consists of two reactions: (1) a rapid, reversible reaction, (2) a slow, irreversible reaction. The λ_{max} of the products of the second irreversible reaction is greater than that of the first reversible reaction. Though all the reversible amine interactions are weak, the more strongly interacting systems (hydroxylamine and hydrazine) show a pH dependence according to eq 4, and the weakly interacting systems (butylamine) show a pH independence. An example of the pH dependence of hydrazine interaction is shown in Figure 5. In the case of $BzAP^+$ and $APAD^+$, a small non-pH-dependent component is present in the reaction of hydrazine and hydroxylamine. The interaction of butylamine and glycine with $BzAD^+$ was so weak as to be nonmeasurable ($K_{tot\epsilon}$ is less than 0.4). The rate and equilibrium data are collected in Table V.

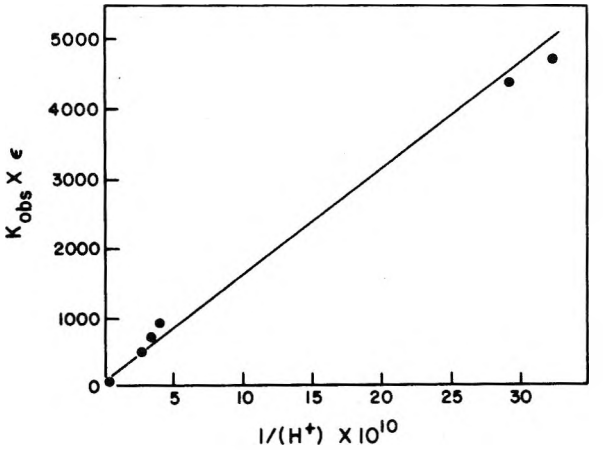


Figure 5. Plot of $K_{tot\epsilon}$ vs. $(H^+)^{-1}$ for the interaction of hydrazine with NAD^+.

Table VI. Association Constants for the Interaction of Imidazole with Pyridinium Ions at 25.0 °C, μ = 0.63 M

Registry no.	Pyridinium ion	λ_{max}, nm	K_{tot}, M^{-1} (pH)[a]	$K_{tot}\epsilon$, M^{-2} cm^{-1} (pH)[a]	$K_{xy}\epsilon$, M^{-1} cm^{-1}	$K_x\epsilon$, M^{-2} cm^{-1}
62430-65-3	NAD^+	305	0.15 ± 0.04(10.1)	84.7 (10.1)	3.8×10^{-9}	
62430-66-4	$APAD^+$	325	0.45 (10.1)	3130 ± 170 (10.1)		
				630 (9.5)	2.5×10^{-7}	89
				270 ± 40 (8.0)		
62475-94-9	$PAAD^+$	325	1.15 ± 0.08(10.1)	11 500 (10.1)	8.4×10^{-7}	982
				1070 (8.0)		
62430-67-5	$BzNic^+$	315		111 ± 2 (9.8)		
				112 ± 2 (9.0)		
				100 (8.0)		
62430-68-6	$BzAP^+$	335		110 (9.8)		
				66 (9.5)		87
				110 (9.0)		
				62 (8.0)		
62461-60-3	$BzCP^+$	335		22 ± 6 (10.0)		

[a] pH values at which the measurement was made are given in parentheses.

Table VII. Association Constants for the Interaction of Various Anions with Pyridinium Ions[a]

Registry no.	Nucleophile	Pyridine nucleotide	μ, M	λ_{max}, nm	$K_{tot}\epsilon$, M^{-2} cm^{-1} (pH)
62430-78-8	N_3^-	NAD^+	1.0	300	201 (9.5)[c]
62430-79-9	SCN^-		1.0	300	862 (5.85)
62430-80-2	Thiourea		0.6	315	260 (10.8)
62430-81-3	SCN^-	$APAD^+$	1.0	290	873 (3.6)
	SCN^-		1.0	300	659 (5.8)
62430-82-4	SCN^-	$PAAD^+$	1.0	300	344 (5.9)
62430-83-5	SCN^-	$MeNic^+$	1.0	320	190 (6.2)
	SCN^-		1.0	300	547 (5.8)
62461-61-4	SCN^-	$MeIsoNic^+$	1.0	300	617 (5.9)
			1.0	310	477 (5.9)

[a] Measured at 25.0 ± 0.1 °C.

The interaction of imidazole can be broken down into K and ϵ in the case of the NAD^+, $APAD^+$, and $PAAD^+$ reactions at higher pH. At lower pH only $K_{tot}\epsilon$ could be measured. In the case of $APAD^+$, a pH study was carried out on $K_{tot}\epsilon$ and both pH-independent and OH^--dependent terms $K_b\epsilon$ and $K_{xy}\epsilon$, respectively, were found. The $K_{tot}\epsilon$ values for $BzNic^+$ and $BzAP^+$ are independent of pH. A summary of these results is shown in Table VI. In contrast to the reaction of primary amines, the reaction of imidazole, a secondary amine, is entirely reversible.

The interactions of various weakly interacting anions are pH independent. These data are collected in Table VII. An attempt was made to measure the equilibrium of hydroperoxide anion, HO_2^-, with NAD^+. The equilibrium is very slowly established, and because it is necessary to use alkaline solutions (pH 11) to get appreciable concentrations of HO_2^- (pK = 11.5), competing hydrolysis reactions take place. A new band at 320 nm could be seen in alkaline solutions containing H_2O_2, which could not be seen in the control alkaline solutions. The rate of reaction of HO_2^- with NAD^+ is estimated to be 2 M^{-1} s^{-1}.

Those nucleophiles which do not form measurable complexes with NAD^+ ($K_{tot}\epsilon < 250$ M^{-2} cm^{-1}, or no distinct λ_{max}) are thiourea, urea, thiosulfate, nitrite, and phenyl sulfinite.

Discussion

Strong nucleophiles interact with the pyridinium ring to form 1–4 adducts as is indicated by (a) the NMR spectrum of the TG and the SO_3^{2-} adducts[13] and (b) deuterium exchange in the 4 position in heavy water of the cyanide adduct.[24]

In Table VIII are compiled rate and equilibrium data for nucleophilic interactions with NAD^+. The rate data for cyanide were taken from Lindquist and Cordes,[25a] and the rate data for hydroxide were taken from our previous work.[4,33] The order of reactivity follows the series $RS^- > SO_3^{2-} > OH^- > CN^-$, while the order of affinity follows the series $CN^- > SO_3^{2-} > RS^- > OH^-$. The reactivity order does not follow the affinity order, and neither the reactivity nor affinity order follows the basicity order. This situation is analogous to the cases of nucleophilic interactions with organic cations, such as triarylcarbonium ions, tropylium ions, and diazonium ions. The rates of the above reactions are all correlated by eq 10 with N_+, a parameter characteristic only of the nucleophile.[25b] The order of reactivity of the nucleophiles in Table VIII follows the N_+ series $RS^- > SO_3^{2-} > NH_2NH_2 > NH_2OH > OH^- > CN^-$. However, we do not get a linear correlation with N_+ according to eq 10. The points for CN^- and SO_3^{2-} give a slope of 0.96. On the other hand, the points for all the nucleophiles except SO_3^{2-} give a slope of 2.05 with an R^2 value of 0.998.

$$\log k_1 = \log k_0 + N_+ \quad (10)$$

The original interpretation[25b] of the constant selectivity of reactive and unreactive electrophiles toward nucleophiles according to eq 10 was that the transition states for the reactions are very reactant-like, lying somewhere between the solvent-separated and intimate ion pair structures. It was assumed that the cation in the transition state has its solvent shell little perturbed from the ground-state solvent shell. The inherent property of the nucleophile, N_+, was interpreted as the degree of solvation energies of the nucleophiles. If eq 10 is followed by both strong and weak electrophiles, then not

Table VIII. Equilibrium Constants and First-Order Rate Constants for the Interaction of Nucleophiles with NAD+[a]

Nucleophile	pK_a[k]	Log k_1	Log K_b	Log K_{xy}	P_+, log $K_{xy\epsilon}$	N_+[b]	γ	$\gamma + 7.9\sigma_I$
CN^-	9.4	0.74[d]	2.34	−7.06	−3.34	3.67	2.44	7.02
SO_3^{2-}	7.0	3.3	1.61	−5.39	−1.74	7.90	4.02	9.78
OH^-	15.75	1.45[f]	−0.75	−16.50	−12.12	4.75	−3.58	−1.60
TG	10.3	>4	0.55	−9.75	−5.81	9.06[c]	+0.53	2.50
ME	9.50	>4	0.26	−9.24	−5.54		+0.35	2.32
NH_2OH	(5.97)[g]	2.2	*h*	−10.76	−6.78	5.05	+1.24	2.42
$MeONH_2$	(4.60)[g]	1.38	*h*	−11.2[i]	−7.2			
NH_2NH_2	(8.1)[g]	3.3	*h*	−11.8[i]	−7.8	5.66	+0.81	2.00
N_3^-	4.72				2.30	7.6		
SCN^-	0.85				2.94			
Thiourea	*g*				2.42[j]			
ImH	14.52				−8.1	3.66		

[a] Determined at 25 ± 2 °C, ionic strength at 0.6 M, except for hydroxylamine where the ionic strength was 1.2 M. Units of k_N are $M^{-1}\,s^{-1}$. Units of K_b are M^{-1}. [b] N_+ values are from Ritchie.[25c] [c] N_+ value for TG was determined here by observing its rate of reaction with malachite green.[25b] [d] From Lindquist and Cordes.[25a] [e] Estimated value. [f] Calculated from data in Johnson and Morrison,[4] and Guilbert and Johnson.[33] [g] The value given is for ionization from RNH_3^+; the ionization constant of RNH_2 is too small to measure. [h] Cannot measure separately. [i] Estimated. [j] Log $K_{tot\epsilon}$. [k] pK_a values from Jencks.[21]

only is there a constant selectivity of carbonium ions for nucleophiles, but there is also a constant selectivity of nucleophiles (both strong and weak) for carbonium ions. In eq 10 k_0 is the first-order water rate constant, and is a measure of the reactivity of the carbonium ion. For a single nucleophile N_1 reacting with a series of carbonium ions $E_1, E_2, E_3, \ldots, E_x$, eq 11 follows, where $k_{N_1E_x}$ are the rate constants for the interaction of N_1 with the series of $E_1, \ldots, E_x$, $N_+(N_1)$ is the N_+ value for N_1, and k_{0E_x} is the first-order rate constant for the interaction of water with E_x (the reactivity of E_x).

$$\log k_{N_1E_x} = N_+(N_1) + \log k_{0E_x} \qquad (11)$$

The dichotomy of mechanisitic interpretations according to eq 10 and 11 has been clarified by the treatment of Pross,[26a] which takes into account the desolvation of both the cation and the nucleophile. The constant selectivity of electrophiles or nucleophiles is the result of the cancellation of two opposing effects. (a) The selectivity of strongly solvated reactive electrophiles and nucleophiles will be reduced in comparison to weakly solvated, unreactive electrophiles and nucleophiles, owing to the necessity of desolvating the ground state to reach the transition state structure. (b) The selectivity of a strong electrophile or nucleophile will be decreased in comparison to a weak electrophile or nucleophile, due to the more reactant-like transition state for the strong reagents.

It is of interest to look into the nature of the transition state structure as a function of the nucleophile. From linear free energy correlations of k_1 with K_1 the degree of product-likeness can be calculated for various nucleophiles. In the case of the reactions of cyanide and sulfite with nicotinamide cations, these values are 54 and 94%, respectively.[13,25c] For the reaction of hydroxide with quinolinium ions, this value is 36%.[26b] Calculations from the data of the reaction of nucleophiles with cations which follow N_+ give the following product likenesses: hydroxide–tropylium ion, 70%;[26b] cyanide–diazonium ion, 65%;[26c] hydroxide–diazonium ion, 32%;[26c] amines–triaryl carbonium ion, 82%.[26d] Since variations of transition state structure are found in both the cations which follow N_+ and in pyridinium ions, it is unlikely that the marked variation of transition state structure in the pyridinium ion series results in the poor N_+ correlation. Recently, ester carbonyl addition reaction rates have been correlated with N_+.[25c] This means that the interpretations of the reaction mechanism for electrophile–nucleophile interaction can be extended to uncharged electrophiles.

The equilibrium constants for addition to the pyridinium

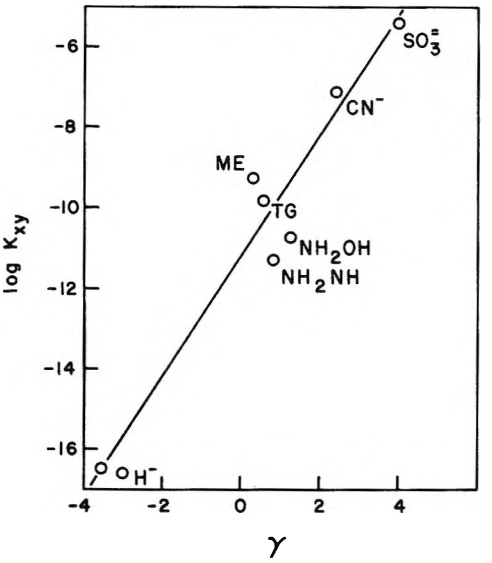
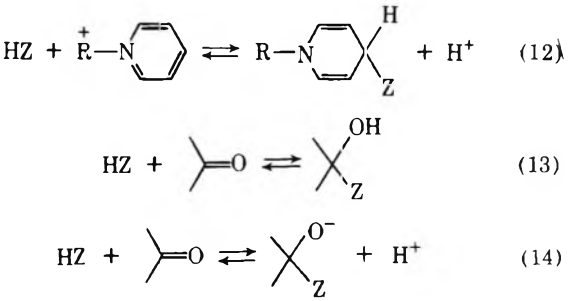


Figure 6. Plot of log K_{xy} vs. γ for nucleophilic addition to NAD+.

ring, eq 12, can be correlated with the equilibrium constants for addition to the carbonyl carbon, eq 13. The latter reactivity



is related to the γ value.[27] The value of the equilibrium constant for eq 12 is given by K_{xy}. A plot of log K_{xy} vs. γ gives an intercept of −11.2, a slope of 1.45, and an R^2 value of 0.90, as seen in Figure 6. A similar plot of log $K_{xy\epsilon}$ vs. γ gives an intercept of −7.28, a slope of 1.35, and an R^2 value of 0.90. Because the relationship between eq 12 and 13 does not have the same stoichiometry, the relationship between eq 12 and 14, which have the same stoichiometry, was tested. The ionization of alcohols is related to $\Sigma\sigma_I$ values.[28] In the present case of varying the Z substituent only, the free energy of eq 14 is given by $\gamma + 7.9\sigma_I$. Equations 14 and 12 are no better correlated than

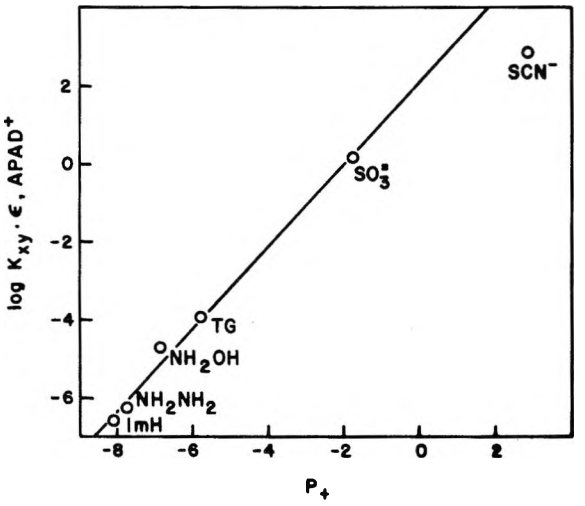


Figure 7. Plot of log $K_{xy\epsilon}$ for APAD$^+$ vs. P_+ (log $K_{xy\epsilon}$ for NAD$^+$).

eq 13 and 12. A plot of log K_{xy} vs. $\gamma + 7.9\sigma_I$ gives an intercept of -13.2, a slope of 0.89, and an R^2 value of 0.87. A plot of log $K_{xy\epsilon}$ vs. $\gamma + 7.9\sigma_I$ gives an intercept of -9.09, a slope of 0.84, and an R^2 value of 0.88.

The equilibrium constants for the addition of nucleophiles to pyridinium ions are better correlated to the equilibrium constants of the same nucleophiles to other pyridinium ions than to the carbonyl carbon. For example, a plot of log $K_{xy\epsilon}$ for APAD$^+$ vs. log $K_{xy\epsilon}$ for NAD$^+$ yields an intercept of 2.05, a slope of 1.05, and an R^2 value of 0.99, when all the nucleophiles except CNS$^-$ in Table VIII are included (Figure 7). Including CNS$^-$, the intercept is 0.86, the slope is 0.87, and the R^2 value is 0.98 (Figure 7). The value log $K_{xy\epsilon}$ is suggested as a better measure of equilibrium nucleophilic activity to the pyridinium ring, and is given the label P_+. Thiocyanate, undoubtedly, interacts by a charge transfer interaction, which is different from the covalent interaction of the other nucleophiles in Table VIII. The negative deviation of CNS$^-$ in Figure 7 suggests a lesser sensitivity to electrophilic character of the pyridinium to charge transfer interaction than to covalent interaction.

The K_{eq} of interaction of a nitrouracil with anionic reagents, Z$^-$, and of quinazolinium ion with HZ both correlate with γ.[30] The rate constants for the latter reaction were found to correlate with basicity, with hydroxide giving a negative deviation. For those nucleophiles in the present study having known N_+ values (5), we found that the reactivity order follows N_+, with a positive deviation for hydroxide. The correlation of K_{eq} with γ in the above examples of heteroaromatic addition reaction and in the present example of pyridinium ion reaction is expected, because γ measures the relative affinity of Z$^-$ for H, as compared to the hydroxy carbon atom (in the case of carbonyl addition) or dihydroheteroaromatic carbon (in the case of heteroaromatic ring addition). The different correlations of the rates of reaction represent a point of difference between our studies and those of Pitman.[30] Too few rate constants were available from either study for a complete description of this process.

There appears to exist a continuum of types of interaction, from covalent interaction in the case of strongly interacting systems to charge transfer complexation in the case of weakly interacting systems. In the case of thiolate complexation with pyridinium compounds, the solvent effect on $K_{obsd\epsilon}$ can be used to diagnose the presence of a contact charge transfer complex or a covalent adduct. It is useful to compare MeNic$^+$ and MeIsonic$^+$, because the latter compound can only form charge transfer complexes and not covalent complexes, while the former can form both types of complexes.[31] A change in solvent from 0 to 50% dioxane causes a sixfold increase in $K_{obsd\epsilon}$ and a dramatic increase in the sharpness of the band for MeNic$^+$. It only causes a 1.9-fold increase in $K_{obsd\epsilon}$, and no change in the bandwidth for MeIsonic$^+$, which cannot undergo ring addition. The weak interaction for MeNic$^+$ in water probably represents a charge-transfer phenomenon, which changes to a covalent complex formation in solvents of lower dielectric constant. In the case of the stronger interaction of thioglycolate with NAD$^+$, a structural study was made by NMR spectroscopy. In the presence of mercaptide, the pyridinium bands of NAD$^+$ decreased somewhat, and new signals typical of the dihydropyridine structure appeared. Weakly basic amines, such as imidazole, which react with NAD$^+$ in a pH-independent reaction, represent another example of the charge transfer interaction.

The effect of ring substituents on the pyridinium ring is to change the transition state structure of the ring addition reaction. In the case of sulfite addition to the nicotinamide ring, it was previously found that the transition state is 94% productlike. [13]In comparing the rate and equilibrium constants for sulfite addition to the acetylpyridine vs. the nicotinamide ring, a larger effect is observed for the equilibrium constant (35- to 120-fold more favorable for the acetylpyridine derivative) than for the rate constant (6- to 7-fold faster for the acetylpyridine derivative). This larger equilibrium-than-rate effect is explicable for the acetylpyridine derivatives, by a less productlike transition state than in the case of the nicotinamide series.[32] The reactivity–selectivity rules of chemistry appear to be operating, in the case of addition to the pyridinium ring.

The effect of boration of the riboside linkage adjacent to the pyridinium ring[13] has about the same effect on ring addition reactions for all of the nucleotides, regardless of the structure of the pyridinium ring or the nucleotide (NAD$^+$ vs. APAD$^+$ or NADP, etc.). In all cases the ring addition equilibrium is reduced three- to sevenfold.

In conclusion, we have found that the affinity of nucleophiles for the pyridinium ring correlates with γ, the affinity of nucleophiles for the carbonyl carbon. A better correlation is obtained with P_+, the affinity of nucleophiles with the pyridinium ring. The rate of nucleophilic addition follows the N_+ order, but does not follow eq 10. These correlations are useful in predicting the inhibition constants and rate of inhibition of pyridine nucleotide requiring dehydrogenases, where the mechanism of inhibition is complex formation with NAD$^+$ or NADP.[34]

Acknowledgment. The work of Mr. Harry Silvis in obtaining the equilibrium constants of the NAD$^+$–RSH system is gratefully acknowledged.

Registry No.—BzAP$^+$Cl$^-$, 5096-12-8; benzyl chloride, 100-44-7; 3-acetylpyridine, 350-03-8; MeAP$^+$I$^-$, 6965-62-4; methyl iodide, 74-88-4; MeCP$^+$I$^-$, 4685-10-3; MeNic$^+$I$^-$, 6456-44-6; MeIsonic$^+$I$^-$, 5613-08-1; methyl nicotinate, 93-60-7; Nic, 59-67-6; IsoNic, 55-22-1; BzCP$^+$Cl$^-$, 7146-29-4; BzNic$^+$Cl$^-$, 5096-13-9; phenylboronic acid, 98-80-6; boric acid, 10043-35-3.

References and Notes

(1) This work was supported by Public Health Service Grant GM-16856.

(2) Abbreviations used follow: ZH, a nucleophile; MeNic$^+$, 1-methylnicotinamide cation; BzNic$^+$, 1-benzylnicotinamide cation; MeIsonic$^+$, 1-methylisonicotinamide cation; PAAD$^+$, pyridine-3-aldehyde adenine dinucleotide; APAD$^+$, 3-acetylpyridine adenine dinucleotide; BzAP$^+$, 1-benzyl-3-acetylpyridinium ion; MeAP$^+$, 1-methyl-3-acetylpyridinium iodide, NAD$^+$, β-nicotinamide adenine dinucleotide; NADB, borate adduct of NAD$^+$; NADSO$_3^-$, sulfite adduct of NAD$^+$; NADBSO$_3^-$, NAD$^+$ complexed with borate and sulfite; NMN, nicotinamide adenine mononucleotide; NMNSO$_3^-$, sulfite adduct of NMN$^+$; NADP, nicotinamide adenine dinucleotide phosphate; deamino APAD$^+$, 3-acetylpyridine deaminoadenine dinucleotide; ThioNAD$^+$, thionicotinamide adenine dinucleotide; deamino-NAD$^+$, nicotinamide deaminoadenine dinucleotide; B, borate; PhB, phenylborate; BzCP$^+$, 1-benzyl-3-carboxymethylpyridinium ion; EtOH, ethanol; ME, 2-mercaptoethanol; TG, thioglycolate; Gly, glycine.

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New Routes to Heterobicyclic Ring Systems via Meta-Bridging. 4. Reactions of Nitroquinoline and Dinitropyridine

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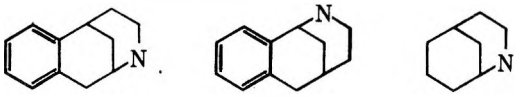
The first examples of heteroaromatic meta-bridging of pyridines and quinolines with amidines and carbanions are described. The effect of aza functionality on the mode of reaction is discussed. Reactions of the corresponding *N*-oxides are also described. The meta-bridged products, highly functionalized aza and diaza bicyclics, result from bis nucleophilic addition of amidines or carbanions to the electron-deficient heterocycles.

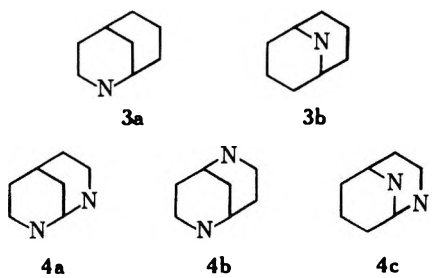
The formation of highly functionalized derivatives of the ring systems **1a**, **1b**, and **2** from reaction of electron-deficient



1a **1b** **2**

naphthalenes and benzenes with amidines has recently been reported.[2,3] Such products are readily formed by cyclization of anionic σ complex (Meisenheimer complex) intermediates which result from nucleophilic addition of amidine to the aromatic, a reaction we have termed "meta-bridging".[13] This type of reaction proceeds in two steps and is distinctly different from the 1,3-dipolar cycloadditions reported by Katritzky[1b] which also yield meta-bridged products.

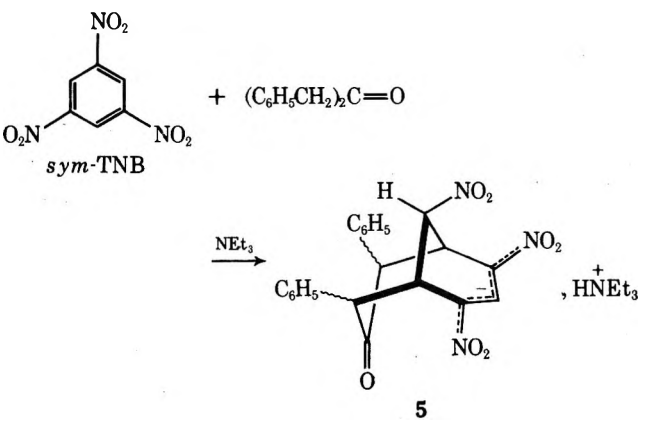
Electron-deficient pyridines form anionic σ complexes[4-7]



3a **3b** **4a** **4b** **4c**

and the activating effect of heterocyclic nitrogen in nucleophilic aromatic substitution has been of interest in this regard.[8] It was thus of interest to investigate the meta-bridging reactions of electron-deficient pyridines. With such substrates, meta-bridging with carbanions could yield either of the ring systems **3a** or **3b**, whereas with amidines **4a**, **4b**, or **4c** could result.

The meta-bridging reactivity of dibenzyl ketone with *sym*-trinitrobenzene (TNB) in the presence of triethylamine has been studied in some detail.[9] The reaction occurring has been well characterized and leads to the bridged product **5**. Isomers with both cis and trans phenyls have been isolated,[9]



sym-TNB **5**

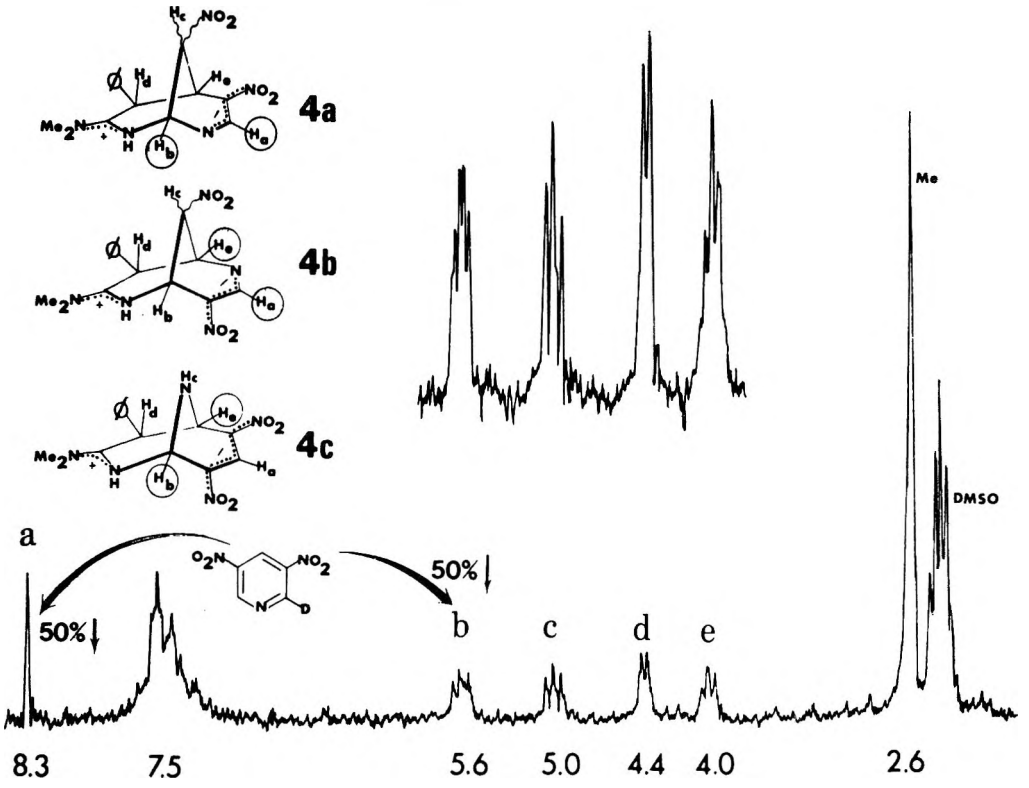
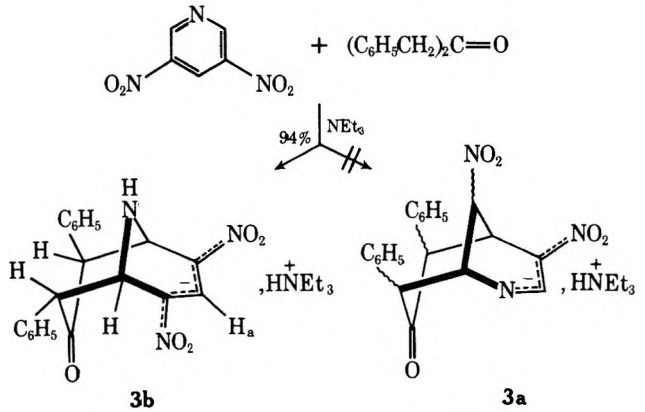


Figure 1.

and stereochemistry at the one carbon bridge has been determined by x-ray crystallography in the cis isomer.[10]

Reaction of 3,5-dinitropyridine (DNP) with dibenzyl ketone and triethylamine under conditions similar to those used in the reaction with TNB gave bridged ion **3b** in 94% yield. There was no evidence for **3a**. The visible spectrum of **3b** showed a characteristic 517-nm maximum of the nitropropene nitronate function.[4,9] Confirmation of structure **3b** is provided by the

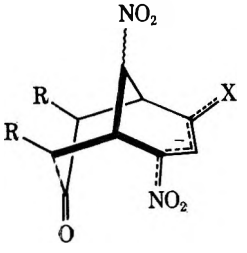


3b **3a**

^{1}H NMR spectrum, which shows the expected low-field singlet for H_a at δ 8.6. Trans orientation of the phenyl groups is evidenced by one distinct five-proton multiplet at δ 7.2, as well as two- and three-proton multiplets centered at δ 7.8 and 7.4. The remainder of the spectrum is recorded in the Experimental Section.

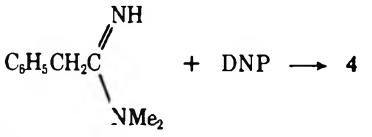
It is of interest that not even a trace of **3a** could be detected in the product. All the 1-X-substituted 3,5-dinitrobenzenes (X less electron withdrawing than NO_2) bridged previously *always* yielded ions in which the X function was part of the delocalized negative charge, i.e., as in **6**.[1] At present we have no explanation for this change in reactivity pattern.

Mixing equivalent quantities of DNP and α-phenyl-*N,N*-dimethylacetamidine in ethanol results in an orange solution with a visible maximum at 506 nm characteristic of



6

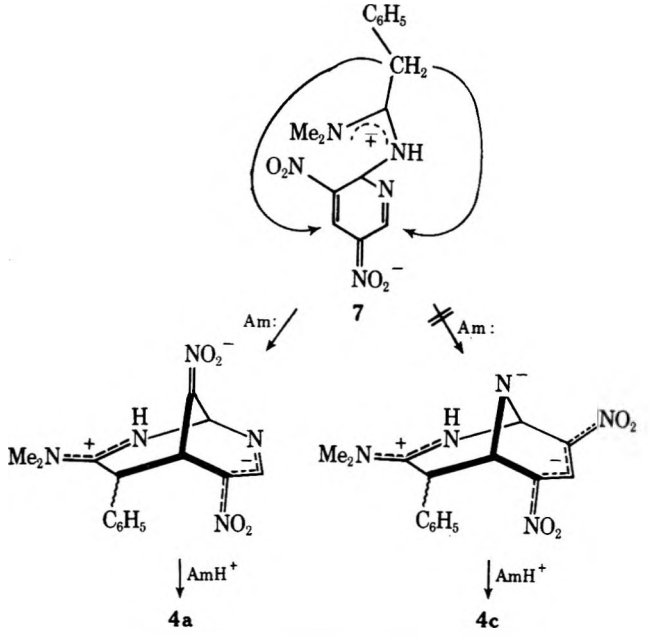
dinitropyridine σ complex intermediates.[4-7] Crystals of **4** are formed after 3 h and these analyze correctly for a 1:1 adduct of the amidine and DNP. They have a strong maximum at 365 nm (Me_2SO).



The ^{1}H NMR spectrum of **4** (Me_2SO-d_6) is shown in Figure 1. Based on analogous reactions of α-phenyl-*N,N*-dimethylacetamidine with electron-deficient benzenes[2,3] **4a**, **4b**, and **4c** are all possible products. Structure **4c** can be ruled out because the nitropropene nitronate functionality in such a product would absorb strongly in the region of 500 ± 20 nm.[2,3,11] Deuterium substitution at C-2 in DNP confirms that the product is not **4c** (vide infra). A distinction between **4a** and **4b** cannot be made on the basis of the visible and ^{1}H NMR spectra as the chemical shift assignments, made from comparisons with spectra of the adduct of α-phenyl-*N,N*-dimethylacetamidine and TNB,[3] will fit either structure. Only in **4a**, however, do both H_a and H_b diminish by 50% when 2-deuterio-DNP is used as the starting material. These peaks do diminish in intensity as expected (see Figure 1 and Experimental Section).

The formation of **4a** is in accord with the reactivity of DNP in nucleophilic addition reactions[7] and it is formed via the expected cyclization pathway.[1] In alcoholic solutions, nu-

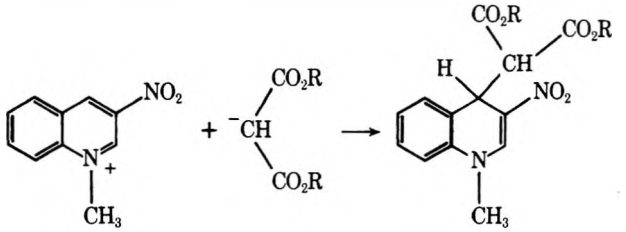
cleophilic addition to C-4 of DNP is difficult to detect.[7] The adducts formed result from attack at C-2. We have previously established that α-phenyl-*N,N*-dimethylacetamidine attacks electron-deficient aromatics initially via nitrogen,[3] and the intermediate complex expected is thus **7**. All our previous studies on related systems,[1,11] i.e., reactions of 1-X-substituted 3,5-dinitrobenzenes, show that the mode of cyclization in unsymmetrical complexes such as **7** is controlled by the ability of the ortho substituent (NO_2 or =N— in **7**) to accommodate accumulating negative charge in the transition state for the cyclization step.[1] This yields the kinetically controlled product. The observation that all 1-X-3,5-dinitrobenzenes thus bridge to yield ions in which the X function bears formal charge in the *final* product, i.e., **6** (X = CN, CO_2R, COR), is



in accord with the formation of **4a** rather than **4c**.[1,11] It is in this regard that the reaction of DNP and dibenzyl ketone, which gives the unexpected product, i.e., **3b** and not **3a**, seems puzzling.

The reactions of both α-phenoxy-*N,N*-dimethylacetamidine and *N,N*-dimethylpropionamidine with DNP yield bridged ions which are in all respects analogous to that obtained with α-phenyl-*N,N*-dimethylacetamidine (see Experimental Section).

In considering the reactivity of dinitropyridines in meta-bridging, we supposed that a single nitro group would be adequate to activate quinoline in such a bridging reaction. It has been reported previously that 3-nitroquinolinium methiodide reacts with carbanions to yield addition products.[12] It has also



been reported that *N*-ethoxyquinolinium iodide **8** reacts with the enamine of cyclohexanone and morpholine, **9**, to give **10**.[13] Examination of **10** shows that it is a quinoline which has been meta-bridged by the enamine. Since there is no nitro group on C-3 in **8**, charge localization at this site associated with the intramolecular cyclization step is accommodated by reaction with a second equivalent of starting quinolinium salt. We presumed that the presence of a nitro group at C-3 of the quinoline ring system would provide a substrate, **11**, which was

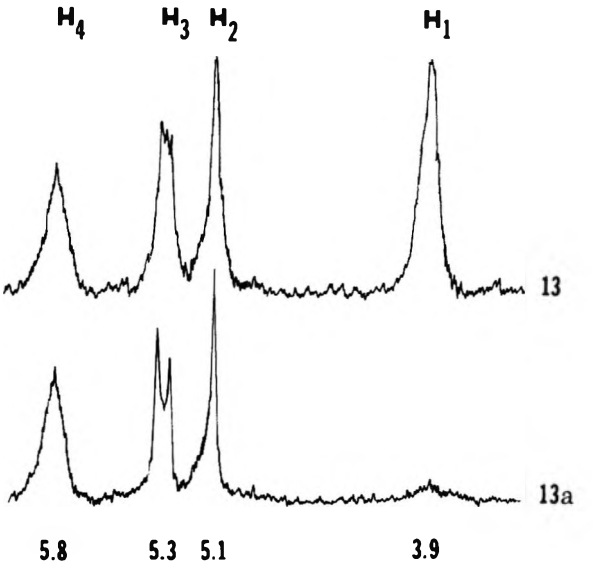
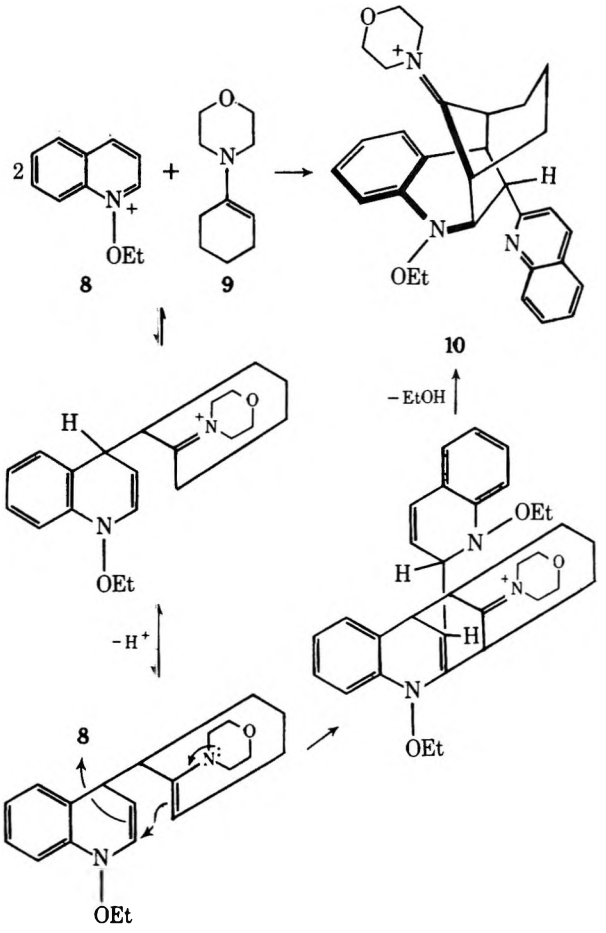
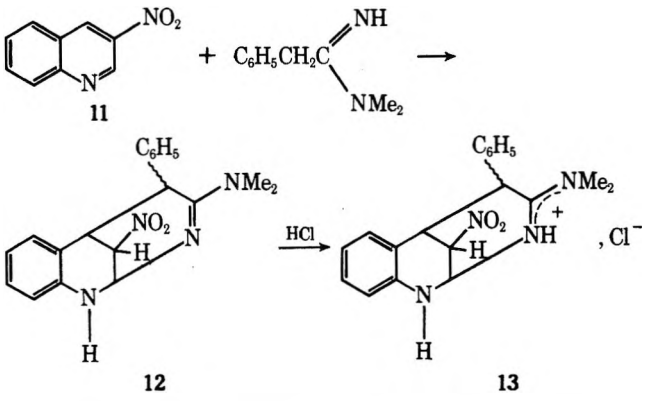


Figure 2.

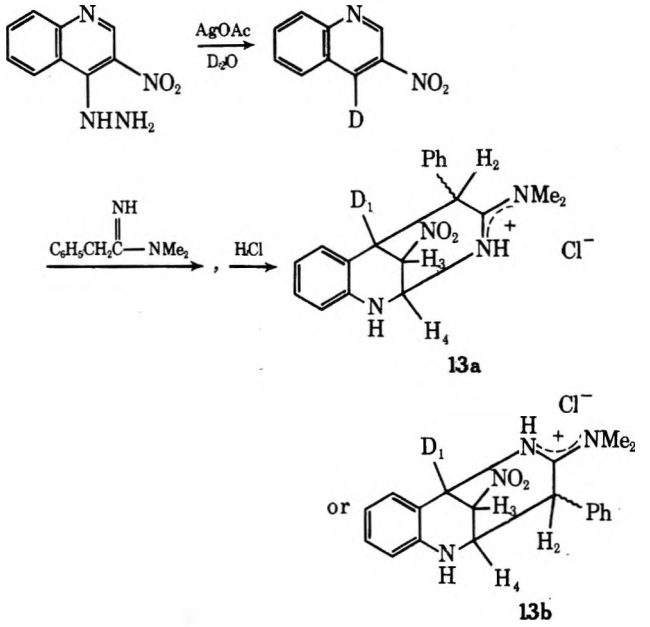


sufficiently reactive to undergo bridging without first being quaternized, and which would not add a second equivalent of electrophilic aromatic. Reaction of **11** with α-phenyl-*N,N*-dimethylacetamidine yielded the bridged product **12** as white crystals, mp 138–139 °C. These readily reverted to starting material when dissolved in Me_2SO. Addition of methanolic HCl to **12** yields the stable hydrochloride salt **13**, mp 195–196 °C. The assignment of structures **12** and **13** is based on the ^1H NMR spectra (see Experimental Section), elemental analyses, and comparative spectral data with naphthalene and pyridine adducts.[3] Such comparative analysis has been extensive[3] and it provides substantial evidence that amidine nitrogen has attacked C-2 of quinoline and not C-4.



11 12 13

In order to confirm the structural assignment for **13**, C-4 deuterated **11** was prepared from 4-hydrazino-3-nitroquinoline[22] by reaction of the latter with AgOAc in D_2O. The two possible products resulting from reaction of this deuterated analogue are **13a** and **13b**. The four one-proton absorptions (H_1–H_4) in **13** which appear between δ 3.9 and 6.0 are shown in Figure 2. The H-1 and H-4 peaks are respectively the high- and low-field absorptions.[3] The partial spectrum of the adduct

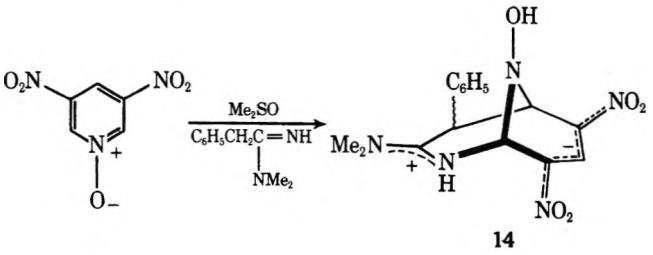


13a

13b

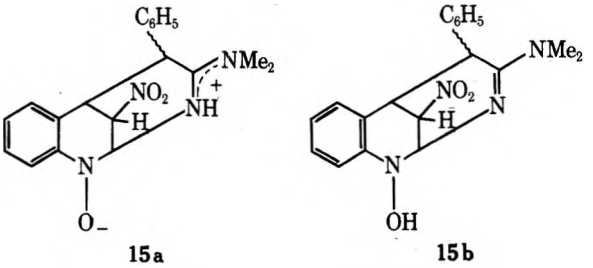
prepared from C-4 deuterated **11** is shown beneath that of **13** in Figure 2. It is clearly consistent only with **13a**, confirming amidine nitrogen attack at C-2 of **11**. The adduct **13** is a strong CNS depressant in mice.[14] Pharmacological data will be reported elsewhere.

It might be expected that 3,5-dinitropyridine and 3-nitroquinoline *N*-oxides would also serve as reactive heteroaromatics, and thus be quite susceptible to nucleophilic attack and meta-bridging. Thus, reaction of 3,5-dinitropyridine *N*-oxide with α-phenyl-*N*,*N*-dimethylacetamidine in Me_2SO yields a solution with ^1H NMR absorptions consistent with formation of the bridged ion **14** (see Experimental Section).



14

All attempts to isolate this product failed, although it is quite stable in Me_2SO in the absence of air. The analogous ion, **15**,



15a 15b

readily forms when 3-nitroquinoline *N*-oxide reacts with α-phenyl-*N*,*N*-dimethylacetamidine in Me_2SO. This product could be either **15a** or **15b** as the ^1H NMR spectrum is consistent with either structure.

Experimental Section

All melting points are uncorrected. ^1H NMR spectra were run on JEOL C-60 HL and MH-100 spectrometers with Me_4Si as an internal reference. Visible and ultraviolet spectra were recorded on a Perkin-Elmer Model 402 UV–visible spectrophotometer. Infrared spectra were recorded on a Perkin-Elmer Model 237 B infrared spectrophotometer. Elemental analyses were cross checked by Galbraith Laboratories, Inc., Knoxville, Tenn., G. I. Robertson Laboratories, Florham Park, N.J., and Integral Microanalytical Laboratories, Inc., Raleigh, N.C.

Preparation of Precursor Aromatics. Both 3,5-dinitropyridine and 2-deuterio-3,5-dinitropyridine were prepared by reported methods.[15,16] There are three published procedures for the preparation of 3-nitroquinoline.[17–19] We have prepared it by each method and found that the cyclization of 2-nitro-2-formylethylideneaniline as described by Morley and Simpson[17] gave the best yields (41%).

Both 3,5-dinitropyridine *N*-oxide and 3-nitroquinoline *N*-oxide were also prepared by published methods.[20,21]

Meta-Bridging Reactions. Preparation of 3b. To a stirred mixture of 0.383 g of 3,5-dinitropyridine and 1.36 g of dibenzyl ketone at 60 ° C was added 0.5 mL of triethylamine. In about 5 min the mixture gelled. Heating to 75 °C with an additional 0.3 mL of amine did not effect dissolution. After an additional 72 h at 50 °C anhydrous ether was added to the gel and the mixture was rapidly stirred for 2 h. The ether was decanted from the solid and a fresh portion of ether was added. After stirring for an additional 2 h the mixture was filtered to give 1.01 g (94%) of an orange powder which when recrystallized from methanol gave orange crystals, mp 119.5–120.5 °C, analyzing correctly $C_{26}H_{32}N_4O_5$: C, 64.98; H, 6.71; N, 11.66. Found: C, 64.85; H, 6.88; N, 11.57.

In Me_2SO **3b** shows absorption maxima at 304 and 517 nm. IR absorption bands occur at 3315, 3020, 1690, 1555, 1470, 1425, 1305, 1250, 1215, 1190, 1130, 1090, 825, 745, and 695 cm^{-1}. The ^1H NMR spectrum (Me_2SO-d_6) shows absorptions at δ 8.55 (1 H, s), 7.78 (2 H, m), 7.43 (3 H, m), 7.17 (5 H, m), 5–6 (2 H, br), 4.94 (1 H, d), 4.85 (1 H, br, s), 4.31 (1 H, d), 3.76 (1 H, br, s), 3.12 (6 H, q), and 1.18 (9 H, t).

Preparation of 4a. Solutions of 0.214 g of DNP in 30 mL of anhydrous EtOH and 0.232 g of α-phenyl-*N*,*N*-dimethylacetamidine in 10 mL of anhydrous EtOH were mixed at room temperature. After a few hours yellow crystals precipitated from the solution. These were filtered, washed with anhydrous Et_2O, and dried to give 0.292 g (68%) of **4a**, mp 178–182 °C. In Me_2SO **4a** shows a single absorption maxima at 365 nm. IR absorption bands (KBr) occur at 2700–3200, 1625, 1525, 1450, 1375, 1225, and 1005 cm^{-1}. The ^1H NMR spectrum (Me_2SO-d_6) shows absorptions at δ 2.71 (6 H, s), 3.98 (1 H, t), 4.40 (1 H, d), 4.98 (1 H, t), 5.55 (1 H, t, br), 7.41 (5 H, m), and 8.33 (1 H, s). Anal. Calcd for $C_{15}H_{16}N_5O_4$: C, 54.37; H, 5.17; N, 21.14. Found: C, 54.34; H, 5.23; N, 21,12.

Formation of **4a** also occurs readily in Me_2SO. A solution of 0.23 g of amidine and 0.21 g of DNP in 1 mL of this solvent was allowed to stand for several days. Ether was then added and the solution was stirred for several hours. The crystals which separated were filtered and dried, and melted at 176–179 °C. The electronic, IR, and ^1H NMR spectra are identical with those of **4a** prepared in ethanol.

Deuterated **4a** was prepared using 2-deuterio-3,5-dinitropyridine in the same fashion as with 3,5-dinitropyridine. A solution of 0.054 g of the amidine in 5 mL of anhydrous ethanol was added to 0.058 g of 2-deuterio-DNP in 10 mL of ethanol. After 3 h the crystals which formed were filtered, washed with ethanol, and dried (0.1 mm) at 80 °C for 4 h to give 0.037 g (33%) of product. The ^1H NMR spectrum of this material in Me_2SO-d_6 shows absorptions at δ 2.76 (6 H, s), 4.03 (1 H, t, J = 1 Hz), 4.43 (1 H, d), 5.00 (1 H, t), 5.58 (0.5 H, dd), 7.41 (5 H, m), and 8.31 (0.5 H, s).

Reaction of DNP and α-Phenoxy-*N,N*-dimethylacetamidine. A solution of 0.33 g of DNP in 0.5 mL of Me_2SO was added to a solution of 0.71 g of the amidine in 1.5 mL of Me_2SO. The mixture was stirred at room temperature for 24 h and then added to 200 mL of anhydrous ether. After stirring for 2 h the ether was decanted off and the residue was stirred with fresh ether. Repeating this procedure two more times provided a brown powder which was filtered and recrystallized from ethanol to yield tan crystals. On standing, the collected ether washings also deposited crystals identical with those obtained from the ethanol recrystallization. A combined yield of 0.54 g (81%) was obtained after drying. The product had mp 183–185 °C and analyzed correctly for $C_{15}H_{16}N_5O_5$: C, 51.87; H, 4.93; N, 20.16. Found: C, 51.93; H, 5.07; N, 20.04. In Me_2SO it shows an absorption at 361 nm. Absorption bands in the IR (KBr) are observed at 2400–3200, 1610, 1580, 1550, 1325, 1230, 1215, and 980 cm^{-1}. The ^1H NMR spectrum (Me_2SO-d_6) shows absorptions at δ 2.88 (6 H, s), 4.35 (1 H, m), 5.46 (3 H, m), 7.42 (5 H, br, s), and 8.30 (1 H, s).

Reaction of DNP and *N,N*-Dimethylpropionamidine. A solution of 0.203 g of DNP in 30 mL of EtOH was added to 0.13 g of amidine. After 48 h the crystals which formed were filtered, stirred in anhydrous Et_2O, and recrystallized from EtOH to give 0.13 g of product, mp 167–168 °C, which analyzed correctly for $C_{10}H_{16}N_5O_4$: C, 44.61; H, 5.62; N, 26.01. Found: C, 44.51; H, 5.64; N, 25.97. The product shows a maximum at 361 nm in Me_2SO and has IR absorptions (KBr) at 1605, 1565, 1540, 1435, 1400, 1375, 1310, 1280, 1235, 1150, 1065, and 885 cm^{-1}. The ^1H NMR spectrum (Me_2SO-d_6) shows absorptions at δ 1.34 (d, 3 H), 2.86 (6 H, s), 3.08 (1 H, m), 3.82 (1 H, m), 5.43 (m, 2 H), and 8.19 (1 H, s).

Preparation of 12. To 0.103 g of 3-nitroquinoline dissolved in 1 mL of Me_2SO was added 0.192 g of α-phenyl-*N,N*-dimethylacetamidine. After 48 h at room temperature the white crystals were filtered off, washed with methanol, and dried at 50 °C to yield 0.14 g (75%) of **12**, mp 138–139 °C. The material rapidly reverted to 3-nitroquinoline and starting amidine when heated in Me_2SO in an attempt to dissolve it in order to take a ^1H NMR spectrum. The IR spectrum (KBr) shows absorption bands at 3190, 2960, 1580, 1540, 1490, 1393, 1305, 1260, 1115, 1030, 915, 750, and 700 cm^{-1}. Anal. Calcd for $C_{19}H_{20}N_4O_2$: C, 67.84; H, 5.99; N, 16.66. Found: C, 67.48; H, 5.94; N, 16.47.

Preparation of 13. The adduct **12**, undissolved, was stirred in methanol and methanolic hydrogen chloride was added dropwise until dissolution was complete. The solvent was evaporated under vacuum and the residue was stirred in ether, filtered, and recrystallized from ethanol–chloroform to give a quantitative yield of **13**, mp 195–196 °C. The IR (KBr) showed absorptions at 2500–3400, 1630, 1600, 1550, 1480, 1260, 1235, 1020, and 750 cm^{-1}. The ^1H NMR spectrum in Me_2SO-d_6 showed absorptions at δ 2.82 (3 H, s), 3.25 (3 H, s), 3.92 (1 H, m), 4.20 (1 H, br), 5.07 (1 H, br, s), 5.30 (1 H, m), 5.80 (1 H, m), 6.85 (2 H, m), 7.19 (2 H, m), 7.54 (5 H, br, s), and 10.98 (1 H, br). Anal. Calcd for $C_{19}H_{21}N_4O_2Cl \cdot \frac{1}{2}H_2O$: C, 59.76; H, 5.81; N, 14.67. Found: C, 59.67; H, 5.47; N, 14.52.

Formation of 14 and 15. Addition of ~0.5 mL of a saturated Me_2SO solution of DNP *N*-oxide to 0.5 mL of a solution containing 2 equiv of α-phenyl-*N,N*-dimethylacetamidine results in a dark orange mixture which has ^1H NMR absorptions consistent with the formation of **14** or its amidinium salt. Resonances for the bridged ion are observed at δ 8.52 (1 H, s), 5.82 (1 H, br, s), and 4.24 (2 H, m). The phenyl and *N*-methyl absorptions overlap those of free amidine (or the cation). Since the phenyl protons integrate for more than 10 H, it is likely that the hydroxyl and amino protons fall in the aromatic multiplet.

Reaction of 3-nitroquinoline *N*-oxide with α-phenyl-*N,N*-dimethylacetamidine in a fashion similar to that for DNP *N*-oxide results in a solution showing single proton multiplets at δ 5.69, 4.91, 4.43, and 3.66 consistent with formation of **15**. Other absorptions overlap free amidine.

Preparation of C-4 Deuterated 11 and Formation of 13a. To a stirred mixture of 3.0 g of AgOAc in 30 mL of D_2O was added 0.8 g of 4-(3-nitroquinolyl)hydrazine.[22] The resulting mixture was refluxed for 2 h and then cooled to room temperature. The mixture was made alkaline with dilute ammonia and extracted with four 50-mL portions of chloroform. After drying the extracts with sodium sulfate and removal of the chloroform the residue obtained was recrystallized from ethanol to give 0.48 g of product, mp 125–127 °C. The ^1H NMR spectrum (Me_2SO-d_6) shows only a sharp singlet at δ ~9.5 and a four-proton multiplet centered at δ 8.0. The undeuterated 3-nitroquinoline shows two coupled doublets (J = 2.5 Hz) at δ 9.5 and 8.5 as well as the four-proton multiplet centered at δ 8.0.

The preparation of **13a** was carried out in the same way as that for **13**, using C-4 deuterated **11** as the starting aromatic.

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Registry No.—**3b**, 62375-61-5; **4a**, 62375-62-6; **4a** deuterated, 62375-63-7; **4a** phenoxy analogue, 62375-64-8; **4a** α-methyl analogue, 62375-65-9; **11**, 17676-53-3; **11** C-4 deuterated, 62375-66-0; **12**, 62375-67-1; **13**, 62375-68-2; **14**, 62375-69-3; **15b**, 62375-70-6; **22**, 23589-54-0; 3,5-dinitropyridine, 940-06-7; dibenzyl ketone, 102-04-5; triethylamine, 121-44-8; α-phenyl-*N,N*-dimethylacetamidine, 56776-16-0; 2-deuterio-3,5-dinitropyridine, 62375-71-7; α-phenoxy-*N,N*-dimethylacetamidine, 59054-96-5; *N,N*-dimethylpropionamidine, 56776-14-8; DNP *N*-oxide, 62375-72-8; 3-nitroquinoline *N*-oxide, 7433-86-5.

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Intramolecular Cyclizations Leading to Bridgehead Bicyclics. 3. 5,5-Diphenyl-2-thiohydantoin Derivatives

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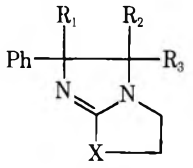
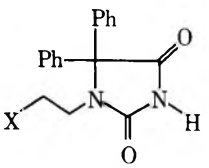
Reaction of 5,5-diphenyl-2-thiohydantoin with 1-bromo-2-chloroethane generated two isomeric imidazo-[2,1-*b*]thiazole derivatives through intramolecular S,N-dialkylation. Chemical, NMR, and mass spectral analyses of the isomeric reaction products confirmed the structures proposed. One of the bicyclic isomers was reduced to an analogue of levamisole.

An earlier investigation of hydantoin alkylating agents as potential central nervous system antitumor agents in this laboratory showed that bicyclic derivatives such as **1a** and **1b**





1a, X = O; R_1 = Ph; R_2 + R_3 = O
b, X = O; R_1 = Ph; R_2 = R_3 = H
c, X = S; R_1 = H; R_2 = R_3 = H
d, X = S; R_1 = Ph; R_2 = R_3 = H
e, X = S; R_1 = Ph; R_2 = H; R_3 = OH

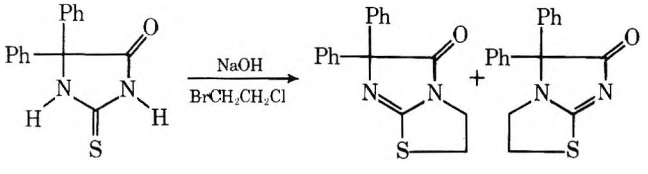
2a, X = SH
b, X = H

were obtainable through an intramolecular alkylation reaction.[2] Levamisole (**1c**), a sulfur-containing analogue of these compounds, is of current clinical interest due to its properties as a general immunostimulant.[3] It, therefore, became of interest to determine whether a similar type intramolecular alkylation would occur when the oxygen atom in the 2 position of the hydantoin ring was replaced by sulfur. If successful, this reaction would yield the basic ring system of levamisole.

Our initial approach to the attempted production of **4** utilized a synthetic pathway similar to that employed for the preparation of **1a**. 2-Bromoethanol was reacted with the sodium salt of **3** in an attempt to produce a hydroxyethyl derivative. While N-3 alkylation was expected, S-alkylation was also a possibility.[4] Although many sets of experimental conditions were employed, the reaction of **3** with 2-chloroethanol, 2-bromoethanol, or 2-bromoethanol tetrahydropyranyl ether produced unreacted **3** or its hydrolysis product 5,5-diphenylhydantoin (DPH).

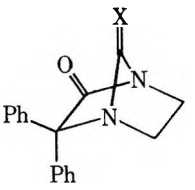
In contrast to the resistance to alkylation found with the 2-haloethanols, 1-bromo-2-chloroethane reacted with the sodium salt of **3** to give a mixture of two products (Scheme I)

Scheme I

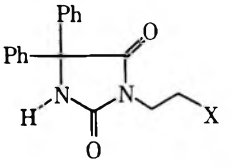


3 **4** **5**

whose elemental compositions and NMR spectra suggested structures **4**, **5**, or **6a**. While it had been possible to differentiate between **1a** and **6b** on the basis of the large difference in the chemical shifts of the two sets of methylene protons[2] in the NMR spectrum of **1a**, it was not possible to do this for **6a** vs. **4** and **5**. The lower electronegativity of sulfur relative to oxygen resulted only in an unseparated multiplet for the four



6a, X = S
b, X = O



7a, X = SH
b, X = H
c, X = Br
d, X = $[SC(NH_2)_2]^+Br^-$

added methylene protons of the two isomeric products. Acid hydrolysis of **6a** would be expected to yield a non-sulfur-containing piperazine derivative by elimination of the thiocarbonyl bridge. Acid hydrolysis of the two isomeric materials gave products which contained sulfur and gave correct elemental analytical values for **2a** or **7a**. The structures of these compounds were assigned by degradation and synthesis experiments.

The major isomer was shown to be **5** by hydrolysis to **2a** and Raney nickel desulfuration of **2a** to the known[5] 1-ethyl-5,5-diphenylhydantoin (**2b**). An identical sample of **2b** was prepared independently from DPH using the general aminomethylation method of Orazi and Corral.[6,7]

Hydrolysis of the minor isomer **4** to the mercaptoethyl derivative **7a** followed by Raney nickel reduction gave 3-ethyl-5,5-diphenylhydantoin (**7b**), a known compound,[8] which was independently synthesized by alkylation of DPH.[8]

Protons attached to the ring nitrogens at the 1 and 3 positions in the hydantoin ring are distinguished by characteristic chemical shifts. In deuteriochloroform, N-1 and N-3 protons absorb at ca. δ 6.7 and 9.3, respectively.[9] The NH absorptions of **7a** (δ 7.0), **7c** (δ 7.6), **2a** (δ 9.4), and **2b** (δ 8.9) are consistent with this general observation. The NH absorption for **7b** in deuteriodimethyl sulfoxide (δ 9.6) is consistent with the literature values for hydantoin protons in that solvent (N-1, δ 9.3; N-3, δ 11.1). All of these protons were exchangeable with deuterium oxide.

The reduction of the hydantoin amide carbonyl by several hydride reducing agents has been reported.[2,10] Based on that work, the most appropriate reagent for the production of the levamisole analogue **1d** from **4** appeared to be sodium bis(2-methoxyethoxy)aluminum hydride. Only partial reduction was achieved with this reagent, however, with the alcohol, **1e**, being produced. This alcohol was successfully reduced to the desired compound, **1d**, by conversion to an iodide with methyltriphenoxyphosphonium iodide and reduction with sodium cyanoborohydride.[11]

Discussion

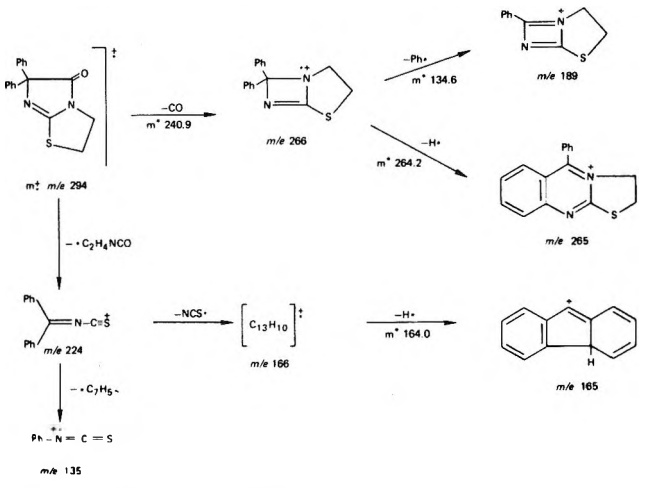
Polish workers,[12,13] using almost identical reaction conditions, claimed that **4** was produced in 70% yield from the reaction of 1,2-dibromoethane with **3**. They did not mention **5**,

the compound found here to be the major isomer. Repetition of their exact experimental conditions gave the same mixture of **4** and **5** described above. The Polish workers' proof of structure rested on elemental analyses, several infrared spectra, and an independent synthesis of **7a** using **7c** and **7d** as intermediates. We repeated their synthesis of **7a** and in several cases obtained products with different melting points. Since in most instances the melting point was the only item given for comparison,[12] we further characterized the compounds mass spectrometrically.

Molecular ions of high to moderate abundance were present for all the compounds examined (see Experimental Section). Mass spectrometry also offered a rapid and facile method for determining the type and position of nitrogen substitution in this series since fragmentation of these compounds was analogous to that of 1- and 3-methyl 5,5-disubstituted hydantoins.[14] The 3-substituted hydantoins (e.g., **7b** and **7c**) exhibited a more facile loss of carbon monoxide (M − 28) and HCO (M − 29) from their molecular ions than did the corresponding 1-alkylhydantoins (e.g., **2b**). Since the N-3 position of the hydantoin ring appeared to be involved in extrusion of isocyanic acid (HNCO, 43 amu) from the molecular ion,[14] substitution there was also evident from ions corresponding to the loss of a substituted isocyanate but not HNCO. Hydantoins **7b** and **7c** showed strong peaks at *m/e* 209 to indicate the loss of RNCO, while the analogous ion in **2b** (*m/e* 237, base peak) corresponded to loss of HNCO.

Besides an abundant molecular ion at *m/e* 294, the mass spectrum of the minor bicyclic isomer, **4**, possessed diagnostic ions at *m/e* 266, 265, 224, 189, 165, and 135. The rearranged ion responsible for the base peak at *m/e* 265 resulted from successive losses of carbon monoxide and a hydrogen radical in a manner analogous to that observed[2] for the corresponding oxygen analogue **1a**. Scheme II shows the postulated formation and structure of these important ions. The major bicyclic isomer, **5**, like the analogous 1-substituted diphenylhydantoins, did not extrude the elements of CO and HCO as readily as **4** or the corresponding 3-substituted hydantoins. The molecular ion of **5** produced the base peak and, although the fragmentation pattern was similar to that of **4**, distinct differences existed in the relative abundances of the major ions, reflecting the structural isomerism.

Scheme II. Postulated Fragmentation Pathway and Ion Structures for **4**[a]



[a] Metastables (m*) indicative of a decomposition are indicated if observed.

The fragmentation pattern of the levamisole analogue **1d** was quite similar to that reported for the parent compound.[15] Unlike levamisole, phenyl disubstitution on the same carbon atom was also indicated by ions at *m/e* 166 and 165.

Experimental Section[16]

2,3,5,6-Tetrahydro-6,6-diphenylimidazo[2,1-*b*]thiazole (1d). Methyltriphenoxyphosphonium iodide (1.55 g, 3.4 mmol) and **1e** (0.50 g, 1.7 mmol) were stirred at room temperature for 2 h in dry hexamethylphosphoric triamide (5 mL). When sodium cyanoborohydride (0.43 g, 6.8 mmol) was added to the solution, the color of the reaction mixture changed from brown to colorless. After heating for 2 h at 70 °C, the solution was cooled, diluted with chloroform, and extracted with ten 10-mL portions of 10% HCl solution. The HCl extracts were made basic with 10% aqueous sodium hydroxide solution and this solution was extracted with chloroform. The solvent was evaporated and the residue dissolved in ether. The ether solution was washed several times with water and dried over anhydrous sodium sulfate. Removal of the solvent gave a solid which was recrystallized from 70% ethanol to give 0.16 g (33%) of a NBP-negative white solid: mp 146–147.5 °C; IR 1585, 1570, 1270, 1200, 1180, 1165, 1090, 1055, 1015, 980, 855, 770, 745, 700, 660 cm^{-1}; NMR ($CDCl_3$) δ 3.4 (m, 4, CH_2CH_2), 3.80 (s, 2, CH_2), 7.3 (m, 10, aromatic); mass spectrum *m/e* (rel intensity) 280 (M^+, 100), 279 (12), 224 (98), 203 (M − Ph, 84), 176 (59), 166 (11), 165 (40), 121 (20), 117 (10), 77 (14); IRI 2460.

Anal. Calcd for $C_{17}H_{16}N_2S$: C, 72.81; H, 5.76; N, 9.99; S, 11.43. Found: C, 72.66; H, 5.99; N, 10.12; S, 11.34.

2,3,5,6-Tetrahydro-6,6-diphenylimidazo[2,1-*b*]thiazol-5-ol (1e). A solution of **4** (0.40 g, 1.4 mmol) in dry THF (20 mL) was added dropwise to a stirred, room temperature solution of sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) (0.9 mL of 70% solution in benzene, 3 mmol) in dry THF (5 mL). The reaction mixture was refluxed for 1 h and water (5 mL) was added with ice-bath cooling. The solvents were evaporated in vacuo at room temperature and the residue extracted with several portions of chloroform. The combined extracts were washed with a saturated aqueous NaCl solution and dried over anhydrous sodium sulfate. Removal of the solvent gave a solid which was recrystallized from chloroform–benzene to give 0.24 g (59%) of a NBP-negative, white solid: mp 184.5–186.5 °C; IR 3200–3000, 1580, 1560, 1290, 1164, 1090, 1070, 985, 930, 825, 750, 695 cm^{-1}; NMR (Me_2SO-d_6) δ 3.2–3.6 (m, 4, CH_2CH_2), 5.55 (d, *J* = 7 Hz, 1, CHOH), 6.55 (d, *J* = 7 Hz, 1, OH), 7.1–7.6 (m, 10, aromatic); mass spectrum *m/e* (rel intensity) 296 (M^+, 7) 279 (20), 278 (100), 224 (14), 165 (9), 147 (14), 139 (6), 103 (27), 77 (6).

Anal. Calcd for $C_{17}H_{16}N_2OS$: C, 68.88; H, 5.45; N, 9.45; S, 10.82. Found: C, 68.98; H, 5.33; N, 9.34; S, 10.60.

1-(2-Mercaptoethyl)-5,5-diphenylhydantoin (2a). Compound **5** (2.3 g, 0.008 mol) was reacted with HCl and worked up as described above for the preparation of **7a** to give a 2.0 g (82%) of product with mp 190.5–191 °C after recrystallization from ethanol: IR 3150, 1770, 1710, 1325, 1290, 1250, 1220, 1175, 1142, 1105, 1075, 1025, 925, 775, 760, 718, 690 cm^{-1}; NMR ($CDCl_3$) δ 1.05 (t, 1, SH), 1.90 (m, 2, CH_2S), 3.5 (m, 2, CH_2N), 7.4 (s, 10, aromatic), 9.4 (b, 1, NH); mass spectrum *m/e* (rel intensity) 312 (M^+, 13), 265 ($M^+ - CH_2SH$, 42), 222 (9), 194 (8), 187 (12), 165 (12), 104 (11), 91 (100), 77 (14); IRI 2645.

Anal. Calcd for $C_{17}H_{16}N_2O_2S$: C, 65.36; H, 5.17; N, 8.97; S, 10.26. Found: C, 65.36; H, 5.28; N, 8.86; S, 9.99.

1-Ethyl-5,5-diphenylhydantoin (2b). Method A. Compound **2a** (1.00 g, 0.003 mol) was reacted with Raney nickel as described in the preparation of **7b** to give 0.51 g (57%) of product, mp 183.5–184 °C. Recrystallization from 50% ethanol gave white crystals: mp 184.5—185 °C (lit.[5] mp 185–187 °C); IR 3150, 1760, 1720, 1700, 1415, 1340, 1280, 1210, 1130, 1050, 990, 885, 775, 760, 720, 700 cm^{-1}; NMR ($CDCl_3$) δ 0.60 (t, 3 CH_3), 3.40 (q, 2, ch_2), 7.35 (s, 10, aromatic), 8.90 (b, 1, NH); mass spectrum *m/e* (rel intensity) 280 (M^+, 21), 238 (17), 237 (M − HNCO, 100), 209 (30), 208 (87), 203 (M − Ph, 10), 194 (23), 165 (37), 132 (35), 104 (56). 91 (56), 77 (47); IRI 2310.

Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.71; H, 5.61; N, 9.89.

Method B. A 37% aqueous solution of formaldehyde (1.8 g, 0.022 mol) was added to a cooled, stirred suspension of DPH (5.04 g, 0.02 mol), morpholine (1.8 g, 0.02 mol), and methanol (20 mL). The suspension dissolved. After 2 h at room temperature, the solution was evaporated in vacuo. Benzene was added and evaporated several times to remove traces of residual water and the resulting high-viscosity oil was subjected to prolonged high-vacuum treatment. This oil was dissolved in dry DMF (30 ml) and sodium hydride in 50% mineral oil (0.5 g of NaH, 0.02 mol) was added with stirring. After hydrogen evolution had ceased, ethyl iodide (3.30 g, 0.02 mol) was added and the solution was stirred for 24 h. The solvent was removed, the residue was washed with hexane, and the residual hexane was removed in vacuo. The residue was stirred with 5% aqueous NaOH solution (100 mL) for 2 h. Insoluble material was filtered. Acidification with concentrated HCl gave the product which was recrystallized from 50%

aqueous ethanol to give 1.98 g (36%) of white crystals, mp 184–184.5 °C, identical with the product from method A.

2,3-Dihydro-6,6-diphenylimidazo[2,1-*b*]thiazol-5(6*H*)-one (4) and 2,3-Dihydro-5,5-diphenylimidazo[2,1-*b*]thiazol-6(5*H*)-one (5). A solution of 3 (27.0 g, 0.1 mol), 1-bromo-2-chloroethane (14.5 g, 0.1 mol), and sodium hydroxide (4.4 g, 0.11 mol) in methanol (200 mL) was refluxed for 12 h. Some insoluble material was removed by filtration, the filtrate evaporated to dryness in vacuo, and the residue extracted with chloroform. This extract was washed first with 5% aqueous KOH solution, then H_2O and dried over anhydrous Na_2SO_4. Removal of the solvent gave 16.80 g of a crude solid which was a mixture of 4 and 5. Two methods were used successfully to separate these compounds.

Method A. The first fraction which separated with C_6H_6 elution on alumina grade II contained 4 which was recrystallized from chloroform to give 2.04 g (6.2%) of white crystals: mp 201–203 °C (lit.[12] 202–203 °C); NBP negative; IR 1710, 1600, 1560, 1240, 1170, 1082, 1030, 1010, 922, 908, 810, 762, 755 cm^{-1}; NMR ($CDCl_3$) δ 3.75 (m, 4, CH_2CH_2), 7.40 (m, 10, aromatic); UV (EtOH) λ_{max} 243 nm (ϵ 7760); mass spectrum *m/e* (rel intensity) 294 (M^+, 52), 266 (30), 265 (100), 224 (34), 189 (16), 165 (33), 135 (35), 104 (8), 77 (16); IRI 2605.

Anal. Calcd for $C_{17}H_{14}N_2OS$: C, 69.41; H, 4.81; N, 9.53; S, 10.90. Found: C, 69.28; H, 4.92; N, 9.48; S, 10.50.

Elution of a second fraction with benzene gave 5 which was recrystallized from chloroform–ethyl acetate to give 11.01 g (33.2%) of white crystals: mp 180–182 °C; NBP negative; IR 1710, 1300, 1210, 1120, 1068, 1008, 970, 945, 930, 918, 906, 870, 850, 770, 765, 740, 718, 700 cm^{-1}; NMR ($CDCl_3$) δ 3.55 (m, 4, CH_2CH_2), 7.30 (m, 10, aromatic); UV (EtOH) λ_{max} 263 nm (ϵ 6990), 241 (19 135); mass spectrum *m/e* (rel intensity) 294 (M^+, 100), 266 (36), 265 (33), 224 (15), 198 (16), 165 (44), 163 (32), 135 (62), 91 (10), 86 (17), 77 (23); IRI 2870.

Anal. Calcd for $C_{17}H_{14}N_2OS$: C, 69.41; H, 4.81; N, 9.53; S, 10.90. Found: C, 69.63; H, 4.92; N, 9.51; S, 10.59.

When 5 was recrystallized from benzene, a complex containing 1 mol of benzene was formed, mp 105–108 °C.

Anal. Calcd for $C_{23}H_{20}N_2OS$: C, 74.16; H, 5.42; N, 7.52; S, 8.60. Found: C, 74.34; H, 5.41; N, 7.58; S, 8.90.

Method B. A crude mixture of 4 and 5 was dissolved in benzene and the solution cooled overnight. Compound 5 (as the benzene complex) separated and was collected by filtration. The filtrate was reduced by 30–50% and refrigerated and a second crop of 5 was collected (total yield of 5, 42%). The resulting filtrate was evaporated to dryness and the residue dissolved in ethyl acetate. After standing overnight at room temperature, a 9.3% yield of 4 was produced.

3-(2-Mercaptoethyl)-5,5-diphenylhydantoin (7a). Method A. Compound 4 (0.50 g, 1.7 mmol) and 20% HCl (5 mL) in absolute ethanol (15 mL) were refluxed for 4 h. Removal of solvent in vacuo produced a white solid which was recrystallized from 95% ethanol to give 0.32 g (60%) of white needles, mp 145–149 °C, solidify and remelt 152–154 °C (lit.[12] 229–230 °C). Recrystallization from chloroform gave mp 152.5–154 °C; IR (EtOH recrystallization) 3200, 1760, 1700, 1138, 1110, 1030, 1000, 930, 910, 890, 875, 788, 757, 720, 696 cm^{-1}; NMR ($CDCl_3$) δ 1.35 (t, 1, SH), 2.80 (m, 2, CH_2S), 3.75 (t, 2, CH_2N), 7.00 (s, 1 NH), 7.35 (s, 10, aromatic); mass spectrum *m/e* (rel intensity) 312 (M^+, 14), 253 (100), 209 (7), 208 (17), 181 (13), 180 (58), 165 (19), 104 (45), 91 (15), 77 (32); IRI 2590.

Anal. Calcd for $C_{17}H_{16}N_2O_2S$: C, 65.36; H, 5.17; N, 8.97; S, 10.26. Found: C, 65.83; H, 5.36; N, 9.10; S, 10.02.

Method B. A solution of 7d (4.35 g, 0.01 mol) and NaOH (1.00 g, 0.025 mol) in water (30 mL) was refluxed for 2 h. After cooling to room temperature, the solution was acidified with 10% sulfuric acid. The resulting solid was filtered, washed with water until the filtrates were neutral, and recrystallized from 95% ethanol to give 2.10 g (67%) of a white solid, mp 144–145 °C. The IR, NMR, mass spectral, and GC properties were identical with those of the material produced by method A.

3-Ethyl-5,5-diphenylhydantoin (7b). Method A. Raney nickel W-7 (prepared from 20 g of alloy) was stirred with 7a (1.00 g, 0.003 mol) in absolute ethanol at room temperature for 12 h. The nickel was filtered washed with 3% NaOH solution. The filtrates and washings were combined and evaporated to dryness. The residue was added to water (50 mL), the mixture acidified with concentrated HCl, and the solution extracted with ethyl acetate. The extracts were washed three times with water and dried over anhydrous sodium sulfate. Evaporation of the solvent gave a solid which was recrystallized from 50% aqueous ethanol to give 0.40 g (44%) of white crystals: mp 153.5–155 °C (lit.[8,10] 156 °C); IR 3250, 1760, 1680, 1480, 1415, 1340, 1015, 1007, 855, 795, 760, 715, 695 cm^{-1}; NMR ($CDCl_3$) δ 1.10 (t, 3, CH_3), 3.4 (q, 2, CH_2), 7.35 (s, 10, aromatic) 9.56 (b, 1, NH); mass spectrum *m/e* (rel intensity) 280 (M^+, 42), 251 (19), 209 (M^+ – C_2H_5NCO, 51), 208 (23), 203 (M^+ – Ph, 15), 181 (27), 180 (100), 165 (18), 104 (48), 77 (33); IRI 2235.

Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.58; H, 5.61; N, 9.86.

Method B. Compound 7b, prepared from DPH and ethyl iodide by the method of Hoffman,[8] gave white crystals, mp 156 °C (lit.[8] 156 °C). The IR, NMR, and mass spectrum for this material were the same as those produced from method A.

3-(2-Bromoethyl)-5,5-diphenylhydantoin (7c). A solution of DPH (25.2 g, 0.10 mol) and KOH (5.6 g, 0.10 mol) in 95% ethanol (300 mL) was added dropwise over a 6-h period to a stirred, refluxing solution of 1,2-dibromoethane (100 g, 0.53 mol) in 95% ethanol (200 mL). After reflux for an additional 9 h, the solvent was removed and the residue dissolved in ethyl acetate. This solution was washed first with 5% aqueous NaOH solution, then water, and finally was dried over anhydrous sodium sulfate. Removal of the solvent in vacuo gave a white solid which was contaminated with a small amount of dimeric (1,2-disubstituted ethane) product. Two recrystallizations from acetone gave 22.3 g (62%) of white crystals: mp 155.5–156 °C (lit.[13,17] 156–157 °C); IR 3200–3050, 1760, 1700, 1310, 1260, 1230, 1190, 1130, 1100, 1030, 1000, 985, 935, 890, 830, 775, 758, 700 cm^{-1}; NMR ($CDCl_3$) δ 3.70 (m, 4, CH_2CH_2), 7.40 (s, 10, aromatic), 7.6 (b, 1, NH); mass spectrum *m/e* (rel intensity) 360 (M + 2, 20), 358 (M^+, 20), 329 (10), 209 (M – BrC_2H_4NCO, 69), 208 (19), 181 (25), 180 (100), 165 (20), 104 (53), 91 (21), 77 (37); IRI 2565.

Anal. Calcd for $C_{17}H_{15}N_2O_2Br$: C, 56.83; H, 4.22; N, 7.80; Br, 22.24. Found: C, 57.18, H, 4.30; N, 7.93; Br, 22.09.

3-[2-(Amidinothio)ethyl]-5,5-diphenylhydantoin Hydrobromide (7d). A solution of 7c (3.59 g, 0.01 mol), thiourea (0.76 g, 0.01 mol), and 95% ethanol (10 mL) was heated to reflux. After 1 h the solution almost completely solidified. After heating for a total of 2 h, the resulting solid was filtered and recrystallized from 95% ethanol to give 2.83 g (65%) of product: mp 280–280.5 °C (lit.[12] mp 260–262 °C); IR 3400–3150, 1755, 1700, 1640, 1110, 970, 880, 760, 740, 728, 695 cm^{-1}.

Anal. Calcd for $C_{18}H_{19}N_4BrO_2S$: C, 49.65; H, 4.41; N, 12.87; Br, 18.35; S, 7.36. Found: C, 49.18; H, 4.69; N, 12.81; Br. 18.24; S, 7.87.

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Registry No.—1d, 62476-40-8; 1e, 62506-10-9; 2a, 62476-41-9; 2b, 54508-20-2; 3, 21083-47-6; 4, 42748-70-9; 5, 62476-42-0; 7a, 42748-71-0; 7b, 39588-47-1; 7c, 13272-33-8; 7d, 42748-72-1; 1-bromo-2-chloroethane, 107-04-0; DPH, 57-41-0; 1,2-dibromoethane, 106-93-4; thiourea, 62-56-6.

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(16) Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Infrared spectra were measured with Perkin-Elmer 621 and 137 spectrometers as Nujol mulls unless otherwise specified. NMR spectra were determined in deuteriochloroform or deuteriodimethyl sulfoxide on a Varian T-60 instrument. Chemical shifts are given as δ values with reference to Me_4Si. Raney nickel alloy was from Alpha. Elemental analyses were carried out by the NIAMDD, NIH. A Hewlett-Packard 5750B gas chromatograph equipped with a flame ionization detector and a linear temperature programmer was used to analyze reaction products for impurities. A 1.83 m × 3 mm o.d. stainless steel column packed with 3% OV-1 on 100/120 mesh Gas Chrom Q was operated either isothermally

in the range 190–240 °C or temperature programmed from 200 to 280 °C at 4 °C/min. Isothermal retention indices (IRI)[18,19] were determined in the temperature range 180–240 °C. Electron impact mass spectra were obtained on a Du Pont 21-492B gas chromatograph–mass spectrometer system consisting of Varian 2740 gas chromatograph interfaced to the mass spectrometer via a single stage glass jet separator. All spectral data reported here were acquired from samples of the pure compound by direct probe insertion into the ion source. When mixtures did occur, the components were separated on a 1.83 m × 2 mm i.d. glass column packed with 3% Se-30 on 100/120 mesh Gas Chrom Q and operated under the conditions described above. Mass spectra were recorded for all peaks of interest. Exact masses and most probable elemental compositions of the major ions in **4**, **1d**, and levamisole (**1c**) were obtained from high-resolution mass spectra run on a JEOL JMS-01SG-2 mass spectrometer. Compounds were tested for alkylating ability with *p*-nitrobenzylpyridine (NBP) as previously described.[2]

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Chemistry of Cyclobutene-1,2-dicarbonitrile. 2. Cycloadducts

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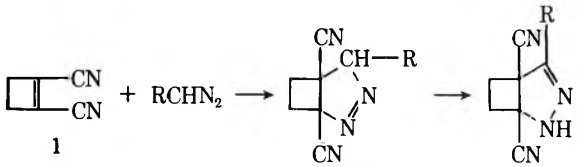
Cyclobutene-1,2-dicarbonitrile (**1**) undergoes [3 + 2] cycloaddition with diazomethane to give 2,3-diazabicyclo[3.2.0]hept-2-ene-1,5-dicarbonitrile (**2**) and with ethyl diazoacetate to give ethyl 3,4-diazabicyclo[3.2.0]hept-2-ene-2-carboxylate (**4**). Upon irradiation, **1** dimerizes to *anti*-tricyclo[4.2.0.0^{2,5}]octane-1,2,5,6-tetracarbonitrile (**7**). The preparation of acid, amide, and ester analogues of **7**, by dimerization and solvolytic processes, is described. In the presence of acrylonitrile, α-chloroacrylonitrile, 1-cyanovinyl acetate, dimethyl maleate, and furan, irradiation of **1** yields mixtures of **7** and bicyclo[2.2.0]hexane-1,2,4-tricarbonitrile (**15**), 2-chlorobicyclo[2.2.0]hexane-1,2,4-tricarbonitrile (**16**), 2-(1,2,4-tricyanobicyclo[2.2.0]hexyl) acetate (**17**), dimethyl 1,4-dicyanobicyclo[2.2.0]hexane-2,3-dicarboxylate (**18**), and 3-oxatricyclo[5.2.0.0^{2,6}]non-4-ene-1,7-dicarbonitrile (**19**), respectively. The adduct **18** undergoes a thermal stereospecific cycloreversion to give dimethyl 3,6-dicyano-2,6-octadiene-1,8-dioate (**21**). Spectral data suggesting similar cycloreversions for the other related adducts are noted.

The strain present in the cyclobutene ring system allows cycloaddition processes to occur with cyclobutene-1,2-dicarbonitrile[1] (**1**) at conditions under which analogous cyclohexenes and cyclooctenes react only sluggishly or not at all.[2] Since results concerning the normal Diels–Alder reaction of **1** with conjugated dienes have been reported recently,[1] this paper will describe only our observations regarding the reactions of cyclobutene **1** with diazoalkanes to give [3 + 2] cycloadducts and with activated olefins to give [2 + 2] cycloadducts, the latter being a photoinitiated process.

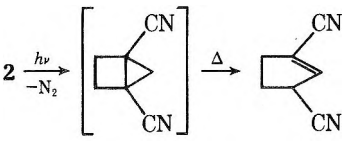
The reaction of diazomethane with **1** occurred readily at room temperature to give the known[3] adduct 2,3-diazabicyclo[3.2.0]hept-2-ene-1,5-dicarbonitrile (**2**). A similar reaction with ethyl diazoacetate gave ethyl 3,4-diaza-1,5-dicyanobicyclo[3.2.0]hept-2-ene-2-carboxylate (**4**), arising by a [1,3]



2, R = H **4**, R = $CO_2C_2H_5$
3, R = $CO_2C_2H_5$

prototropic rearrangement of the initially formed adduct **3**. The evidence for the rearrangement to **4** included the presence of strong absorption bands for the NH and C=N groups, but none for the –N=N– group, in the infrared region (at ca. 3280, 1700, and 1560 cm^{-1}, respectively), and the lack of a resonance for the hydrogen α to an azo function (ca. δ 5.5) in the ^{1}H NMR spectrum. Energetically, the rearranged form **4** may be favored over **3** because of the conjugation introduced between the carbonyl and the imino groups.

Because of the favored hydrazone structure, **4** was photolytically and (relatively) thermally stable; at 175 °C for 24 h, there was no evolution of nitrogen, although only 20% of **4** was recovered. On the other hand, the adduct **2** was photolabile in the presence of a photosensitizer (acetone), undergoing a

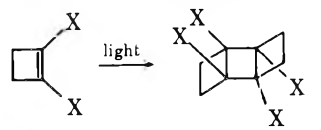


5 **6**

slow evolution of nitrogen. The major organic product isolated, by preparative VPC, was cyclopentene-1,3-dicarbonitrile (**6**), probably arising via thermolysis of initially formed bicyclo[2.1.0]pentane-1,3-dicarbonitrile (**5**). Although no comparisons were made, the dinitrile adduct **2** is apparently appreciably more stable than the related ester dimethyl 2,3-diazabicyclo[3.2.0]hept-2-ene-1,5-dicarboxylate,[3,4] since the latter ester reportedly[3] undergoes facile and rapid loss of nitrogen in the absence of a sensitizer, conditions under which the dinitrile **2** was remarkably stable (a 70% recovery after 72 h irradiation).

The cyclobutene **1** is a strong absorber of light at ca. 234 nm (ϵ_{max} 12 200 in acetonitrile).[2,5] This, coupled with the strain present in the cyclobutene ring system,[6] allows photoinitiated [2 + 2] cycloaddition of **1** with suitable olefins to occur.

Cyclobutene **1** undergoes self-dimerization[8] to yield *anti*-tricyclo[4.2.0.0^{2,5}]octane-1,2,5,6-tetracarbonitrile (**7**). We



1, X = CN **7**, X = CN
8, X = CO_2CH_3 **11**, X = CO_2CH_3
9, X = CO_2H **12**, X = CO_2H
10, X = $CONH_2$ **13**, X = $CONH_2$

studied this reaction, using both sunlight and a medium-pressure (unfiltered) mercury vapor lamp as light sources. In sunlight (in a quartz apparatus), the reaction was extremely slow, with a 20% conversion after several weeks; this process was not subject to photosensitization, since comparable con-

Table I. Photocatalyzed Dimerization of Cyclobutene-1,2-dicarbonitrile (1)[a]

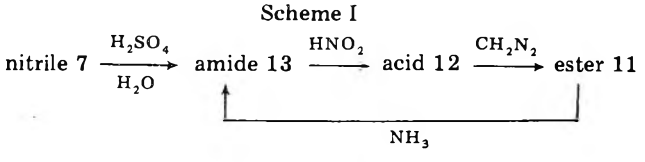
Solvent	Sensitizer	Time, h	Mol % yield (7)
Methanol	None	120	12
Acetone	Acetone	24	75
Benzene	None	144	17
Benzene	Benzophenone[b]	48	56
Benzene	Benzophenone[b]	96	85
Methylene chloride	Benzophenone[b]	40	82
Methylene chloride	Benzophenone[b]	96	89

[a] Used an unfiltered medium-pressure mercury vapor lamp through a quartz window at ca. 15–20 °C. Concentration of 1 in solvent was varied from ca. 0.3–1.2 M with no apparent effect on yield. [b] Ca. 10–15 mol % relative to 1.

versions were obtained in either methylene chloride or in acetone as solvents. With the "artificial" light source, however, the reaction was practical only in the presence of a sensitizer (Table I). The extreme insolubility of the dimer 7 prevented acquisition of NMR data. However, a solution in trifluoromethanesulfonic acid (which remained colorless for several hours) allowed NMR spectral data of the protonated species to be obtained.[9] Thus, in this solvent, 7 exhibited a broad multiplet centered at ca. δ 2.75 (from Me_4Si). On a higher resolution instrument, this multiplet was resolved into a pair of doublets, $J \sim 8.2$ Hz (chemical shift between hydrogens is 0.53 ppm).[10] The ^{13}C NMR spectrum consisted of three resonances, at δ 26.8, 44.4, and 111.9, for methylene, quaternary, and protonated nitrile carbons, respectively.

For comparative purposes, several derivatives of the nitrile 1 were also photodimerized. Thus, the dimethyl ester 8 gave good yields (even in sunlight) of the tricyclic ester 11,[8,11] the acid 9 gave the dimer 12, and the amide 10 gave the tricyclic amide 13. The latter derivative showed remarkable thermal stability. It could be sublimed unchanged under high vacuum at about 300 °C; at the same temperature but at 20 mm pressure, sublimation was accompanied by slow cycloreversion and loss of ammonia to *cis,cis*-1,5-cyclooctadiene-1,2,5,6-tetracarboxdiimide.[2] In structural studies, these derivatives were all interrelated chemically (Scheme I). Thus treatment

Scheme I



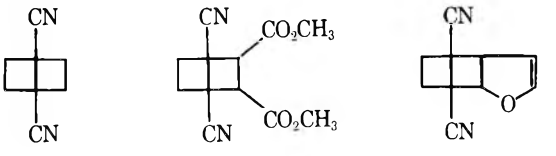
of the nitrile 7 with sulfuric acid followed by water or methanol gave the amide 13, identical with that prepared by dimerization of 10. Although this amide 13 resisted further hydrolysis under mild conditions, it could be converted to the acid 12 by treatment with nitrous acid. The latter, with diazomethane, gave the tricyclic ester 11, identical with that prepared from 8. The tricyclic ester 11 could be converted to the amide 13 by reaction with methanolic ammonia; this was a slow process, requiring several weeks at room temperature. There was no evidence of cycloreversion to cyclooctadienes[8] occurring during any of these reactions, run, to be sure, under very mild conditions.

The cyclobutene 1 also underwent [2 + 2] cycloaddition with other olefins. The parent derivative, bicyclo[2.2.0]hexane-1,4-dicarbonitrile (14), from the reaction with ethylene has been reported.[12] In our hands, cyclobutene-1,2-dicarbonitrile underwent benzophenone-sensitized cycloadditions with acrylonitrile, α-chloroacrylonitrile, 1-cyanovinyl acetate,

Table II. [2 + 2] Cycloadducts with Cyclobutene-1,2-dicarbonitrile[a]

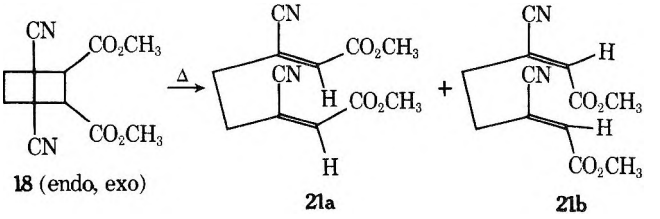
Reactant	Mol % yield Dimer 7	Mol % yield Codimer
Ethylene		57 (14)[b]
Acrylonitrile	42	40 (15)
α-Chloroacrylonitrile	28	8 (16)
1-Cyanovinyl acetate	42	46 (17)
Dimethyl maleate	81	10 (18)
Furan	<10	<10 (19)[c]
2-Chloromaleic anhydride	19	0–1
2-Bromomaleic anhydride	16	0–1
2,3-Dichloromaleic anhydride	21	0–1
Fumaronitrile	11	0
Dimethyl acetylenedicarboxylate	39	0

[a] See Experimental Section for conditions. [b] From ref 12. [c] Adduct 20 isolated in 15–20% yield.

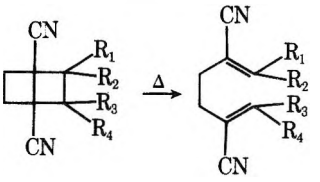


dimethyl maleate, and furan to give bicyclo[2.2.0]hexane-1,2,4-tricarbonitrile (15), 2-chlorobicyclo[2.2.0]hexane-1,2,4-tricarbonitrile (16), 2-(1,2,4-tricyanobicyclo[2.2.0]hexyl) acetate (17), dimethyl 1,4-dicyanobicyclo[2.2.0]hexane-2,3-dicarboxylate (18), and 3-oxatricyclo[5.2.0.$0^{2,6}$]non-4-ene-1,7-dicarbonitrile (19), in variable yields (Table II). Self-dimerization of cyclobutene 1 to give 7 was a competing process in all of these reactions. In addition, the reaction with furan gave the normal [4 + 2] Diels–Alder adduct 20, 9-oxatricyclo[4.2.$1^{2,5}$.0]non-3-ene-1,6-dicarbonitrile,[1,2] as the major product. With 2-chloro-, 2-bromo-, and 2,3-dichloromaleic anhydrides, there was little indication that any of the desired bicyclic anhydrides were obtained. Fumaronitrile and dimethyl acetylenedicarboxylate also failed to undergo (photo) cycloaddition with the cyclobutene 1. Spectral evidence suggesting the presence of endo–exo isomers was obtained from some of the reaction products (see Experimental Section), and these isomers of the adduct 15 from acrylonitrile were actually isolated.

Products related to these cycloadducts, i.e., bicyclo[2.2.0]-hexanes substituted at the bridgehead positions, have been the subject of extensive recent investigations (see ref 12 and references cited therein). Adducts such as these undergo facile stereospecific [$\sigma 2_s + \sigma 2_a$] cycloreversion, giving 1,5-hexadienes. No quantitative study of this was made using the

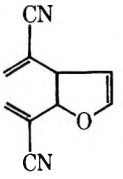


Scheme II

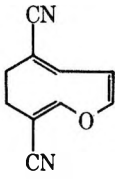


From adduct	Registry no.	R_1	R_2	R_3	R_4	Product hexadiene, absorption for group, cm^{-1} =CH	C=C	$=CH_2$	Registry no.
14[12]	52999-04-9	H	H	H	H		1632	945	52999-05-0
15	62198-07-6 (endo) 62249-47-2 (exo)	CN	H	H	H	3120	1630	960	62198-12-3
16	62198-08-7	CN	Cl	H	H		1640, 1600	960	62198-13-4
17	62198-09-8 (endo) 62249-48-3 (exo)	CN	OAc	H	H		1635	960	62198-14-5
18	62198-10-1 (endo) 62249-49-4 (exo)	CO_2CH_3	H	CO_2CH_3	H	3070	1640		62198-15-6 (*E*) 62198-16-7 (*Z*)
19	62198-11-2		(See Discussion)			3110	1630, 1615	950	62198-18-9

products synthesized in this work. However, the adduct **18** from dimethyl maleate, as an endo–exo mixture, was smoothly converted upon heating to dimethyl (*E,E*)- and (*Z,Z*)-3,6-dicyano-2,6-octadiene-1,8-dioate (**21a** and **21b**). Significantly, there was no evidence for the presence of the *E,Z* isomer of **21**. This cycloreversion was demonstrated qualitatively on a micro scale with several of the other adducts. Thus after holding the samples at their melting points (120–130 °C) for several minutes, infrared spectral examination clearly revealed the presence of strong absorptions for conjugated olefinic and vinylidenic unsaturation, suggesting that the cleavage occurred in the direction shown in Scheme II. The strong vinylidenic absorption (at 950 cm^{-1}) for the cycloreversion product from the furan adduct **19** suggests that the cleavage, not unexpectedly, occurred in the other direction, to give **22a** rather than the alternative **22b**.



22a



22b

Experimental Section[13]

2,3-Diazabicyclo[3.2.0]hept-2-ene-1,5-dicarbonitrile (2). A solution of 3.5 g of cyclobutene **1** in ether was treated with an excess of ethereal diazomethane at room temperature; there was no immediate discharge of color upon addition, but after a short induction period a rapid reaction occurred with the simultaneous precipitation of a white solid. After several hours standing, the latter was collected to give **2** (3.92 g) as fine, white crystals: mp 134–136 °C (from tetrahydrofuran at −70 °C) (lit.[3] mp 139–140 °C); IR (KBr) 2270 (CN), 1565 cm^{-1} (N=N); ^1H NMR[14] (acetone-d_6) δ 5.37 (s, CH_2N=N, 2) 2.2–3.2 (m, CH_2, 4); mass spectrum *m/e* (rel intensity) 146 (1.2, M^+), 118 (50, M − N_2), 91 (100, 118 − HCN). Anal. Calcd for $C_7H_6N_4$: C, 57.52; H, 4.14; N, 38.34. Found: C, 57.52; H, 4.07; N, 37.55.

Ethyl 3,4-Diaza-1,5-dicyanobicyclo[3.2.0]hept-2-ene-2-carboxylate (4). To a solution of 5.2 g of **1** in 100 mL of tetrahydrofuran was added 6.7 g of ethyl diazoacetate. After the solution was allowed to stand at room temperature for several weeks, concentration to a volume of about 25 mL gave 4.0 g of **4** as white crystals: mp 146–148 °C, melt dec at 180 °C (from tetrahydrofuran); IR (KBr) 3280 (NH), 2220 (CN), 1760 (C=O), 1640 cm^{-1} (C=N); ^1H NMR (acetone-d_6) δ 10.07 (broad s, NH, <1 H), 4.41 (quartet, ester CH_2, 2), 3.0 (s, ring CH_2, 4), 1.36 (t, CH_3, 3); mass spectrum *m/e* (rel intensity) 218 (59, M^+), 190 (29, M − N_2), 172 (32), 145 (30), 118 (22).

Photolytic Decomposition of Adduct 2. A solution of 1.0 g of **2** in ca. 150 mL of acetone, in a quartz apparatus, was irradiated with a medium-pressure (unfiltered) mercury vapor lamp for several days at room temperature. Nitrogen was evolved at the rate of ca. 2mL/h (has buret; similar treatment of a solution of **2** in methylene chloride gave no nitrogen) for 50 h or so, then no more during another 115 h. The amber-colored solution was stripped under reduced pressure. Recrystallization of the residual solid at −70 °C gave a total of 0.44 g of recovered unreacted **2**; nothing more could be crystallized. Removal of the solvent and taking up the residual oil in ether allowed removal of a small amount of an insoluble material. After evaporation of the ether, preparative VPC allowed isolation of cyclopentene-1,3-dicarbonitrile (**6**): IR (neat) 3080 (CH=), 2230 and 2240 (CN), 1620 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ 6.5 (m, CH=, 1), 3.6–4.0 (m, CH, 1), 2.0–3.0 (m, CH_2, 4); mass spectrum *m/e* (rel intensity) 118 (20, M^+), 91 (100, M − HCN), 64 (12, M − 2HCN).

General Procedure for Photocatalyzed Reactions of 1 and Analogues. The reactor was similar to those available commercially (e.g., from Ace Glass Co., No. 6522); it consisted essentially of a jacketed (for coolant circulation) tube provided with adaptors for a condensor and a concentric (inner) quartz thimble (for the lamp) and with a glass frit at the bottom for introduction of nitrogen. Irradiation was by a 100-W medium-pressure Hanovia mercury vapor immersion lamp. The liquid capacity of the assembled reactor was about 160 mL. The reactions were carried out at room temperature by using tap water in the cooling jacket and with a slow nitrogen sweep for agitation.

Tricyclo[4.2.0.$0^{2,5}$]octane-1,2,5,6-tetracarbonitrile (7) (See Table I). Irradiation of a solution of 20 g of **1** and 5 g of benzophenone in 150 mL of methylene chloride for 4 days gave 17.8 g of **7** as an insoluble, crystalline mass: mp 183–184 °C (with subsequent resolidification of the melt at 190 °C or so; the resulting solid, mp 255–257 °C) (lit.[8] mp 182 °C; IR (KBr) 2260 (CN), 805 cm^{-1} (very strong); ^1H and ^{13}C NMR, see Discussion; mass spectrum *m/e* (rel intensity) 208 (9, M^+), 181 (5, M − HCN), 104 (100, $C_6H_4N_2$), 77 (87, 104 − HCN). Alternatively, allowing a solution of 25 g of freshly distilled **1** in 500 mL of methylene chloride to stand in the sunlight in a stoppered quartz flask for 4 weeks afforded 3.78 g of **7** as well-formed, insoluble crystals.

Tetramethyl Tricyclo[4.2.0.$0^{2,5}$]octane-1,2,5,6-tetracarboxylate (11). A. Irradiation of 8. A solution of 5.10 g of the ester **8** in 150 mL of acetone, upon irradiation for 24 h, gave 2.40 g (two crops) of the dimer **11**, mp 134–136 °C (from ether at −70 °C) (lit.[11b] mp 135–136 °C).

B. Esterification of 12. A solution of the dimer acid **17** (prepared from the amide **13**, see below) in a mixture of ether and tetrahydrofuran was treated with an excess of ethereal diazomethane. After the solution was allowed to stand for 1 h at room temperature, the solvents were removed in vacuo; the residual oil was recrystallized from ether at −70 °C to give **11**, mp 132–133 °C, identical with the material prepared by dimerization of **8**.

Tricyclo[4.2.0.$0^{2,5}$]octane-1,2,5,6-tetracarboxylic Acid (12). A. Irradiation of 9. A suspension of 2.0 g of the acid **9** and 0.5 g of benzophenone in methylene chloride, with agitation by a slow nitrogen purge, was irradiated in the photochemical reactor for 4 days. The mixture remained heterogeneous, although solution–precipitation appeared to be occurring. The solid (0.41 g), mp 247–250 °C, was removed and another 0.37 g was recovered from the methylene chloride solution. Both crops were combined and recrystallized (with difficulty) from a mixture of acetone and ether at −70 °C: mp 259–261 °C

(giving a red melt with gaseous decomposition); IR (KBr) broad absorptions at ca. 3000, 2650, 1800, 1425, and 1200–1300 cm^{-1}; ^1H NMR (acetone-d_6) δ 2.4–2.9 (A_2B_2 m, CH_2); ^{13}C NMR (acetone-d_6) δ 177.12 (CO_2H), 53.89 (quaternary C), 26.18 (CH_2). Anal. Calcd for $C_{12}H_{12}O_8$: C, 50.71; H, 4.26. Found: C, 50.44; H, 3.93.

B. Hydrolysis of 13. The amide **13** (see below) (0.5 g) was added to 17 mL of 75% sulfuric acid in a 100-mL beaker at 35 °C. After the mixture was stirred at room temperature for 10–15 min (solution was incomplete), 4.0 g of sodium nitrite was added, a few crystals at a time, over a 2-h period, keeping the beaker covered with a watch glass. After about 3 g of the salt had been added, each addition caused the appearance of a transient green color. The mixture was stirred at room temperature overnight and was then poured over 50 mL of crushed ice. A white solid appeared, but redissolved as the ice melted. The solution was concentrated to a volume of 15–20 mL under high vacuum and at room temperature. Cooling the residual viscous solution to −20 °C gave 4.5 g of insoluble sodium sulfate. The filtered solution was taken up in a mixture of isopropyl alcohol and tetrahydrofuran. This solution was washed once with aqueous saturated salt solution, once with saturated calcium chloride solution, and again with the salt solution. The organic phase was stripped in vacuo, and the residue was stripped several times from toluene at 35–40 °C to dry. Recrystallization of the residue from a mixture of ether, tetrahydrofuran, and pentane gave the dimer acid **12** as white crystals, mp 265–268 °C, identical with the product obtained by dimerization of **9**.

Tricyclo[4.2.0.$0^{2,5}$]octane-1,2,5,6-tetracarboxamide (13). A. Irradiation of 10. A suspension of 2.0 g of **10**[1,3] (prepared by the cautious addition of a solution of **1** in concentrated sulfuric acid to ice[2]) in benzene was irradiated under nitrogen agitation for 4 days. The resulting solid product (1.90 g), after washing with benzene and water, was treated with 700 mL of boiling water in several portions to give 1.28 g of the insoluble amide **13**, mp 358–360 °C.

B. Hydrolysis of 7. The nitrile **7** (0.5 g) was added to 10 mL of concentrated sulfuric acid; solution was complete in 30 min. After 2 days at room temperature, the colorless solution was added slowly to 150 mL of methanol, giving the insoluble amide **13** immediately. This product, 0.66 g, totally insoluble in hot water, methanol, acetic acid, and dimethylformamide, was "purified" by dissolving in 5 mL of sulfuric acid, filtering, and reprecipitating with 150 mL of methanol to give snow-white crystals of **13**: mp 355 °C dec with loss of ammonia; IR (KBr) 3230 and 3130 (NH_2), 1665 and 1610 cm^{-1} ($CONH_2$). Anal. Calcd for $C_{12}H_{16}N_4O_4$: C, 51.43; H, 5.75; N, 19.99. Found: C, 51,43; H, 5.82; N, 19.97.

C. Ammonolysis of 11. A solution of the ester **11** (0.50 g) in 250 mL of methanol was saturated with ammonia at 25–30 °C. Prolonged standing at room temperature in a stoppered flask caused the slow appearance of a crystalline solid. After 9 weeks, the solid was collected to give 0.08 g of **13**, mp 351–353 °C dec, identical with the samples prepared by the other methods.

Bicyclo[2.2.0]hexane-1,2,4-tricarbonitrile (15) was prepared by irradiation of a solution of 5 g of **1**, 10 mL of freshly distilled acrylonitrile, and 2 g of benzophenone in methylene chloride for 44 h. After removal of 2.06 g of insoluble **7**, the solvent and other volatiles were removed under reduced pressure at room temperature. The residual semisolid was taken up in ether to give 3.06 g of a tan-colored solid, mp 103–105 °C. This was taken up in 100 mL of acetone, removing another 0.05 g of insoluble **7**. The acetone solution was concentrated to about one-third volume and chilled at −70 °C to give off-white solid, mp 107–109 °C. Fractional crystallization from mixtures of tetrahydrofuran and ether gave *endo*- and *exo*-**15** as the less and more soluble components, respectively. *endo*-**15**: mp 119–121 °C; IR (KBr) 2260 (CN), 1450, 1235 cm^{-1}; ^1H NMR (acetone-d_6) δ 4.48 (dd, $J \sim 8$, 11 Hz, CH, 1), 2.5–3.7 (m, CH_2, 6); mass spectrum *m/e* (rel intensity) 157 (19, M^+), 130 (9.1, M − HCN), 103 (12, M − 2HCN), 66 (100, C_4H_4N). *exo*-**15**: mp 127–128 °C; IR (KBr) 2260 (CN), 1450, 1180 cm^{-1}; ^1H NMR (acetone-d_6) δ 4.17 (dd, $J \sim 8$, 8 Hz, CH, 1), 2.6–3.3 (m, CH_2, 6); mass spectrum *m/e* (rel intensity) 157 (19, M^+), 130 (12, M − HCN), 103 (16, M − 2HCN), 66 (100, C_4H_4N).

2-Chlorobicyclo[2.2.0]hexane-1,2,4-tricarbonitrile (16) was prepared by irradiation of a solution of 5 g of **1**, 15 g of freshly distilled α-chloroacrylonitrile, and 2 g of benzophenone in methylene chloride for 45 h. After removal of 1.01 g of insoluble **7**, the solution was worked up as described under the preparation of **15** to give another 0.31 g of **7** and 0.74 g of **16** (from ether at −70 °C). Recrystallization once from a mixture of acetone and ether and then from tetrahydrofuran and ether gave **16** as off-white crystals: mp 129–131 °C dec; IR (KBr) 2260 (CN), 756 cm^{-1} (C–Cl); ^1H NMR (acetone-d_6) δ 3.4–4.2 (AB quartet, CH_2CCl, 2), 2.6–3.4 (m, CH_2, 4); mass spectrum *m/e* (rel intensity) 191, 192, 193 (8.1, 1.1, 3.0, M^+), 153 (17, M − HCl, 2 H), 129 (10, M − HCl, CN), 128 (13), 66 (100, C_4H_4N).

2-(1,2,4-Tricyanobicyclo[2.2.0]hexyl) acetate (17) was prepared by irradiation of a solution of 5 g of **1**, 21 g of α-acetoxyacrylonitrile, and 2 g of benzophenone in methylene chloride for 2 days. Removal of 1.75 g of insoluble **7** and treatment as described for the preparation of **15** gave another 0.35 g of **7** and (from ether at −70 °C) 1.08 g of **17**, mp 105–108 °C. Evaporation of the ether mother liquor and recrystallization of the residue from carbon tetrachloride at −20 °C gave another 3.75 g of **17**, mp 105–108 °C. Recrystallization of the combined crops three times from acetone and ether gave **17** as off-white crystals: mp 118–120 °C; IR (KBr) 2270 (CN), 1760 and 1220 cm^{-1} (ester); ^1H NMR ($CDCl_3$ + acetone-d_6) δ 2.3–3.8 (m, 6), 2.25 (2 s, CH_3, 3);[15] mass spectrum *m/e* (rel intensity), 215 (small, M^+), 146 (2.4), 118 (9.4), 80 (67), 52 (41), 43 (100).

Dimethyl 1,4-dicyanobicyclo[2.2.0]hexane-2,3-dicarboxylate (18) was prepared by irradiation of a solution of 25 g of **1**, 75 mL of dimethyl maleate, and 5 g of benzophenone in methylene chloride for 5 days. After removal of 7.58 g of insoluble **7**, the reaction solution was stripped at room temperature. Chilling of an ethereal (100 mL) solution of the residual oil at −70 °C gave 5.06 g of dimethyl fumarate. After removal of this, the ether solution was stripped again at room temperature and the residual oil was extracted twice with a 1:1 mixture of cyclohexane and ether. The residual insoluble oil was taken up in carbon tetrachloride and stored in the refrigerator. Long standing (2 weeks) caused slow crystallization of **18**: 0.75 g, mp 116–117 °C (from acetone); IR (KBr) 2270 (CN), 1755, 1740, and 1240 cm^{-1} (ester);[16] ^1H NMR ($CDCl_3$) δ 3.89 and 3.82 (2 singlets, CH_3, 6)[15] (overlapping with) 3.8–4.4 (3–4 single peaks, CH, 2), 2.4–3.2 (m, CH_2, 4); mass spectrum *m/e* (rel intensity) 248 (18, M^+), 233 (9, M − CH_3), 217 (9, M − OCH_3), 189 (30, M − CH_3CO), 157 (25, 189 − CH_3O, H), 145 (34), 131 (35), 104 (22), 59 (100, CH_3CO_2).

After removal of the solid **18**, the carbon tetrachloride solution was stripped, and the residual oil was distilled through a short-path column under high vacuum at 100 °C (steam bath) to remove dimethyl maleate. The residual semisolid was taken up in ether, and an insoluble material was removed. The latter was recrystallized several times from a mixture of tetrahydrofuran and ether and then from acetone at −70 °C to give dimethyl 3,6-dicyano-2,6-octadiene-1,8-dioate, probably the *Z,Z* isomer, **21a**,[17] as white crystals: mp 109–111 °C; IR (KBr) 3070 (HC=), 2220 (CN), 1720 and 1205 (ester), 1640 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ 6.50 (s, HC=, 2), 3.86 (s, CH_3, 6), 2.76 (s, CH_2, 4); mass spectrum *m/e* (rel intensity) 248 (7, M^+), 233 (8, M − CH_3), 217 (8, M − CH_3O), 189 (27, M − CO_2CH_3), 59 (100, CH_3CO_2). The ether-soluble portion of the residue from the original distillation, after removal of the ether, was extracted several times with hot cyclohexane. The insoluble residue was recrystallized from ether containing a little tetrahydrofuran to give impure **21**, mp 90–95 °C. The cyclohexane solution was evaporated and the residual material was recrystallized once from a mixture of ether and pentane and once from ether and tetrahydrofuran, both at −70 °C, to give dimethyl 3,6-dicyano-2,6-octadiene-1,8-dioate, probably the *E,E* isomer, **21b**,[17] as white crystals: mp 124–126 °C; IR (KBr) identical with that for **21a**; ^1H NMR ($CDCl_3$) δ 6.55 (s, HC=, 2), 3.89 (s, CH_3, 6), 3.12 (s, CH_2, 4); mass spectrum essentially identical with that for **21a**.

3-Oxatricyclo[5.2.0.$0^{2,6}$]non-4-ene-1,7-dicarbonitrile (19). A solution of 5 g of **1**, 25 mL of furan, and 2 g of benzophenone in methylene chloride was irradiated for 2 days. The solvent was removed, and the residual amber-colored oil was mixed with 35 mL of ether. After removal of insoluble **7** (0.20 g), the ether solution was chilled at −70 °C to give 1.53 g of a white, crystalline solid. This was recrystallized from tetrahydrofuran containing a little ether at −70 °C to give **3-oxatricyclo[4.2.1.^{2,5}.0]non-3-ene-1,6-dicarbonitrile**[1,2] **(20)** as the first crop, mp ca. 145 °C. A second crop of crystals, collected after adding more ether to the mother liquor, was recrystallized twice from a mixture of ether and tetrahydrofuran at −70 °C to give **19** as soft, white plates: mp 119–120 °C; IR (KBr) 3120 (HC=), 2250 (CN), 1620 (C=C), 1140, 1040 cm^{-1}; ^1H NMR (acetone-d_6) δ 6.75 (m, OCH=, 1), 5.34 (s, HCO?, 1), 5.27 (d, HC=?, 1), 4.08 (m, HCC=, 1), 2.5–3.0 (A_2B_2 pattern, CH_2, 4); mass spectrum *m/e* (rel intensity) 172 (37, M^+), 145 (17, M − HCN), 144 (28), 143 (41, M − CHO), 120 (86, M − 2CN), 117 (35), 116 (53), 104 (22, $C_6H_4N_2$), 68 (29, furan).

Acknowledgment. We are grateful to Mr. A. N. Widener for his careful assistance in carrying out much of the experimental work.

Registry No.—**1**, 3716-97-0; **2**, 62198-17-8; **4**, 62198-19-0; **6**, 62198-20-3; **7**, 53399-93-2; **8**, 1128-10-5; **9**, 16508-05-7; **10**, 23335-15-1; **11**, 62198-21-4; **12**, 62198-22-5; **13**, 62198-23-6; **20**, 62249-50-7; diazomethane, 334-88-3; ethyl diazoacetate, 623-73-4; acrylonitrile,

107-13-1; α-chloroacrylonitrile, 920-37-6; α-acetoxyacrylonitrile, 3061-65-2; dimethyl maleate, 624-48-6; furan, 110-00-9.

References and Notes

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(9) Although this solvent certainly affected the cyano groups in **7**, the integrity of the carbon skeleton remained basically unchanged for at least several hours.
(10) We are indebted to Professor L. M. Stock for these measurements (on a 270-MHz instrument).
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(13) Melting points, determined in a Mel-Temp apparatus, are uncorrected; IR spectra were determined on a Perkin-Elmer Model 137 Infracord; NMR spectra were determined (vs. internal Me_4Si) on Varian T60 and XL100 instruments; mass spectra were obtained on a CEC 110B instrument (70 eV), and data include some pertinent fragments produced.
(14) The ^{13}C NMR spectrum ($CDCl_3$) was not entirely satisfactory because of low solubility and some decomposition during the time required for data acquisition. However, two and possibly three methylene resonances (the latter quite far upfield and probably representing the $CH_2N{=}N$ carbon), and one due to a quaternary carbon were found (at ca. δ 29.0, 30.2, 51.5, and 50.5, respectively).
(15) The double resonance for the methyl hydrogens suggests the presence of endo, exo isomers.
(16) The double carbonyl absorption at 1755 and 1740 cm^{-1} suggests the presence of endo, exo isomers.
(17) The structures are assigned tentatively on the basis of the methylene hydrogen resonances at δ 2.76 and 3.12, deshielded by a *trans*- and *cis*-methoxycarbonyl group, respectively.

Dimers of Cyclobutene-1,2-dicarbonitrile and 1,3-Butadiene-2,3-dicarbonitrile. Preparation and Chemistry

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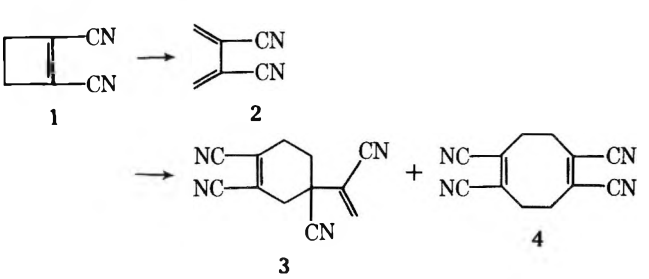
Thermal dimerization of 1,3-butadiene-2,3-dicarbonitrile (**2**) produces mixtures of 4-vinyl-1-cyclohexene-α,1,2,4-tetracarbonitrile (**3**) and *cis,cis*-1,5-cyclooctadiene-1,2,5,6-tetracarbonitrile (**4**). The **3**:**4** product ratio is temperature independent, but both the rate of dimerization and the product ratio are affected by solvent polarity. The photodimer of cyclobutene-1,2-dicarbonitrile, *anti*-tricyclo[4.2.0.$0^{2,5}$]octane-1,2,5,6-tetracarbonitrile (**5**), undergoes stereospecific thermal cycloreversion to *cis,trans*-1,5-cyclooctadiene-1,2,5,6-tetracarbonitrile (**6**), which is itself thermally labile, yielding **4** at higher temperatures. Both **4** and **6** isomerize at 280 °C to **7a**, bicyclo[3.3.0]oct-2-ene-1,2,5,6-tetracarbonitrile. Upon irradiation, **4** and **6** yield **3** and the isomeric, highly stable tricyclo[3.3.0.$0^{2,6}$]-octane-1,2,5,6-tetracarbonitrile (**8**). By virtue of the strain present in the molecule, **6** undergoes reactions preferentially at the trans double bond. It acts as a dienophile toward butadiene, furan, and diene **2**, undergoes [2 + 3] cycloaddition with diazomethane and ethyl diazoacetate, gives double-bond addition products with (basic) ethanol, piperidine, and hydrogen (catalyst), isomerizes to **4** in the presence of bromine or iodine, and forms complexes with certain transition metal reagents. The dimer **3** adds bromine and undergoes cycloaddition with **2** and diazomethane at the exocyclic double bond. Diazomethane also slowly adds to **4**. The furan adduct of **6** is converted photolytically to **8** and thermally to **6**, and also exhibits dienophilic reactivity.

Cyclobutene-1,2-dicarbonitrile (**1**) and its valence tautomer, 1,3-butadiene-2,3-dicarbonitrile (**2**), exhibit a rich and varied chemistry. As a part of our investigation of these reactive, strongly electron-deficient systems, a number of dimers of the general formula $[C_4H_4(CN)_2]_2$ were prepared. We found some of these dimers themselves to have diverse and interesting chemical and physical properties. Particularly studied were thermal and photochemical behavior, cycloaddition, addition, and hydration processes, and reactions with transition metals. While preliminary accounts from another laboratory of related work have appeared,[1] we wish to report additional observations in this area.

Electron-deficient dienes related to **2** are known to be labile toward dimerization. For example, both methyl 1,3-butadiene-2-carboxylate[2] and 1,3-butadiene-2-carbonitrile[3,4] are greatly prone, even at room temperature, to undergo a Diels–Alder dimerization to yield substituted vinylcyclohexenes. The diene **2**, in our experience, was much more stable than this. It did undergo dimerization to 4-vinyl-1-cyclohexene-α,1,2,4-tetracarbonitrile[1b] (the VCH dimer **3**), upon prolonged heating in various solvents in the presence of a polymerization inhibitor (e.g., hydroquinone). The rate of dimerization was, of course, a function of temperature and, if the temperature was high enough to permit the cycloreversion of **1** to occur (100 °C or so), the process was essentially the same using either diene **2** or the cyclobutene **1** as an in situ source of **2**. Thus in aromatic hydrocarbon solvents, the time required for complete dimerization varied from 2 weeks or so at 80 °C (several months at room temperature) to 24 h at 140 °C (5 h at 165 °C[1a]). Yields of **3** were consistently 75–80%, regardless of the temperature; the only significant by-product was the isomeric *cis,cis*-1,5-cyclooctadiene-1,2,5,6-tetracarbonitrile[1] (the COD dimer **4**), formed in 15–20% yields. The latter dimer has been prepared by another method[1c,d] (see



1 2 3 4

Table I. Dimerization of Butadiene-2,3-dicarbonitrile (2)

Solvent	Reaction conditions		% conversion	% selectivity	
	Temp, °C	Time, h		3	4
Acetonitrile	80	168	100	>95	<5
Benzene	80	336	90	80	15–20
Hexane	120[a]	65	(6)	(60–70)	(30–40)

[a] Used cyclobutene-1,2-dicarbonitrile (1) as an in situ source of 2.

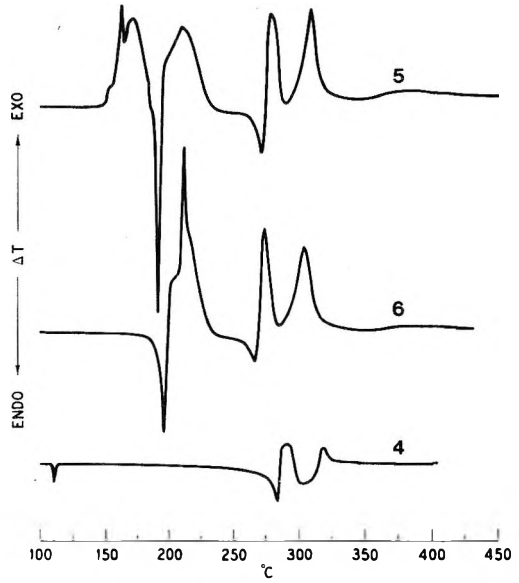
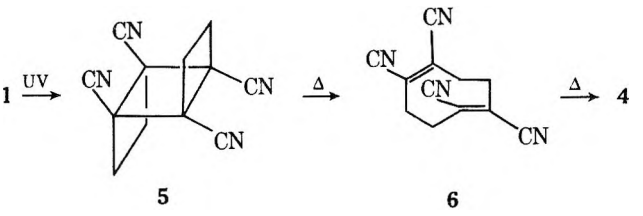


Figure 1. Differential thermal analyses (DTA) of dimers **4**, **5**, and **6** (ca. 5 mg sample under nitrogen, open pan, 10 °C/min).



below, also), but it was not previously reported as a product of the thermal dimerization of **2**.[1a,b] While the relative yields of **3** and **4** were not affected by temperature (nor by starting with either **1** or **2**), solvent polarity played a large role in both product distribution and rate of dimerization. Thus, some qualitative observations (Table I) demonstrated that a polar solvent favored both a more rapid dimerization and the formation of **3** (because of the low conversions and solubility problems, the results using hexane are only very approximate).

The VCH dimer **3** might arise by a concerted [2 + 4] Diels–Alder cycloaddition. However, the solvent effect noted suggests that there may be a polar or a charge-separated transition state. The origin of the COD dimer **4** in this thermal process is not so clear; there was no **3** ⇌ **4** interconversion under these reaction conditions. Because of the large solvent effect on both the rate and the product distribution, it is improbable that the two dimers arise from a common intermediate. COD dimers formed during the thermal dimerization of butadienes are normally considered to arise from an initial [2 + 2] cycloadduct, a *cis*-1,2-divinylcyclobutane. Whether such was involved in this instance is far from certain, since no evidence for such an intermediate (or its trans isomer) could be found. For the present, the origin of **4** in this thermal process remains mechanistically obscure.[5]

Because of ease of polymerization upon irradiation, no interesting photochemistry of diene **2** was found. However, photolytic dimerization of **1** afforded high yields of *anti*-tricyclo[4.2.0.0^{2,5}]octane-1,2,5,6-tetracarbonitrile (**5**).[1d,7] It has been reported previously that this dimer undergoes a remarkably clean [$_{\sigma}2_a$ + $_{\sigma}2_s$] cycloreversion to give high yields of *cis,trans*-1,5-cyclooctadiene-1,2,5,6-tetracarbonitrile (**6**).[1d,8] We independently made a study of this latter process, and found that the best method for the preparation of **6** was the prolonged reflux of a suspension of the (insoluble) dimer **5** in benzene, in which **6** has reasonable solubility; under these conditions, there was practically no formation of the isomer **4**. Other solvents, such as acetone, tetrahydrofuran (THF), and carbon tetrachloride, were not as satisfactory for this transformation. Indeed, there were indications that acetone and THF took part to some minor extent in formation of by-products.[9] The **5** → **6** conversion could also be carried out in the solid state,[1d] e.g., by sublimation under high vacuum at 175 °C, but this was not as satisfactory in our hands as the "solution" method. This conversion was sensitive to temperature, as expected, since **6** was thermally unstable and could be converted easily to the stable **4**. Thus, while the tricyclooctane **5** gave practically only **6** in hot benzene (in 3 days), refluxing **5** in xylene for 40 h gave 69% of **4**, and heating **5** in dichlorobenzene at 175 °C for 40 h gave **4** almost quantitatively.

Differential thermal and gravimetric analyses (DTA/DGA) of these dimers suggested temperatures at which some of these processes occurred. Thus, DTA revealed that **5** did not melt (no endothermic peak, see Figure 1), but underwent a sharp (exothermic) transformation to **6** at ca. 163 °C, perhaps accompanied by a secondary, slower isomerization to **4** at ca. 170 °C. The dimer **6**, after melting at ca. 190 °C (sharp endotherm), was converted to **4** at 200–210 °C, which then melted at 270 °C. The latter, above its melting point, underwent other transformations (at 280, 310, and ca. 375 °C), but these have not been related to any particular process. The pure dimer **6** was stable to 190–195 °C (Figure 1), where it melted; transformations above 200 °C were similar to those noted for **5**. The COD dimer **4** underwent an endothermic transformation at 110 °C (Figure 1), which, though intriguing, has neither been rationalized nor studied further.[10] Otherwise, it was stable until it melted at ca. 290–295 °C; this is appreciably higher than the melting point previously reported for **4** (230–231 °C[1d]) and normally observed in this work (ca. 260–270 °C; however, cf. footnote 25). Above this temperature, this dimer exhibited the same exothermic maxima as did **5** and **6**. TGA revealed that there were fragmentation processes occurring at higher temperatures. Although the dimers **5** and **6** showed some minor loss of weight below 175 °C or so, they were remarkably free of fragmentation to about 250–275 °C. The nature of the lower temperature fragmentation is unknown, although the dimer **6** released some hydrogen cyanide upon storage. Rapid degradation occurred above 275 °C or so, with total weight loss of ca. 50, 60, and 15%, respectively, for **4**, **5**, and **6** (the much lower weight loss for **6** is inexplicable). Except as noted below, no discrete products arising from high-temperature degradation could be isolated or characterized. It may be of significance that no phthalonitriles could be de-

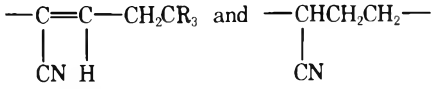
Table II. Irradiation of Dimers 3, 4, and 6

Dimer	Irradiation source[a]	Solvent, sensitizer[b]	Product % yield[c] 2	3	4	8
3	Hg	CH_2Cl_2, BP		96		
4	Sun (Pyrex)	Acetone			>90	+[d]
	Sun (quartz)	CH_2Cl_2			>90	
	Sun (quartz)	Acetone			>55	+[d]
	Hg	Acetone				30
	Hg	CH_3CN, BP		25		6
6	Sun (Pyrex)	Acetone			70	+[d]
	Sun (quartz)	Acetone			54	10
	Hg	Acetone				~30
	Hg	Benzene, BP		12	44	28
	Hg	CH_3CN, BP	12	12		5

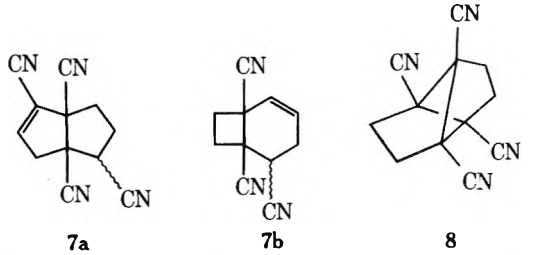
[a] Hg is medium-pressure mercury vapor lamp, unfiltered, in quartz apparatus. [b] BP is benzophenone. [c] Isolated yields. [d] Detected but not isolated in a pure state.

tected (by HPLC) among the thermal decomposition products; in theory, at least, these could have arisen by loss of hydrogen cyanide and acrylonitrile from **4** or **6** (and would approximate the 50% weight loss found by TGA for **4**).

Since thermal analyses suggested that other products might be formed at higher temperatures, these processes were studied further. Heating any of the dimers **4, 5,** or **6** for a short time under nitrogen at 275 °C, followed by high-vacuum sublimation, gave the product **7**, probably as a mixture of epimers. The yield was higher starting from **4** (75% crude yield, vs. 10% or so from **6**), so this dimer may be the actual precursor. Based entirely upon spectral data, the structure **7a**, bicyclo[3.3.0]oct-2-ene-1,2,5,6-tetracarbonitrile, rather than the isomeric **7b**, bicyclo[4.2.0]oct-2-ene-1,2,5,6-tetracarbonitrile, has been assigned the product. Of these two possibilities, 270-MHz ^{1}H NMR (Figure 2)[12] suggests the presence of



linkages, thus pointing to **7a** rather than **7b**. The vinyl hydrogen (at δ 7.23) consists of a triplet ($J \sim 3$ Hz). The next hydrogen (δ 4.11), due to the HCCN group, is somewhat more complex than might be anticipated, but it is assumed that this may be due to the presence of mixed epimers (this is the asymmetric center in either **7a** or **7b** not "fixed" stereochemically that may give rise to epimers). The "allylic"



7a **7b** **8**

methylene hydrogens (at δ 3.55) appear as a classical AB quartet pattern with further coupling ($J \sim 3$ Hz) to the vinylic hydrogen; this pattern specifically excludes **7b**, since the corresponding hydrogen in this would be split not only by the vinylic proton but also by that on the sp^3 carbon bearing the cyano group, leading to a far more complicated appearance. The methylene hydrogens in the saturated C_5 ring are split into two complex groups, resonances corresponding to three protons centered at ca. δ 2.6 and that of one (obscured somewhat by the solvent peak) at ca. δ 2.1. No thermal analyses were made of **7**; thus, any pattern of its formation or decomposition in the DTA of the dimers **4** or **6** (Figure 1) was not deduced.

Interesting degradations were also found during investi-

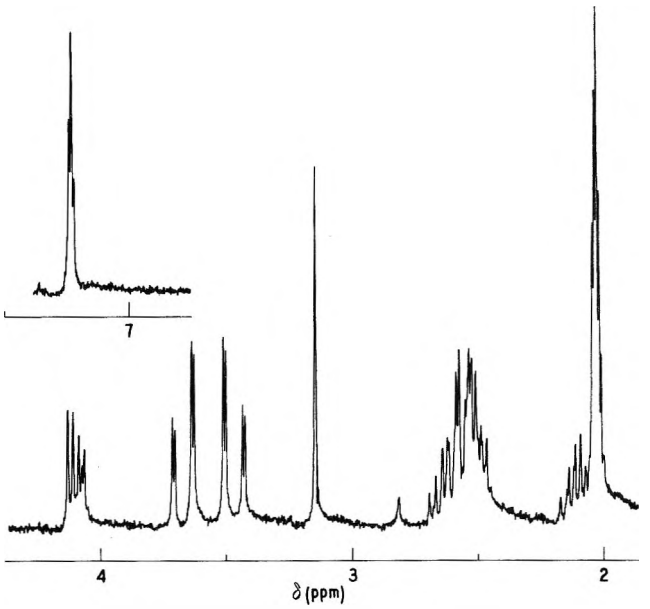
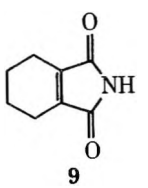


Figure 2. 270-MHz ^{1}H NMR spectrum of **7** in CD_3CN (saturated solution; measured downfield from internal tetramethylsilane); resonance at δ ca. 2.0 is due to solvent impurity, that at δ ca. 3.15 due to water.

gation of the photolytic behavior of some of these dimers (Table II). The VCH dimer **3** was essentially stable to UV irradiation. However, both of the COD dimers **4** and **6**, depending upon the conditions, underwent extensive rearrangement and degradation. The major processes that were recognized included the conversion of **6** into **4** (isolated in good yield when carried out in benzene, in which **4** is insoluble), isomerization of either **4** or **6** to **3**, degradation of **6** to the diene **2** (photolytically labile toward polymerization), and isomerization of either of the COD dimers **4** or **6** to a new dimer, tricyclo[3.3.0.$0^{2,6}$]octane-1,2,5,6-tetracarbonitrile (**8**) (see below for a more convenient synthesis of **8**). There was no evidence for the processes **6** → **5** (the reverse of the thermal cycloreversion), **4** → **5**, or **4** → **6**, nor for the formation of **7** under any irradiation conditions. As observed for the thermal conversion of **5** to **6**, the use of "reactive" solvents (i.e., THF or acetone) for the photolytic reactions resulted in the formation of byproducts incorporating these solvent molecules.[13]

While there was no evidence for the formation of **8** among the thermal transformation products of **4** or **6** just noted,[14] there is ample precedent for the photochemical formation of tricyclo[3.3.0.$0^{2,6}$]octanes from 1,5-cyclooctadienes.[15] The structure assigned to the dimer **8** was consistent with both its chemical behavior and spectral analyses. It was a remarkably



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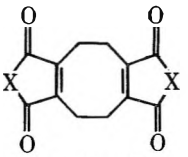
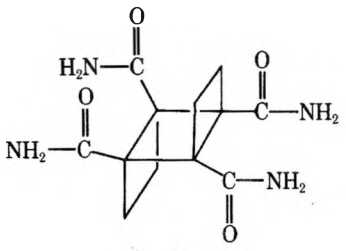


10a, X = NH
b, X = O



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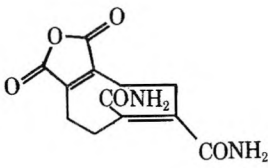

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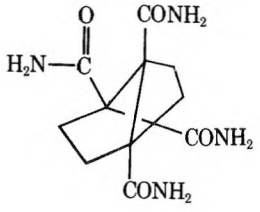

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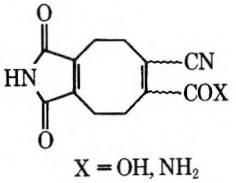


X = OH, NH_2

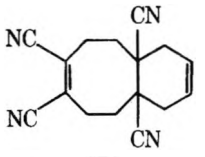
14

stable compound, surviving unchanged for at least 30 min at 300 °C (its tetraamide **13** was stable to 400 °C). Its symmetry was demonstrated by NMR data; in Me_2SO-d_6, its ^1H NMR spectrum consisted of a singlet (δ 2.57), while its ^{13}C NMR spectrum was three lines (at δ 24.62, 53.51, and 112.2 for methylene, quaternary, and cyano carbons, respectively[16]).

The spatial relationship of the cyano groups in these dimers, as well as a measure of the relative stability of related anhydride or imide structures, was indicated by the results of some hydrolysis studies. Thus, by quenching a sulfuric acid solution of the nitrile with methanol (or ice water), cyclohexene-1,2-dicarbonitrile (as a ring equivalent of the dimer **3**), **4**, **5**,[7] **6**, and **8** gave imide **9**, diimide **10a** (or dianhydride **10b**), tetraamide **11**,[7] diamido anhydride **12**, and tetraamide **13**, respectively. Since the tricyclic dimers gave only amide, existing fused C_4 or C_5 ring systems did not allow formation of another C_5 (imide or anhydride) ring fused onto them. The fused C_6–C_5 and cis,cis C_8–C_5 systems (i.e., imides or anhydrides from **3** and **4**) exhibit little strain. Interestingly, and quite expectedly, the cis,trans dimer **6** gave the "fused" anhydride at the cis and the "open" diamide at the trans double bond (giving a verification of the structure assigned to **6**). With **6**, these hydration studies revealed that one of the (trans) cyano groups was considerably more resistant to hydration than the others; except under prolonged treatment with sulfuric acid, a substantial amount of a partially hydrated product **14** was isolated (cf. footnote 34; see below also). The reasons for this behavior are not readily obvious.

The strain existent in the cis,trans dimer **6** allowed it to undergo a number of reactions which failed with the strain-free isomer **4**. While cycloaddition with furan and cyclopentadiene has been noted,[1d] we independently found that butadiene, furan, and even diene **2** itself react exclusively at the trans-substituted double bond[18a] of **6** under relatively mild conditions to give the cycloadducts bicyclo[6.4.0]dodeca-4,10-diene-1,4,5,8-tetracarbonitrile (**15**), 13-oxatricyclo-[6.4.$1^{9,12}$.0]trideca-4,10-diene-1,4,5,8-tetracarbonitrile (**16**), and bicyclo[6.4.0]dodeca-4,10-diene-1,4,5,8,10,11-hexacarbonitrile (**17**), a $[C_6H_4(CN)_2]_3$, respectively. The adducts **15** and **16** were also prepared by heating the tricyclic dimer **5**, the precursor of **6**, with the diene at 100 °C. The reaction of **6** with furan was especially rapid, being practically complete (by ^1H NMR monitoring) shortly after mixing at room temperature. In contrast to this facile reactivity, the isomer **4** underwent no cycloaddition with these dienes, even under forcing conditions.

Attempts to confirm these structures by hydrolysis studies were not as satisfactory as with **4** and **6**.[18b] Thus, quenching sulfuric acid solutions of **15** and **17** with ice gave products that



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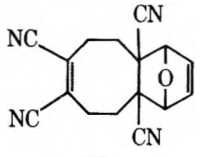

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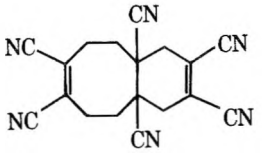

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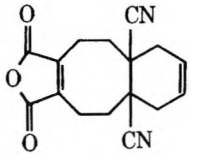

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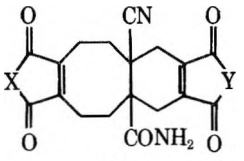


19

X, Y = O, NH

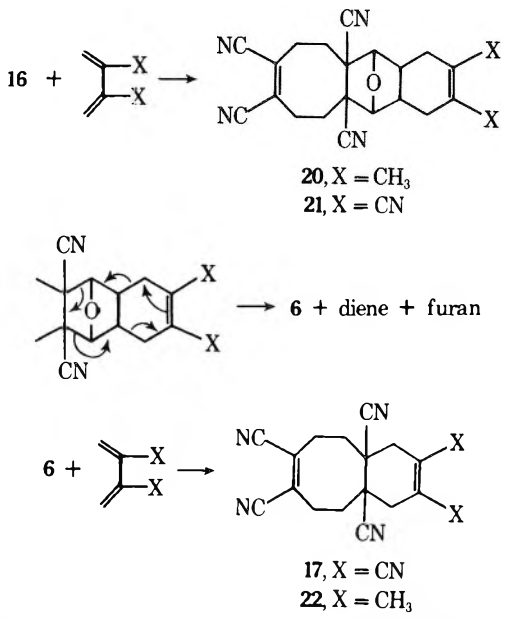
contained cyano, amide (or acid), anhydride, and (from **17**) imide groups, suggesting structures **18** and **19**, respectively. Again, the relative inertness of one of the cyano groups is intriguing but inexplicable (cf. **14**).

Investigation of the thermal behavior of these adducts gave some interesting results. That the furan adduct **16** yields only the parent cis,trans "strained" cyclooctadiene **6** upon thermolysis,[1d] demonstrating uniquely the stereospecificity of both the forward and retrograde Diels–Alder processes in this system, was found independently in the present work. Thus, sublimation of **16** under high vacuum, even at 235 °C, gave **6** as the sublimate with no more than traces of the isomeric **4**. In contrast, the butadiene adduct **15** sublimed unchanged at 220 °C, while the adduct **17**, though not sublimed, survived for some time at 250 °C.

The furan adduct **16** was also photolytically labile. Thus, upon irradiation it extruded furan and gave an excellent yield of the dimer **8**. Since the reaction of **6** with furan is rapid, the synthesis of **8** from **6** could be accomplished in high yield simply by irradiation of a solution of **6** and furan in methylene chloride. This finding suggests that the route to **8** may depend upon the geometry present in the cis,trans isomer **6** (i.e., the reaction path may involve **4** → **6** → **8**, rather than **6** → **4** → **8**), and adduction with furan effectively "locks" the geometry at the intermediate stage to allow the desired reaction vs. degradation to **2** or isomerization to **3** or **4**. Alternatively, another reaction path involving a stepwise cycloreversion of the furan adduct **16** may be operable. At any rate, irradiation of the dimer **4** in the presence of furan gave no improvement in the yield of **8** (cf. Table II).

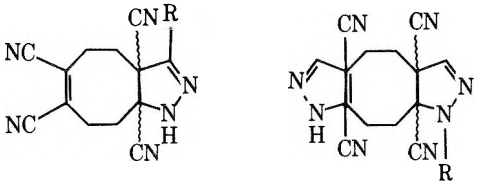
The adduct **16** exhibited some other interesting chemistry. Thus, the remaining double bond in the furan portion of the molecule underwent reaction with selected dienes. With furan itself, while **16** was by far the major product when the dimer **5** was heated with excess furan, there was evidence that further reaction occurred to give a product $(C_{12}H_3N_2)\cdot 2(C_4H_4O)$.[19] Reaction of **16** with 2,3-dimethylbutadiene occurred readily at room temperature with extrusion of furan to give the diene adduct of **6** itself, 10,11-dimethylbicyclo[6.4.0]dodeca-4,10-diene-1,4,5,8-tetracarbonitrile

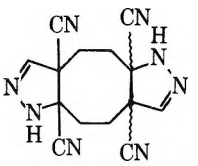
Scheme I



(22). On the other hand, reaction of **16** with diene **2** at room temperature gave the adduct **21** retaining the furan moiety, 17-oxatetracyclo[8.6.$1^{2,9}$.$0.0^{3,8}$]heptadeca-5,13-diene-1,5,6,10,13,14-hexacarbonitrile. However, when the reaction of **16** with **2** was carried out at 80 °C, furan extrusion again occurred to give the adduct **17** analogous to **22**. While no further study of these processes was made, a plausible explanation for this diverse behavior is outlined in Scheme I. An NMR study of the reaction of **16** with 2,3-dimethylbutadiene at room temperature gave no evidence for the intermediacy of **20** itself, showing only the direct formation of **22** and furan[20] at the expense of **16** and the diene. Why cyano groups lend stability to this system (i.e., **21**) is not clear; this same trend was evident also in the order of stability of the adducts, **17** > **15** (≫ **16**).

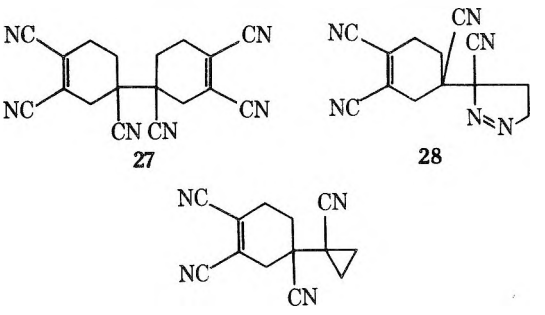
In addition to [4 + 2] Diels–Alder processes, **6** underwent [3 + 2] cycloadditions with diazoalkanes. The reaction with ethereal diazomethane was almost instantaneous to give a high yield of 9,10-diazabicyclo[6.3.0]undeca-4,10-diene-1,4,5,8-tetracarbonitrile (**23**), the "hydrazone" tautomer of an initially formed 1-pyrazoline. With excess diazomethane over a prolonged period, a second cycloaddition occurred, along with a methylation, to give what was apparently 12-methyl-6,7,12,13-tetraazatricyclo[9.3.$1^{4,8}$.0]pentadeca-5,13-diene-1,4,8,12-tetracarbonitrile (**24**), or an isomer (cf. **25**). The dimer



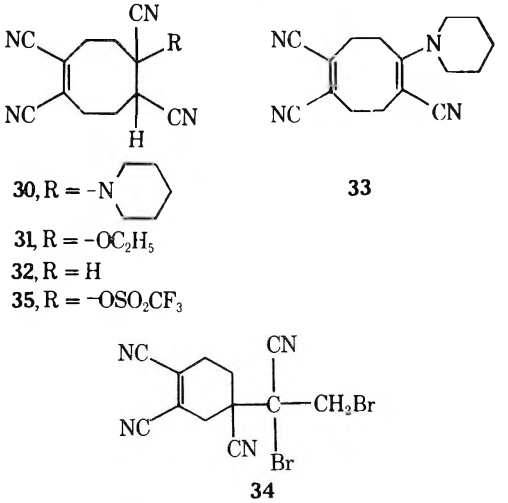


4 underwent very slow cycloaddition with diazomethane to give the normethyl analogue of **24**; in this instance, however, ^{1}H NMR data, showing double singlet resonances for both the nitrogen and olefinic hydrogens, suggested that the product may have been a mixture of isomers (e.g., **25a** and **25b**[21]). The dimer **6** also underwent reaction with ethyl diazoacetate to give **26**, ethyl 9,10-diazo-1,4,5,8-tetracyanobicyclo[6.3.0]-undeca-4,10-diene-11-carboxylate (again the "hydrazone" tautomer of an initially formed 1-pyrazoline). No attempt was made to ascertain the relative positions of the cyano groups in these derivatives. No thermal cycloaddition reactions occurred with either tetracyanoethylene or dimethyl acetylenedicarboxylate and **6**.

For comparison, the reactivity of the VCH dimer **3** toward cycloaddition was also assessed. With the diene **2**, reaction occurred slowly with **3** at 130–140 °C to give a low yield of what is thought to be **27**, 3,3′-bicyclohexenyl-1,1′,3,3′,4,4′-hexacarbonitrile, another $[C_4H_4(CN)_2]_3$ (cf. **17**). With diazomethane, **3** underwent facile reaction at the exocyclic double bond to give epimers (i.e., erythro and threo) of 3-(3-cyclohexenyl)pyrazoline-1′,3,3′,4′-tetracarbonitrile (**28**), which lost nitrogen thermally to give epimers of 4-cyclopropyl-1-cyclohexene-1,1′,2,4-tetracarbonitrile (**29**).



A number of other reagents underwent reaction at the trans double bond of **6** under conditions which the dimer **4** was essentially inert. Thus, piperidine, ethanol in the presence of a base, and hydrogen (over palladium) added to **6** to give 6-(1-piperidino)-1-cyclooctene-1,2,5,6-tetracarbonitrile (**30**), 6-ethoxy-1-cyclooctene-1,2,5,6-tetracarbonitrile (**31**), and 1-cyclooctene-1,2,5,6-tetracarbonitrile (**32**), respectively. Interestingly, the piperidine adduct **30** lost hydrogen cyanide



at its melting point (165 °C) to give apparently the cyanoenamine[23] **33**, 6-(1-piperidino)-1,5-cyclooctadiene-1,2,5-tricarbonitrile. This behavior is similar to that found for the addition products of amines with **1**.[24] On the other hand, **6** gave little brominated product upon treatment with bromine. Rather isomerization occurred rapidly to give **4** in practically quantitative yield. Only catalytic amounts of bromine were required, and isomerization resulted similarly under conditions favoring either radical or ionic addition, e.g., under normal light, or in a polar, aprotic solvent in the presence of large amounts of lithium bromide. Iodine also effected isomerization, but at a somewhat slower rate. This conversion,

Table III. Combustion Analyses

Registry no.	Compd	Formula	Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
41793-19-5	3	$C_{12}H_8N_4$	69.22	3.87	26.90	69.35	4.05	26.15
53399-95-4	4	$C_{12}H_8N_4$	69.22	3.87	26.90	68.87	3.82	26.54
53399-94-3	6	$C_{12}H_8N_4$	69.22	3.87	26.90	68.85	3.82	26.13
62198-24-7	10a	$C_{12}H_{10}N_2O_4$	58.54	4.09	11.37	54.24	4.21	11.32
62198-25-8	12	$C_{12}H_{12}N_2O_5$	54.54	4.54	10.60	55.06	4.65	10.60
62198-26-9	13[a]	$C_{12}H_{16}N_4O_4$	51.42	5.75	20.00	50.45	6.85	19.83
62198-27-0	15	$C_{16}H_{14}N_4$	73.26	5.38	21.36	73.14	4.86	20.61
62198-28-1	17	$C_{18}H_{12}N_6$	69.22	3.87	26.90	69.13	3.97	26.80
62198-29-2	18[b]	$C_{16}H_{15}NO_5$	63.78	5.02	4.65	62.82	5.79	5.83
62198-30-5	19	$C_{18}H_{15}N_3O_6$	58.54	4.09	11.38	58.11	4.09	11.01
62198-31-6								
62198-32-7	21	$C_{22}H_{16}N_6O$	69.46	4.24	22.09	68.96	4.58	21.45
62198-33-8	25	$C_{14}H_{12}N_8$	57.53	4.14	38.33	56.92	4.36	37.84
62198-34-9								

[a] On the crude reaction product. [b] See footnote 37.

complementing the thermal and photolytic 6 → 4 isomerization processes (vide supra), is probably the best procedure for the preparation of 4. Thus, addition of a little bromine (or iodine) to a benzene solution of 6, prepared in this solvent from 5 (vide supra), caused rapid and nearly quantitative precipitation of the insoluble dimer 4. In the same manner, treatment of 5 (the precursor of 6) with bromine in hot benzene gave 4. In related work, the VCH dimer 3 added a molecule of bromine only under irradiation to give 4-(1,2-dibromoethyl)-1-cyclohexene-1,1′,2,4-tetracarbonitrile (34).

A limited study was made of the reactions of 4 and 6 with transition metal reagents. The cis,trans isomer 6 readily formed complexes of the type (*cis,trans*-1,5-cyclooctadiene-1,2,5,6-tetracarbonitrile)bis(triphenylphosphine)M(0) (M = Ni, Pd) when treated with tetrakis(triphenylphosphine)-nickel(0) and -palladium(0), respectively. The nickel complex slowly decomposed in air, while the palladium complex exhibited reasonable air stability. The IR spectra did not reveal the nature of the hydrocarbon–metal bonding, but a simple coordination of the trans double bond to the metal seems most probable. With tetrakis(triethylphosphine)nickel(0), 6 gave a product thought to be (*μ-cis,trans*-1,5-cyclooctadiene-1,2,5,6-tetracarbonitrile)tetrakis(triethylphosphine)dinickel(0), very sensitive to air and handling. When the cis,cis dimer 4 was treated with tetrakis(triphenylphosphine)nickel(0), a brown, insoluble product was formed that did not lend itself to characterization. In contrast, 4 afforded a bright red-orange solid (otherwise uncharacterized) with cuprous chloride, while 6 was apparently unreactive. With 4, silver trifluoromethanesulfonate gave what is thought to be **35**; formally, triflic acid added across one of the double bonds.[25] Under slightly different conditions, 6 gave an ill-defined, insoluble product containing (by IR) two types of nitrile groups and (probably) a sulfonate group (at 2230, 2180, and 1250, 1185 cm^{-1}, respectively).

Experimental Section[26]

Thermal Dimerization of Butadiene-2,3-dicarbonitrile (2). A solution of 15 g of diene 2 and 0.5 g of hydroquinone in 100 mL of benzene, under 200 psig nitrogen pressure, was heated in a rocking autoclave at 95 °C for 65 h. After cooling and venting, an insoluble product was filtered and washed with tetrahydrofuran (THF) and a little acetone to give 2.80 g of crude dimer 4, mp 250–260 °C. Recrystallization from boiling acetone, removing 0.06 g of insoluble polymeric 2, gave the pure dimer 4 as white crystals: mp 268–270 °C dec (lit.[1d] mp 230–231 °C); IR (KBr) 2230 (CN), 1615 cm^{-1} (C=C);[27] UV max (acetonitrile) 225 nm (ε 24 000); ^1H NMR (Me_2SO-d_6) δ 2.98 (s, CH_2);[28] ^{13}C NMR (Me_2SO-d_6) δ 127.5 (C=C), 116.9 (CN), 29.0 (CH_2); mass spectrum *m/e* (rel intensity) 208 (18), 181 (13), 155 (38), 141 (41), 129 (100). After removal of the insoluble 4, the solution was stripped under aspirator pressure to a solid residue. This was stirred with boiling ether to give 11.4 g of (insoluble) dimer 3 (another 0.4 g was recovered from the ether), mp 123–125 °C. Recrystallization from a mixture of acetone, ether, and pentane at −70 °C afforded an analytical sample: mp 125–127 °C (lit.[1a,b] mp 124.5–125 °C); IR (KBr) 2270 and 2260 (CN), 1640 cm^{-1} (C=C);[27] UV max (acetonitrile) 204 and 230 nm (ε 16 600 and 12 500) (lit.[1a,b] 229–230 nm, ε 12 800); ^1H NMR (acetone-d_6) δ 6.52 (s, CH_2=, 2) (a doublet in $CDCl_3$), 3.1–3.3 (m, CH_2, 2), 2.8–3.1 (m, CH_2, 2), 2.3–2.5 (m, CH_2, 2); ^{13}C NMR (acetone-d_6) δ 135.43 (CH_2=), 127.0, 122.8, and 115.6 (C=C), 121.7, 118.3, and 115.9 (CN), 39.35 (quaternary C), 35.64, 28.90, and 26.55 (CH_2); mass spectrum *m/e* (rel intensity) 208 (14), 104 (100).

A solution of 70.0 g of cyclobutene 1 and 0.4 g of hydroquinone in 600 mL of xylene was stirred under nitrogen under reflux for 8 h. After cooling the insoluble solid product (ca. 28 g) was removed and exhaustively extracted with hot acetone, leaving 1.4 g of insoluble polymeric 2. The acetone solution, concentrated to a volume of 200 mL, gave 5.6 g of 4. Further successive concentration gave another 2.7 g of 4, 4.2 g of a mixture of 3 and 4, and finally two crops, 7.3 and 5.0 g, of 3. The xylene solution was stripped under aspirator pressure to give 37 g of an oil. This was taken up in ether, giving 22.0 g of insoluble 3, mp 123–125 °C; a second crop, 0.8 g, was obtained by chilling the ether filtrate at −70 °C. The ether filtrate was distilled in vacuo to give 11.0 g of unreacted 1, bp 60 °C (0.5 mm).

***cis,trans*-1,5-Cyclooctadiene-1,2,5,6-tetracarbonitrile (6).** A mixture of 10.0 g of the dimer 5[1d,7] in 1 L of benzene was stirred under reflux for 20 h. The hot mixture was filtered, removing 0.28 g of insoluble, unreacted 5. Cooling the benzene solution to room temperature gave 0.54 g of the dimer 4. After removal of this, the benzene solution was concentrated to a volume of about 500 mL. Cooling in an ice bath gave 3.89 g of 6. The benzene solvent was removed from the mother liquor, and the residual solid was washed out with ether to give another 5.41 g of 6. Recrystallization from acetone at −70 °C afforded an analytical sample: mp 188.5–189 °C, the clear melt resolidifying at about 191 °C, and this melting at ca. 260 °C dec (lit.[1d] mp 192–193 °C); IR (KBr) 2220 cm^{-1} (CN);[27,29] UV max (acetonitrile) 231–239 nm (ε 13 000);[31] ^1H NMR (acetone-d_6) δ 2.7–3.3 (m); ^{13}C NMR (acetone-d_6) δ 130.5 and 132.2 (C=C), 116.3 and 117.1 (CN), 31.6 and 35.3 (CH_2); mass spectrum *m/e* (rel intensity) 208 (19), 181 (10), 155 (25), 143 (16), 141 (44), 105 (100), 77 (57), 64 (36), 52 (37). This dimer could also be purified by sublimation under high vacuum at ca. 170 °C.

Conversion of 5 to 4. A suspension of 1.0 g of 5 in 50 mL of *o*-dichlorobenzene was stirred under reflux for 40 h. The solid product was filtered and washed with ether to give 0.94 g of 4, mp 261–263 °C (from acetone). Dilution of the dichlorobenzene filtrate with the ether wash gave another 0.05 g of 4.

Bicyclo[3.3.0]oct-2-ene-1,2,5,6-tetracarbonitrile (7). The dimer 4 (0.50 g), in a sublimation apparatus, was heated under a nitrogen atmosphere (at atmospheric pressure) in an oil bath at 280–290 °C for 5 min. Vacuum was then applied to sublime the volatile products. This sequence was repeated twice more on a 0.25-g scale. The combined sublimate was washed with ether to give 0.77 g of crystalline solid. This was resublimed at 170–180 °C under a high vacuum to give an almost white solid, mp 184–186 °C. Recrystallization twice from acetone at −70 °C afforded 7 as small, white crystals: mp 201–202 °C;

IR (KBr) 3070 (HC=), 2250 and 2235 (CN), 1630 (C=C), 1445, 1422, 1320, 1300, 1280, 900 cm^{-1}; ^1H NMR (acetonitrile-d_3), see Discussion, Figure 2; ^{13}C NMR (acetone-d_6) δ 151.1 (HC=), 117.3 (C=), 61.8 and 53.2 (quaternary Cs), 41.5 (methine C), 44.5, 37.5, and 29.9 (methylene Cs); mass spectrum *m/e* (rel intensity) 208 (15), 181 (11), 154 (20), 141 (18), 130 (20), 129 (100), 128 (15).

Photochemical Isomerizations and Degradations of Dimers 3, 4, and 6. These studies were carried out in quartz tubes (for studies utilizing irradiation from the sun), or in a glass–quartz reactor with an immersion-type medium-pressure mercury vapor lamp described previously.[7] The results are summarized in Table II.

A. Irradiation of VCH Dimer 3. A solution of 5.0 g of **3** and 2.0 g of benzophenone in methylene chloride was irradiated with the mercury vapor lamp for 4 days at room temperature in a slow nitrogen sweep. After removal of 0.05 g of an insoluble, amorphous material, the solvent was removed in vacuo. The residue was recrystallized from a mixture of acetone and ether at −70 °C to give, in two crops, 4.80 g of recovered, unreacted **3**.

B. Irradiation of COD Dimer 4. A solution of 1.0 g of **4** and 0.25 g of benzophenone in acetonitrile was irradiated as described under A for 40 h. After filtration of 0.08 g of an insoluble solid, and removal of the solvent in vacuo, the residue was taken up in THF. Concentrating the solution to a volume of 10 mL gave ca. 0.07 g of an unsaturated nitrile [IR (KBr) 2230, 1665 cm^{-1}] otherwise uncharacterized. The THF mother liquor was chilled at −70 °C to give 0.06 g of **8** (see below). The solvent was removed from the filtrate; recrystallization of the residue from a mixture of THF and ether at −70 °C gave 0.25 g of **3**.

A solution of 0.75 g of **4** in 100 mL of acetone was allowed to stand in the sunlight (quartz tube) for 18 days. The resulting yellow solution was concentrated to a volume of 10 mL; unreacted **4** (0.12 g) was removed. Chilling the filtrate at −70 °C gave 0.16 g of a crystalline solid which proved (by IR) to be a mixture of **4** and **8**. Further crystalline crops (ca. 0.50 g) were essentially unchanged **4**.

C. Irradiation of COD Dimer 6. A solution of 0.75 g of freshly sublimed **6** in acetone was irradiated as described under A for 5 days. Solvent was removed from the resulting yellow solution, and the residue was taken up in a little THF. An insoluble solid, 0.25 g, was removed and recrystallized twice from THF to give **tricyclo[3.3.0.0^{2,6}]octane-1,2,5,6-tetracarbonitrile (8),** as white crystals: mp 300 °C; IR (KBr) 2270 cm^{-1} (CN);[27] NMR, see Discussion; mass spectrum *m/e* (rel intensity) 208 (8), 181 (16), 156 (100), 155 (11), 143 (24), 105 (36).

A solution of 0.80 g of **6** and 0.5 g of benzophenone in benzene was irradiated in the same manner for 2 days. Insoluble dimer **4** gradually precipitated and was removed (0.35 g). The benzene solution was stripped in vacuo. Recrystallization of the residue from a mixture of THF and ether gave, in two crops, a total of 0.22 g of **8**. Evaporation of the THF–ether mother liquor at room temperature gave ca. 0.10 g of the VCH dimer **3**.

A solution of 2.0 g of **6** and 0.5 g of benzophenone in acetonitrile was irradiated in the same manner for 2 days. After removal of a small amount of an insoluble material, the solvent was removed in vacuo. The residue was taken up in 10 mL of THF, giving 0.10 g of insoluble **8**. Dilution of the THF filtrate with 10 mL of ether and chilling at −70 °C gave 0.24 g of diene **2**. Dilution of the mother liquor with more ether gave, at −70 °C, 0.18 g of a solid, unsaturated nitrile (by IR) not further characterized. Adding pentane to the filtrate gave 0.25 g of the VCH dimer **3**.

Hydrolysis of Cyclohexene-1,2-dicarbonitrile and Dimers 4, 6, and 8. A solution of the nitrile in sulfuric acid was allowed to stand for several days at room temperature, and was then poured into either a limited amount of ice water or into a large volume of methanol. Insoluble products were filtered, while soluble products were isolated by conventional solvent-removal and/or extraction methods.

A. Cyclohexene-1,2-dicarbonitrile (0.50 g) in 5 mL of sulfuric acid, quenched after 24 h with 25 mL of ice water, gave 0.15 g of an insoluble, partially hydrolyzed product, and, by extraction of the aqueous solution with methylene chloride, cyclohexene-1,2-dicarboximide (**9**):[32] mp 171–173 °C (from a mixture of THF and ether); IR (KBr) 3230 (NH), ca. 1730 cm^{-1} (broad and strong imide carbonyl).

B. COD Dimer 4 (0.5 g) in 5 mL of sulfuric acid was quenched after about 5 days by pouring into 150 mL of methanol. After the solution was heated under reflux for 24 h, the solvent was removed in vacuo. Pouring the residue into 200 mL of ice and water gave the diimide **10a:** mp 321–325 °C (from THF and ether at −70 °C); IR (KBr) 3280 (NH), 1790 (w), and 1700 cm^{-1} (strong imide carbonyl).

A similar sulfuric acid solution of **4**, after 7 days, was poured into 25 mL of crushed ice. The resulting solid, 0.46 g, was recrystallized twice from boiling methanol[33] to give the dianhydride **10b:** mp 263–265 °C (no depression when mixed with authentic[34] **10b;** lit.[35] mp 265–268 °C); IR (KBr) 1850 (w) and 1785 (anhydride C=O), 1670 cm^{-1} (C=C).

C. COD Dimer 6 (1.0 g, resublimed) in 8 mL of sulfuric acid was quenched after 1 week by pouring into 30 mL of crushed ice. The solution was extracted several times with methylene chloride, during which a crystalline solid began to appear in the aqueous phase. Stripping of the extracts gave 0.18 g of **14** as a white solid, mp 171–179 °C (from THF containing a little ether), apparently a mixture of 5-carboxy-6-cyano-1,5-cyclooctadiene-1,2-dicarboxylic anhydride and the 5-carbamoyl analogue:[36] IR (KBr) 3460 and 3350 (OH and NH), 2220 (CN), 1850 (w) and 1760 (anhydride C=O), 1670 (C=O), 1600, 1265, and 1220 cm^{-1} (C–O). The aqueous residue was cooled in ice to give 0.94 g of **12,** 5,6-dicarbamoyl-1,5-cyclooctadiene-1,2-dicarboxylic anhydride:[33] mp 216–218 °C dec (from hot water); IR (KBr) 3450 and 3200 (NH_2), 1840 (w) and 1760 (anhydride C=O), 1670 (s) and 1560–1610 cm^{-1} (m) (amide C=O).

D. Dimer 8 (0.06 g) in 5 mL of sulfuric acid was quenched after 1 week by pouring into 200 mL of methanol. The fine white solid which precipitated slowly was collected and washed with methanol and ether to give tricyclo[3.3.0.0^{2,5}]octane-1,2,5,6-tetracarboxamide (**13**): mp ca. 405 °C dec; IR (KBr) 3230 and 3120 (NH_2), 1690 and 1610 cm^{-1} ($CONH_2$).

Bicyclo[6.4.0]dodeca-4,10-diene-1,4,5,8-tetracarbonitrile (15). A mixture of 2.0 *g* of **6,** 0.5 g of hydroquinone, 50 g of butadiene, and 50 mL of benzene was heated in an autoclave at 100 °C for 3 days. After cooling, 2.35 g (93%) of **15** was removed as an insoluble white solid: mp 267–270 °C dec (from boiling acetone); IR (KBr) 3080 (HC=), 2270 and 2250 (CN), 1635 cm^{-1} (C=C); ^1H NMR (hexafluoroacetone deuterate) δ 5.85 (s, HC=, 2), 2.7–3.2 (m, CH_2, 4), 2.58 (s, CH_2, 4), 2.2–2.5 (m, CH_2, 4).

A similar reaction of 2.0 g of **5,** 0.5 g of hydroquinone, 50 mL of butadiene, and 100 mL of benzene at 100 °C for 2 days gave 2.36 g of **15**.

13-Oxatricyclo[6.4.1^{9,12}.0]trideca-4,10-diene-1,4,5,8-tetracarbonitrile (16). A filtered solution of 5.0 g (24 mmol) of **6** in methylene chloride (100 mL) was mixed with 15 mL of furan, giving a rise in temperature from 24 to 30 °C in 1–2 min (NMR monitoring of a similar reaction in $CDCl_3$ showed that the reaction was complete almost upon mixing). After allowing to stand at room temperature overnight, the solution was chilled at −70 °C to give 2.91 g of **16** (a second crop, 3.83 g, resulted in a quantitative yield), mp 148–152 °C. Recrystallization from acetone or THF afforded an analytical sample: mp 166–168 °C dec (lit.[1d] mp 188–189 °C); IR (KBr) 3140 (HC=), 2250 (CN), 1585 (C=C), 1470, 1450, 1315, 1030, 970, 890, 865 cm^{-1}; ^1H NMR (acetone-d_6) δ 6.85 (AB quartet, HC=, 2), 5.40 and 5.28 (2 s, HCO, 2), 2.4–3.3 (m, CH_2, 8); mass spectrum *m/e* (rel intensity) 208 (4.5), 104 (34), 67 (100).

A mixture of 2.0 g of **5,** 25 mL of furan, and 50 mL of benzene was heated in an autoclave at 100 °C overnight. Volatile materials were removed in vacuo from the reaction solution. The residual oil was treated with acetone, giving 0.66 g of an insoluble material; evaporation of the acetone gave 2.38 g of soluble products. The latter was treated with ether for 5 days (Soxhlet extractor). The ether-insoluble residue, mp 155–160 °C dec, was mixed with the acetone-insoluble product and the combined solids were fractionally crystallized from THF. Early crystalline fractions were (insoluble) starting dimer **5,** followed by the COD dimer **4**. The last fractions were the furan adduct **16**. An intermediate fraction, mp 265–270 °C, was leached with benzene, and the soluble portion was chromatographed on silica, eluting with benzene. The major fraction was a white, crystalline solid: IR (KBr) 2250 (CN), 1480, 1470, 1450, 1030, 920, 905, 865, 840 cm^{-1} (see footnote 19).

Bicyclo[6.4.0]dodeca-4,10-diene-1,4,5,8,10,11-hexacarbonitrile (17). A solution of 1.49 g (7.15 mmol) of **6,** 0.75 g (7.2 mmol) of diene **2,** and 0.1 g of hydroquinone in 50 mL of benzene, stirred under reflux, gradually deposited a white solid. After 28 h, the mixture was filtered to give 1.77 g (80%) of **17,** mp 281–284 °C dec; ca. 0.5 g of **2** was recovered from the filtrate. Recrystallization from acetone gave **17** as white crystals: mp 285–288 °C dec; IR (KBr) 2250 (CN), 1640 and 1630 cm^{-1} (C=C); ^1H NMR (Me_2SO-d_6) δ 2.8–3.2 (m, allylic CH_2, 10), ca. 2.5 (m, CH_2, 4). The same adduct **17** gradually precipitated from an acetone solution of **2** and **6,** held at room temperature for a few days.

Hydrolysis of adducts 15 and 17 was carried out by quenching sulfuric acid solutions of the adducts with ice as described for the dimers above.

A. Adduct 15 (0.22 g) in 5 mL of sulfuric acid after 1 week was added to 25 mL of ice. Extraction with methylene chloride gave 1-

carboxy-8-cyanobicyclo[6.4.0]dodeca-4,10-diene-4,5-dicarboxylic anhydride (**18**): mp 244–245 °C (from THF and ether at −70 °C); IR (KBr) 2280 (CN), 1890 (w), and 1760 cm^{-1} (anhydride C=O).[37]

B. Adduct 17 (0.50 g) in 10 mL of sulfuric acid after 1 week was added to 75 mL of ice. A white solid which slowly precipitated was collected (0.36 g) and recrystallized twice from boiling THF to give 1-carbamoyl-8-cyanobicyclo[6.4.0]dodeca-4,10-diene-4,5,10,11-tetracarboxylic anhydride imide (**19**) as white crystals: mp 316–318 °C; IR (KBr) 3470, 3400, and 3220 (NH), 2270 (w, CN), 1890 (w), 1850 (w), 1760 (s), 1780 (s), 1670 (s), 1610 cm^{-1} (m) (anhydride, imide, and amide C=O).

Chemistry of the Furan Adduct 16. A. Irradiation. A solution of 1.0 g of the adduct **16** and 0.25 g of benzophenone in methylene chloride was irradiated in the apparatus and in the manner described for the dimers **3**, **4**, and **6** for 24 h. The reaction solution was stripped in vacuo, and the residue was washed with ether to give the insoluble dimer **8** as essentially the only product.

A solution of 1.5 g of the dimer **6**, 0.25 g of benzophenone, 10 mL of furan, and benzene, after allowing to stand for 1 h (a little acetone was added to dissolve a solid that appeared), was irradiated in the same manner. A small amount (0.02 g) of insoluble **8** was removed, and the solvent was evaporated in vacuo. Treatment of the residual solid with methylene chloride gave 0.32 g of insoluble **8**. The methylene chloride solution gave an additional 0.66 g of **8** in several crops (65% total yield).

B. Reaction with 2,3-Dimethylbutadiene. A solution of 0.80 g of the adduct **16** and 3 mL of dimethylbutadiene in 25 mL of methylene chloride was allowed to stand at room temperature for 2 weeks. After removal of volatile materials in vacuo, the residual solid was washed with ether to give 0.99 g of an insoluble solid. This was taken up in 10 mL of acetonitrile, removing a small amount of insoluble **22** (see below). Analysis of the acetonitrile solution by HPLC showed that two materials were present, starting **16** and the product **22**. These were separated by preparative HPLC (on a 4 ft × 1 in. Porasil-packed column, eluting with 10% acetonitrile in chloroform); the adduct **22** eluted first (60–75 min) followed by the starting adduct **16** (90–120 min). The adduct **22**: mp 225–227 °C dec; IR (KBr) 2360 (CN), 1640 cm^{-1} (C=C); ^1H NMR (Me_2SO-d_6) δ 2.8–3.1 (t, CH_2, 4), 2.2–2.6 (m, CH_2, 8), 1.65 (s, CH_3, 6); ^{13}C NMR (Me_2SO-d_6) δ 127.82 and 122.73 (C=C), 119.38 and 117.23 (CN), 42.69, 34.10, 27.58, and 17.68 (four sp^3 carbons; it is presumed that the fifth one is masked by the Me_2SO solvent peaks in the same region, δ 36.6–42.9); mass spectrum *m/e* (rel intensity) 290 (14), 275 (6.2), 208 (4.7), 144 (11), 104 (8.7), 82 (100), 67 (36).

C. With Butadiene-2,3-dicarbonitrile (2). A filtered (to remove traces of polymeric **2**) solution of 1.38 g (5 mmol) of **16**, 0.54 g (5 mmol) of **2**, and 0.01 g of hydroquinone in the minimum amount of methylene chloride was allowed to stand at room temperature for 7 weeks as a white solid precipitated gradually. Filtration and washing with methylene chloride gave 1.19 g (59%; a similar reaction mixture, after 19 days, gave 17%) of **21**. The methylene chloride was removed from the filtrate, and the resulting solid was washed with ether to give 0.76 g of solid which, by IR spectral analysis, was largely unreacted **16**. A sample of the crude **21** was dissolved at room temperature in 100 mL of acetone. Addition of ether and chilling at −70 °C gave the adduct **21** as white crystals: mp 320–322 °C dec; IR (KBr) 2240 and 2220 (CN), 1610 (C=C), 922 cm^{-1} (C-O-C); ^1H NMR (Me_2SO-d_6, poor spectrum because of low solubility) δ ca. 4.5 and 4.7 (HCO), 2.2–3.0 (m, CH and CH_2).

A similar solution of 5 mmol each of **2** and **16**, with 0.10 g of hydroquinone, in 50 mL of benzene, was stirred under reflux for 24 h. The resulting mixture was filtered hot to give 0.54 g (35%) of insoluble **17**, mp 283–285 °C dec. Removal of benzene from the filtrate and washing the residue with ether gave 0.96 g (3.5 mmol) of unreacted furan adduct **16**.

Reaction of Dimer 6 with Diazoalkanes. A. With Diazomethane. Ethereal diazomethane was added via a buret to a solution of 1.04 g (5 mmol) of **6** in THF until the yellow color persisted. After the solution was allowed to stand (at room temperature) for 30 min, the volatile materials were removed in vacuo. The residue was dissolved in 20 mL of THF, removing and discarding a small amount of an insoluble material. The solution was chilled at −70 °C to give 0.93 g (74%) of **23**: mp 216–218 °C dec (from THF and ether); IR (KBr) 3310 (NH), 3070 (HC=), 2240 and 2230 (CN), 1590 (C=C), 1560 cm^{-1} (C=N, disappeared upon standing); ^1H NMR (acetone-d_6) δ 8.14 (s, NH, 1), 7.00 (s, HC=, 1), 2.4–3.2 (m, CH_2, 8); mass spectrum *m/e* (rel intensity) 223 (3), 196 (2), 27 (100).

A solution of 1.0 g of **6** in 50 mL of THF was allowed to stand with a threefold excess of ethereal diazomethane at room temperature for 11 days. After stripping in vacuo at room temperature, the residue was taken up in THF and reprecipitated by addition of ether to give 0.58 g of a solid; another 0.65 g was recovered from the mother liquor. This product was recrystallized twice from acetone to give white, crystalline **24**: mp ca. 300 °C dec; IR (KBr) 3280 (NH), 2260 (CN), 1650 cm^{-1} (C=N?); mol wt (mass spectrum) 306.

B. With Ethyl Diazoacetate. A solution of 1.04 g (5 mmol) of **6** and 0.60 g (5 mmol) of ethyl diazoacetate in 50 mL of THF was allowed to stand at room temperature for several weeks. The solvent was removed in vacuo, and the residual solid was washed with ether to give 1.59 g (97%) of **26**: mp 133–135 °C dec (from THF); IR (KBr) 3330 (NH), 2250 (CN), 1725 (C=O), 1590 cm^{-1} (C=N); ^1H NMR (acetone-d_6) δ 9.10 (s, NH, 1), 4.38 (quartet, ethyl CH_2, 2), 2.4–3.5 (m, CH_2, 8), 1.33 (t, CH_3, 3).

Reaction of Dimer 4 with Diazomethane. The COD dimer **4** (1.0 g) in THF was allowed to stand with a threefold excess of ethereal diazomethane at room temperature for 11 days. After removal of 0.11 g of precipitated **4**, the solution was evaporated in vacuo. The residual solid, ca. 2 g, was taken up in THF, removing another 0.16 g of insoluble, unreacted **4**. Chilling the solution at −70 °C gave a little more of **4** which was removed. The mother liquor was concentrated to a volume of about 5 mL; chilling the solution at −70 °C gave 0.36 g of **25**; another 0.32 g was recovered from the mother liquor. Recrystallization from THF and then from acetone afforded **25** as white crystals: mp 227–229 °C dec; IR (KBr) 3330 (NH), 3130 (HC=), 2260 (CN), 1600 cm^{-1} (C=N); ^1H NMR (acetone-d_6) δ 8.20 and 7.90 (s, NH, 2), 7.10 and 6.96 (s, HC=, 2), 2.2–3.2 (m, CH_2, 8).

Reactions of VCH Dimer 3. A. With Butadiene-2,3-dicarbonitrile (in Situ from Cyclobutene-1,2-dicarbonitrile). A mixture of 10.0 g of **3** and 5.0 g of **1** (4.8 mmol each) was heated in an oil bath at 140 °C for 8 h and then at 120 °C for 12 h. The viscous melt was poured into THF, removing 0.42 g of an insoluble product. The THF filtrate was mixed with 300 mL of ether, yielding another 4.87 g of a solid. These two solid portions were digested well with THF (ca. 20 °C). The insoluble portion was recrystallized twice from acetonitrile to give ca. 0.10 g (7%) of white crystals tentatively assigned the structure **27**: mp 295–297 °C; IR (KBr) 2250 and 2230 (CN), 1623 cm^{-1} (C=C).

B. With Diazomethane. A solution of 5.4 g (26 mmol) of **3** in THF was treated with a slight excess of ethereal diazomethane. The resulting solution was allowed to stand at room temperature for 30 min. The volatile materials were then removed in vacuo at room temperature. The tacky, yellow residue was taken up in methylene chloride and ether was added to the solution to the cloud point. Chilling at −70 °C gave 2.10 g of an off-white solid. Recrystallization twice from methylene chloride at −70 °C gave the pyrazoline **28** (probably threo): mp 107–109 °C dec; IR (KBr) 2260 and 2240 (CN), 1620 (C=C), 1565 cm^{-1} (N=N?); ^1H NMR (acetone-d_6) δ 4.95–5.30 (m, CH_2N=N, 2), 2.2–3.3 (m, CH_2, 8); mass spectrum *m/e* (rel intensity) 222 (77), 207 (13), 194 (35), 180 (14), 170 (33), 118 (100), 117 (50), 105 (34), 91 (58). After removal of this isomer of **28**, the filtrate was evaporated. The residue was recrystallized twice from a mixture of THF and ether, and then twice from acetone to give the isomeric pyrazoline **28** (probably erythro): mp 115–117 °C dec; IR (KBr) 2240 and 2260 (CN), 1625 (C=C), 1555 cm^{-1} (N=N?); ^1H NMR (acetone-d_6) δ 4.98–5.33 (m, CH_2N=N, 2), 2.3–3.4 (3 m, CH_2, 8); mass spectrum *m/e* (rel intensity) 222 (27), 207 (5), 194 (13), 180 (7), 170 (13), 118 (100), 105 (37), 91 (74).

The (presumed) threo adduct **28** (1.0 g) in toluene was heated at 100 °C (steam bath) for about 2 h. Removal of the toluene and recrystallization of the residue three times from a mixture of THF and ether gave the cyclopropane **29**: mp 144–146 °C; IR (KBr) 3120 (cyclopropane CH?), 2270 and 2250 (CN), 1635 cm^{-1} (C=C); ^1H NMR (acetone-d_6) δ 2.2–2.5 (m, CH_2, 2), 2.7–3.2 (m, CH_2, 4), 1.49 (s, cyclopropane CH_2, 4); ^{13}C NMR ($CDCl_3$) sp and sp^2 carbons at δ 125.99, 121.55, ca. 119.5, ca. 117.6, 114.41, and 114.21, quaternary sp^3 carbons at δ 39.21 (in C_6 ring) and 16.27 (in C_3 ring), and methylene sp^3 carbons at δ 35.71, 28.49, and 26.51 in the C_6 ring and at δ 12.30 and 12.10 in the C_3 ring; mass spectrum *m/e* (rel intensity) 222 (33), 207 (5), 194 (13), 180 (6), 170 (26), 129 (14), 118 (100), 105 (26), 91 (57). Treatment of the (presumed) erythro **28** in the same manner gave a crystalline isomer of **29**: mp 117–118 °C; IR (KBr) virtually identical with that of the isomer, mp 144–146 °C (not characterized further).

C. With Bromine. A solution of 1.04 g (5 mmol) of **3** in 25 mL of methylene chloride in a Pyrex flask was stirred while 0.80 g (5 mmol) of bromine was added; there was no reaction. The solution was transferred to a quartz tube, and the bromine color faded rapidly (in normal, fluorescent light). After standing for a few days, a small amount of an insoluble solid was removed, and solvent was removed from the filtrate. The residue was triturated with ether, recovering 1.53 g (83%) of **34**. Recrystallization afforded white crystals: mp

158–160 °C; IR (KBr) 2250 (CN), 1640 cm^{-1} (C=C); ^1H NMR (acetone-d_6) δ 4.40 (AB quartet with "doubling" caused by diastereomers, CH_2Br, 2), 2.2–3.5 (CH_2, 6); ^{13}C NMR (Me_2SO-d_6) δ 125.7 (C=C), 121.7 and 119.3 (BrCCN in 2 isomers), 116.3 and 114.7 (CN), 53.6 (BrCCN), 44.8 (CCN), 37.8, 33.9, 27.6, and 25.3 (CH_2); mass spectrum *m/e* (rel intensity) 208 (25), 193 (15), 179 (14), 154 (13), 129 (15), 104 (100), 79–82 (4 strong peaks, Br) (spectrum is similar to that of a mixture of **3** and bromine).

Other Reactions of Dimer 6. A. With Piperidine. A solution of 1.04 g (5 mmol) of **6** in 100 mL of methylene chloride was mixed with 0.42 g (5 mmol) of piperidine. The amber-colored solution was allowed to stand at room temperature for 1 week, and then the solvent was stripped in vacuo. The residue, recrystallized twice from THF, gave a nearly quantitative yield of **30:** mp 163–164 °C dec; IR (KBr) 2270 and 2250 (CN), 1620 cm^{-1} (C=C); ^1H NMR (acetone-d_6) δ 3.7–4.1 (m, HCCN, 1), 2.3–3.0 (m, CH_2, 12), 1.5–1.7 (m, CH_2, 6); mass spectrum *m/e* (rel intensity) 266 (15), 162 (24), 128 (12), 27 (100). A sample of the adduct **30,** held at its melting point for 15 min, gave crude **33** as an oil:[23] IR (neat) 2250 and 2180 (CN), 1635 and 1570 cm^{-1} (C=C).

B. With Ethanol. A mixture of 0.5 g of **6** in 5 mL each of ethanol and pyridine was allowed to stand at room temperature. After 4 days, solution was practically complete, the solution was stripped under aspirator pressure. The residual solid was taken up in THF, discarding a small amount of an insoluble material; sequential addition of ether and chilling at −70 °C gave several crops of the ether **31,** mp 157–160 °C. Fractional recrystallization from ethanol, mixtures of acetone and ether, or a mixture of THF and ether gave two isomers, more soluble, mp 169–171 °C, and much less soluble, mp 144–152 °C (still impure) (spectral analyses were almost identical): IR (KBr) 2250 (CN), 1050 cm^{-1} (C–O–C); ^1H NMR (acetone-d_6) δ 3.6–4.1 (complex of overlapping m, CH, CH_2O, 3), 2.3–3.0 (m, ring CH_2, 8), 1.33 (t, CH_3, 3); mass spectrum *m/e* (rel intensity) 294 (1), 199 (100), 172 (15), 171 (15), 146 (22), 144 (22), 117 (19), 45 (24).

C. Hydrogenation. A mixture of 0.5 g of **6,** 0.1 g of palladium hydroxide on diatomaceous earth, and 25 mL of acetonitrile was reduced in a Brown[2] hydrogenator. After removal of the catalyst and the solvent, the product solid was recrystallized from a mixture of THF and ether (Norit), then once from methanol (very difficultly soluble) to give **32** as small, yellow crystals: mp 208–210 °C; IR (KBr) 2260 and 2230 (CN), 1620 cm^{-1} (C=C); ^1H NMR (Me_2SO-d_6) δ 4.02 (t, HCCN, 2), 2.5–2.8 (m, CH_2, 4), 2.0–2.3 (m, CH_2, 4); mass spectrum *m/e* (rel intensity) 210 (10), 183 (19), 157 (18), 156 (19), 143 (11), 130 (24), 129 (14).

D. With Bromine. A solution of 1.04 g (5 mmol) of **6** in 100 mL of benzene was stirred under nitrogen with heating while a solution of 0.80 g (5 mmol) of bromine in 50 mL of benzene was added over a 90-min period. After the first few drops of bromine solution, the brown color persisted, and a white solid slowly precipitated. The mixture was stirred for another 1 h under reflux, and was then filtered hot to give 1.50 g[38] of the dimer **4,** mp 279 °C. Removal of the solvent from the filtrate gave ca. 0.5 g of a lachrymatory semisolid (containing apparently HBr). Treating this with ether gave another 0.02 g of insoluble **4;** nothing more could be isolated. Similar results were found using only catalytic amounts of bromine or iodine (100 and 65–70% conversion in 2 h at room temperature, respectively).

A stirred solution of 1.04 g of **6** and 25 g of lithium bromide in 150 mL of acetonitrile was treated dropwise over a 1-h period at room temperature with a solution of 0.80 g of bromine in 25 mL of acetonitrile. The resulting golden orange solution, after standing at room temperature overnight, was stripped in vacuo. The solid residue was triturated with 80–100-mL portions of methylene chloride until the solid was colorless; the residue, ca. 26 g, was completely water soluble. The methylene chloride (ca. 600 mL) was evaporated in vacuo. The residue was taken up in 25 mL of THF, removing 0.67 g of insoluble **4.** The solution was stripped, and the residue was taken up in ether, giving another 0.16 g of **4.** Evaporation of the ether gave an oily material from which no other discrete material could be isolated.

A mixture of 5.0 g of the tricyclo dimer **5** in 600 mL of benzene was stirred under reflux for 20 h, giving complete solution. A crystal of iodine was added to the hot solution; crystallization of **4** commenced shortly. After the solution had stood at room temperature for 65 h, 5.47 g[36] of **4** was removed; another 0.12 g of **4** was isolated from the mother liquor. Alternatively, 10.0 g of **5** in 1 L of benzene was stirred under reflux for 65 h. A small amount of insoluble material was filtered from the hot solution. Cooling the filtrate in ice gave 6.90 g of dimer **6.** The benzene filtrate was heated to boiling, and a crystal of iodine was added. Handling of the reaction mixture as described above gave a total of 2.96 g of **4.**

E. With Tetrakis(triphenylphosphine)nickel(0).[39] A solution of 1.11 g (1.0 mmol) of the title Ni(0) reagent and 0.21 g (1.0 mmol) of **6** in 9 mL of benzene was prepared under argon and allowed to stand overnight. Addition of hexane caused a yellow-brown oil to separate. Benzene was slowly added until the solution was homogeneous. Yellow-brown crystals began to form. After cooling at 5–10 °C for 2.5 h, the solid (0.32 g) was removed; two additional crops (0.18 g of red crystals and 0.09 g of orange crystals) were collected from the filtrate, giving a 71% total yield of air-sensitive (*cis,trans*-1,5-cyclooctadiene-1,2,5,6-tetracarbonitrile)bis(triphenylphosphine)-nickel(0) (containing one-half a molecule of benzene solvate): mp (red crystals) 217–218 °C dec (in argon); IR (KBr) 2230 and 2180 cm^{-1} (CN) (all three crops had identical IR spectra). Anal. Calcd for $C_{48}H_{38}N_4NiP_2 \cdot 0.5C_6H_6$: C, 73.75; H, 4.98; N, 6.75. Found: C, 74.15; H, 4.74; N, 6.85.

F. With Tetrakis(triphenylphosphine)palladium(0).[39] A solution of 0.96 g (0.83 mmol) of the title Pd(0) reagent and 0.20 g (0.96 mmol) of **6** in 20 mL of benzene was allowed to stand over the weekend. After removal of some red-brown solid, the solution was diluted with 20 mL of hexane, causing an oil to separate. Benzene was added to the rapidly stirred mixture in ca. 1-mL increments until the oil had redissolved; a pale yellow solid began to precipitate before solution was complete. After cooling to ca. 0 °C, 0.57 g of (*cis,trans*-1,5-cyclooctadiene-1,2,5,6-tetracarbonitrile)bis(triphenylphosphine)palladium(0) (again as a benzene solvate) as yellow, air-stable crystals was collected: mp 261–263 °C dec (in argon) (after a single recrystallization from a mixture of benzene and hexane); IR (KBr) 2180 and 2220 cm^{-1} (CN). Anal. Calcd for $C_{48}H_{38}N_4P_2Pd \cdot 0.5C_6H_6$: C, 69.74; H, 4.71; N, 6.38. Found: C, 69.74; H, 4.62; N, 6.36.

G. With Tetrakis(triethylphosphine)nickel(0).[39] A hexane solution of the title nickel reagent, prepared from triethylphosphine and bis(1,5-cyclooctadiene)nickel(0), was mixed with a solution of **6** (ca. 0.2 g) in 5–10 mL of benzene. A brown solid began to precipitate from the initially homogeneous solution. The reaction gave 0.18 gm of (μ-*cis,trans*-1,5-cyclooctadiene-1,2,5,6-tetracarbonitrile)tetrakis(triethylphosphine)dinickel(0) as brown crystals: mp 235–238 °C dec (sealed in argon); IR (KBr) 2170 cm^{-1} (CN). Anal. Calcd for $[C_{12}H_8N_4][Ni(PEt_3)_2]_2$: C, 54.16; H, 8.58; N, 7.02. Found: C, 54.59; H, 8.02; N, 7.61.

Reaction of Dimer 4 with Silver Trifluoromethanesulfonate. A solution of 1.04 g (5 mmol) of **4** and 0.10 g (0.4 mmol) of the title silver reagent in 150 mL of acetonitrile was allowed to stand at room temperature for 10 days. After solvent was removed from the colorless solution in vacuo, the residual material was taken up in 60 mL of THF, giving 0.92 g of insoluble, unreacted **4,** mp 294–295 °C dec.[25] The THF filtrate was evaporated in vacuo. Washing the residue with ether gave 0.25 g of **35:** mp 220–222 °C dec (from a mixture of acetone and ether); IR (KBr) 2270 and 2240 (CN), 1610 (C=C), 1250 (broad), and 1180 cm^{-1} (SO_2). Anal. Calcd for $C_{12}H_8N_4 \cdot CF_3SO_3H$: C, 43.58; H, 2.53; N, 15.64. Found: C, 44.83; H, 2.61; N, 17.99.

Acknowledgments. We are indebted to Mr. A. N. Widener for his careful attention in carrying out a great deal of the experimental work, and to Professor L. M. Stock for many stimulating discussions and helpful suggestions.

Registry No.—**1,** 3716-97-0; **2,** 19652-57-4; **5,** 53399-93-2; **7a,** 62198-35-0; **8,** 62198-36-1; **9,** 4720-86-9; **10b,** 28885-97-4; **14** (X = OH), 62198-37-2; **14** (X = NH_2), 62198-38-3; **16,** 62249-51-8; **22,** 62237-83-6; **23,** 62198-39-4; **24,** 62198-40-7; **26,** 62198-41-8; **27,** 62198-42-9; *erythro*-**28,** 62198-43-0; *threo*-**28,** 62198-44-1; *erythro*-**29,** 62198-45-2; *threo*-**29,** 62198-46-3; **30,** 62198-47-4; *cis*-**31,** 62198-48-5; *trans*-**31,** 62198-49-6; **32,** 62198-50-9; **33,** 62198-51-0; **34** isomer 1, 62198-52-1; **34** isomer 2, 62198-54-3; **35,** 62198-53-2; hydroquinone, 123-31-9; benzophenone, 119-61-9; cyclohexene-1,2-dicarbonitrile, 52477-67-5; tetrakis(triphenylphosphine)nickel(0), 15133-82-1; (*cis,trans*-1,5-cyclooctadiene-1,2,5,6-tetracarbonitrile)bis(triphenylphosphine)-nickel(0), 62228-13-1; tetrakis(triphenylphosphine)palladium(0), 14221-01-3; (*cis,trans*-1,5-cyclooctadiene-1,2,5,6-tetracarbonitrile)bis(triphenylphosphine)palladium(0), 62228-14-2; tetrakis-(triethylphosphine)nickel(0), 52230-29-2; (μ-*cis,trans*-1,5-cyclooctadiene-1,2,5,6-tetracarbonitrile)tetrakis(triethylphosphine)di-nickel(0), 62228-15-3; silver trifluoromethanesulfonate, 2923-28-6.

References and Notes

(1) (a) D. Belluš, K. von Bredow, H. Sauter, and C. D. Weis, *Helv. Chim. Acta,* **56,** 3004 (1973); (b) D. Belluš and C. D. Weis, *Tetrahedron Lett.,* 999 (1973); (c) D. Belluš and G. Rist, *Helv. Chim. Acta,* **57,** 194 (1974); (d) D. Belluš, H.-C. Mez, G. Rihs, and H. Sauter, *J. Am. Chem. Soc.,* **96,** 5007 (1974).
(2) J. C. Westfahl and D. S. Sears, U.S. Patent 2 587 558 (1952).
(3) E. Müller, R. Mayer-Mader, and K. Dinges, Abstracts, 163rd National Meeting

of the American Chemical Society, Boston, Mass., April 1972, No. INDE-44.

(4) C. S. Marvel and N. O. Brace, *J. Am. Chem. Soc.*, **71**, 37 (1949).

(5) Further comments on the processes possibly involved in this dimerization will be made as a part of our findings dealing with the dual reactivity of diene **2** as both a diene and a dienophile in Diels–Alder processes.[6]

(6) R. L. Cobb and J. E. Mahan, to be published.

(7) R. L. Cobb and J. E. Mahan, *J. Org. Chem.*, preceding paper in this issue.

(8) We too arrived at this finding and conclusion independently. We are grateful to Professor L. M. Stock for his help in this interpretation.

(9) For example, THF with **5** (60 h under reflux) gave, in addition to **6** (ca. 70%), a small amount of a crystalline product: mp 160–161 °C (from a mixture of THF and ether); IR (KBr) 2250 (CN), 1075 cm^{-1} (ether); ^1H NMR ($CDCl_3$) δ 3.7–4.4 (m, HCO, 3), ca. 3.5 (t, HCX, 2), 2.55 (m, CH_2CX, 8–9), 1.8–2.4 (m, CH_2CO, 4); mass spectrum *m/e* 280 (parent ion for $C_{12}H_8N_4 + C_4H_8O$), 71 ($C_4H_7O^+$·, base peak).

(10) One possibility is that this endotherm may arise from the formation of a more favorable conformer. With *cis,cis*-1,5-cyclooctadiene itself, conformers are frozen below about −175 °C.[11]

(11) F. A. L. Anet and L. Kozerski, *J. Am. Chem. Soc.*, **95**, 3407 (1973).

(12) We are indebted to Professor L. M. Stock for this data and interpretation.

(13) For instance, irradiation of **6** in THF in the presence of benzophenone gave, by chromatographic separation (SiO_2, using benzene–THF as the eluting solvent), a small amount of a crystalline solid: mp 174–178 °C (from THF and ether); IR (KBr) 2250 (CN), 2020 (?), 1450, 1075 cm^{-1} (ether); ^1H NMR ($CDCl_3$) δ 3.6–4.3 (m, HCO, 3), 1.7–3.0 (m, CH_2, 13); mass spectrum *m/e* (rel abundance) 280 (0.3, M^+ for $C_{12}H_8N_4 + C_4H_8O$), 182 (3.6, $C_{12}H_8N_4 - CN$), 71 (100, $C_4H_8O - H^+$·).

(14) Thermal processes have been used to effect such a transformation with 1,2,5,6-tetrachloro-1,5-cyclooctadiene: K. C. Eberly and R. J. Reid, U.S. Patent 2 626 961 (1953).

(15) (a) R. Srinivasin, *J. Am. Chem. Soc.*, **86**, 3318 (1964); (b) I. Haller and R. Srinivasin, *ibid.*, **88**, 5054 (1966); (c) J. G. Baldwin and R. H. Greeley, *ibid.*, **87**, 4514 (1965); (d) R. G. Salomon, K. Folting, W. E. Streib, and J. K. Kochi, *ibid.*, **96**, 1145 (1974).

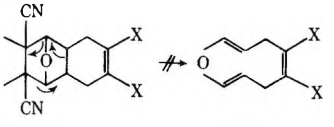
(16) The parent (unsubstituted) tricyclo[3.3.0.0]octane exhibits (^{13}C) resonances[17] at δ 26.8 and 52.2 for methylene and quaternary carbons, very close to those for the sp^3 carbons in **8**. For comparison, the corresponding resonances for **5** (in CF_3SO_3H) are δ 36.8 and 44.4, respectively.[7]

(17) See footnote 10 of ref 1d.

(18) (a) Other workers have demonstrated the Diels–Alder reactivity of trans vis-a-vis cis cycloalkenes; see, e.g., R. Wheland and P. D. Bartlett, *J. Am. Chem. Soc.*, **95**, 4003 (1973). (b) A comment on the stereochemistry at the bridgehead positions in **15–22** was requested by a referee. The hydrolysis studies did not provide this information. However, the stereospecificity of Diels–Alder reactions and the thermal cycloreversion of **16** to **6**[1d] at least suggest that the cyano groups in the bridgehead positions of **15–17** (and also **21** and probably **22**) are in a trans relationship. The ^1H NMR spectrum of **16** (i.e., an AB quartet for the olefinic protons and two singlets for the HCO protons, see Experimental Section) confirms the absence of a plane of symmetry in the molecule and implies a trans fusion of the rings. No further analysis of this was attempted.

(19) While isolation of discrete by-products was extremely difficult, a minute amount of a crystalline material was separated that exhibited (^1H NMR) resonances suggesting two types of OCH hydrogens (δ ca. 5.4 and 4.8) and one type of olefinic hydrogen (δ ca. 6.4).

(20) Disregarding kinetic considerations, observance of the direct formation of furan may obviate the possibility of an alternative cycloreversion process leading to an oxacyclononatriene:



(21) The formation of isomeric pairs of adducts such as these has been observed in at least one other diolefinic system.[22] Alternatively, but less likely in our opinion, the "double" resonances may have been due to "scrambling" of the stereochemical positions of the cyano groups.

(22) M. G. Barlow, R. N. Haszeldine, W. D. Morton, and D. R. Woodward, *J. Chem. Soc., Perkin Trans. 1*, 1798 (1973).

(23) Evidence for this was intense absorption in the infrared region at ca. 2180 and 1570 cm^{-1} (cf. ref 24).

(24) R. L. Cobb and J. E. Mahan, *J. Org. Chem.*, **42**, 1948 (1977).

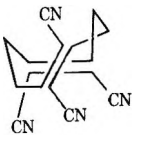
(25) Interestingly, the recovered unreacted **4** from this experiment had the highest melting point observed in this work (294–295 °C dec vs. 268–270 °C dec for an analytical sample; lit.[1d] mp 230–231 °C). This melting point corresponds closely to the endotherm in the DTA indicative of the true melting point (Figure 1). This suggests that the melting point of **4** as ordinarily prepared may be depressed by small amounts of an impurity not easily removed, and that this impurity is the material that actually underwent reaction with silver triflate. It may be noteworthy in this respect also that solutions of **4** (in, e.g., acetone) were often pink; their color gradually faded upon standing.

(26) Melting points (uncorrected) were determined on a Mel-Temp apparatus; IR spectra[27] were recorded on a Perkin-Elmer Model 137 Infracord; NMR spectra were determined (vs. internal Me_4Si) on Varian T60, XL100, and CFT 20 instruments; mass spectra were obtained on a CEC 110B instrument (70 eV).

(27) For rapid routine product determination, IR scanning was most helpful. Spectral areas particularly useful follow: for **3**, a closely spaced "triad" at 1450, 1430, and 1410 cm^{-1}, and the strong vinylidene absorption at 980 cm^{-1}; for **4**, two sets of "triads", (strong) at 1490, 1450, and 1430, and (weaker) at 960, 935, and 910 cm^{-1}; for **5**, single strong absorptions at 1450 and 805 cm^{-1}, and "double", somewhat weaker absorptions at 1285 and 1250 cm^{-1}; for **6**, a single strong absorption at 1450 cm^{-1}, and "double" weaker absorptions at 1030 and 1005 cm^{-1}; for **8**, "paired" absorptions at 1470 and 1450, and at 1310 (2 peaks) and 1285 cm^{-1}.

(28) Also a singlet resonance on a 270-MHz instrument.[12]

(29) Especially intriguing in the IR spectrum of **6** was the lack of absorption for C=C stretching vibrations at ca. 1640 cm^{-1}. Such an absorption band would be expected only for the cis substituted (dicyano) ethylene group, since the "stretching" in symmetrical systems (i.e., trans) is very weak and may be undetected. The absence of the absorption anticipated for the "cis" double bond in **6** suggests that there may be an interaction between the two π-electron systems, perhaps enhanced by the cyano groups, that disrupts the normal stretching vibrations.[30,31] A "preferred" conformation for **6** may thus be **6a** as shown, where the π systems are in close proximity and perhaps "overlapping".



6a

(30) We are indebted to Professor Ralph Becker for his aid in this interpretation.

(31) Ordinarily, the ϵ is "additive", i.e., the sum of the ϵ expected for each group at a particular wavelength. For example, the ϵ for **4** is about twice that for **3** (at ca. 230 nm) (or **1**[7]) where there is only a single chromophore. That the ϵ for **6** is not 2 × 12 000 or so suggests also[29] a disruption of some type in the chromophoric π systems.[30]

(32) R. L. Cobb and J. E. Mahan *J. Org. Chem.*, in press.

(33) The remarkable "stability" of anhydrides of this type toward solvolysis may be related to solubility factors. It was observed generally in this work in both the unsaturated C_6 and C_8 ring system.

(34) Authentic **10b** was prepared substantially by the literature method,[35] mp 273–275 °C after a final purification by high vacuum sublimation at 200 °C.

(35) B. S. Green, M. Lahav, and G. M. J. Schmidt, *J. Chem. Soc. B*, 1552 (1971).

(36) As an 80:20 mixture of these two products. Anal. Calcd: C, 58.31; H, 3.75; N, 6.82. Found: C, 58.39; H, 4.80; N, 6.74. A similar mixture was the major product when a sulfuric acid solution of **6** was quenched after only a 48-h reaction time.

(37) Combustion analyses of this product were not at all satisfactory (carbon about 1% low and nitrogen about 1% high); the results suggest the presence of the corresponding amide as an impurity, and perhaps further hydration of the anhydride.

(38) The bromine-catalyzed isomerization of **6** to **4** invariably gave 110–150 wt % yields of "crude" **4**, although spectral analyses (IR and ^1H NMR) showed that **4** was essentially the only material present. Fractional crystallization of products from reactions run under various conditions yielded only **4**. However, in one reaction where the precursor of **6**, i.e., **5**, was treated with bromine in hot benzene, in addition to a 90% yield of **4**, a trace of a bromine-containing product was obtained by fractional crystallization: white crystals (from THF and ether at −70 °C), mp 181–183 °C; IR (KBr) 2250 (CN), 1495, 1060, 945, 900, 770 cm^{-1}; ^1H NMR (THF) δ 5.35 (AB quartet, HCBr?) (other resonances obscured by solvent); mass spectrum *m/e* (rel intensity) 233 (3), 231 (3), 213 (8), 153 (100), 131 and 133 (ca. 9), 126 (14), 80 and 82 (25, HBr), 79 and 81 (12, Br), 75 (26), 72 (22), 71 (18), 52 (52). Anal. Calcd for $C_{12}H_8Br_2N_4$: Br, 43.5. Found: Br, 39.7.

(39) Preparation and handling were carried out under argon in a drybox.

Addition of Some 1,3-Diaryltriazenes to Tetracyanoethylene

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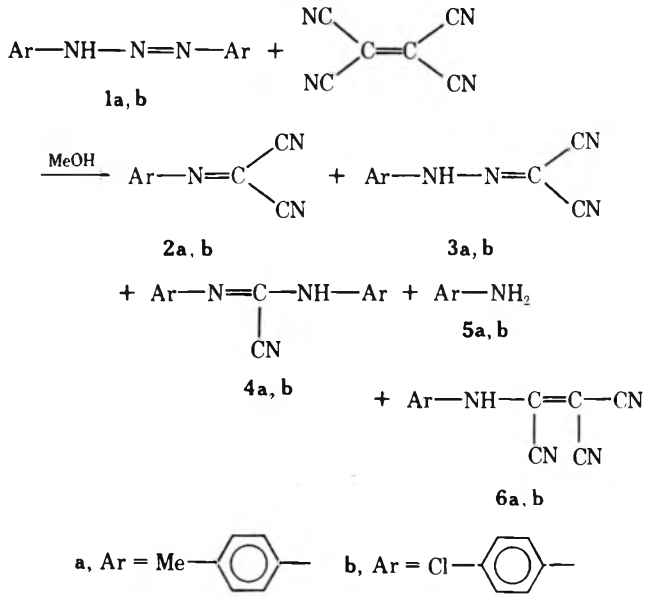
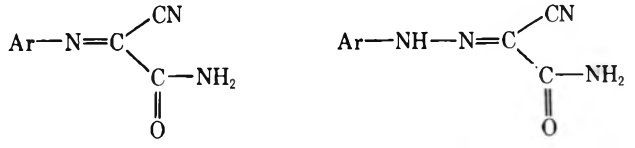
1,3-Diaryltriazenes react with tetracyanoethylene in methanol giving products derived from an addition–fragmentation mechanism. Experiments have been carried out to clarify the reaction scheme.

When equimolecular quantities of 1,3-diaryltriazene (1) and tetracyanoethylene (TCNE) in methanol are mixed at room temperature, an intense blue-green color develops, that quickly fades leaving a clear solution, from which products 2–4 can be separated by column chromatography (Scheme I).

Scheme I

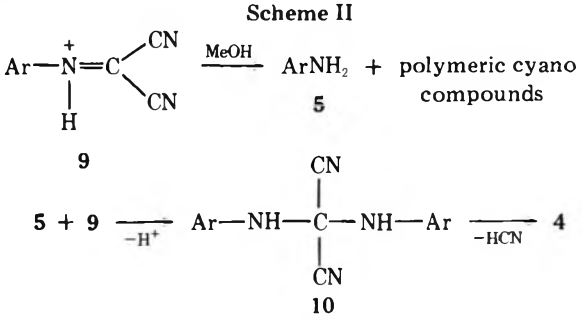


Compounds 2 and 3 are the main reaction products (50–80% yield); 5 and 6 were separated only in traces. In addition to the products reported above, it is possible to separate from the reaction mixture small quantities of the amides 7 and 8.



In excess TCNE the formation of 4 in the reaction is supressed, and the amount of tricyanovinylaniline (6) is greatly increased. This result suggests that 4 is not a primary product, and is formed by addition of aniline to the Schiff base 2, possibly in the protonated form 9. As discussed later, 2 or 9 is an intermediate in the reaction and a precursor of 5 (Scheme II).

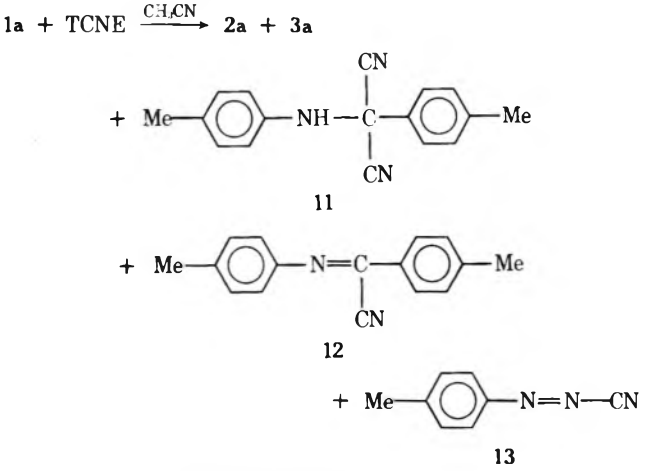
Scheme II



Compound 10 (Ar = *p*-chlorophenyl) was actually separated from the reaction between 1b and tetracyanoethylene in dry ether; it quickly loses HCN, giving 4, on dissolution in methanol. An increase in concentration of tetracyanoethylene in the reaction effectively scavenges the aniline, giving the addition product 6[1] and preventing the formation of 4. The preparation of amidines from imines carrying a nitrile function at the imino carbon atom is already known in the literature.[2]

The reaction between aromatic triazenes and TCNE is highly solvent sensitive. Compound 1a reacts with TCNE in dry ether or in acetonitrile much more slowly, giving 11 and 12 instead of 4a (Scheme III).

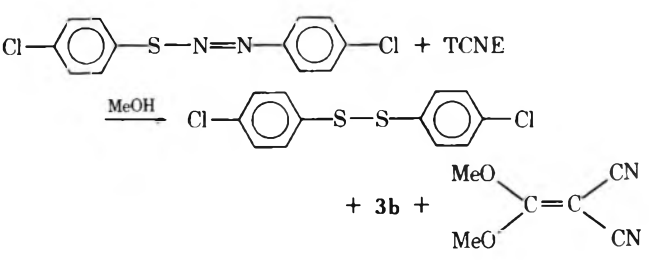
Scheme III



Details of the reaction in these nonprotic solvents are still unclear, although it probably involves a free-radical pathway. Mechanistic details must await further experimental work.

Substitution of the NH group of the triazenes by a sulfur atom retards strongly the reaction with TCNE. Alcoholysis of TCNE is competitive with the reaction between the areneazothiolate and TCNE (Scheme IV).

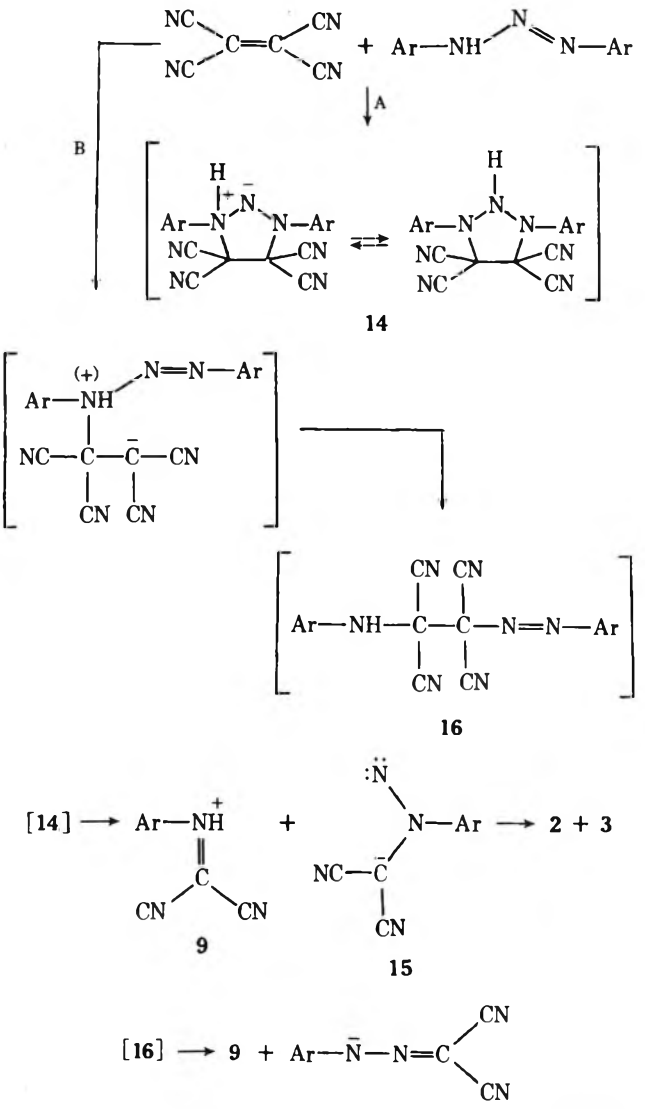
Scheme IV



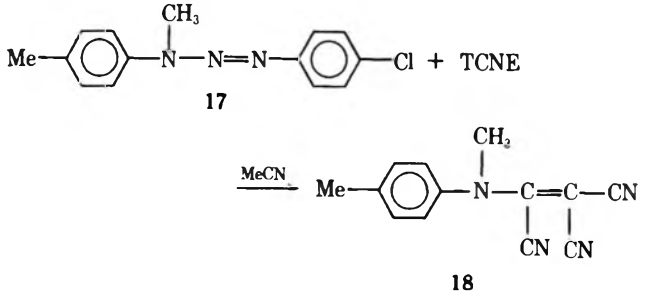
Discussion

Two different mechanistic pathways can be devised to rationalize the products of the reaction in methanol: 1,3-cycloaddition of the aromatic triazene to TCNE, followed by a retro-cycloaddition (Scheme V, path A), or nucleophilic addition of the amino nitrogen to TCNE (path B).

Scheme V



A reaction scheme involving as the first step a nucleophilic addition to the electron-deficient double bond of TCNE is probably followed in the addition of the N-methylated triazene (17) to TCNE in acetonitrile as solvent; in this case the



only identified reaction product was the tricyanovinylaniline (18), and no hydrazone (3b) was formed.

Nucleophilic addition to electron-deficient double bonds is also involved in the TCNE or diphenylketene catalyzed

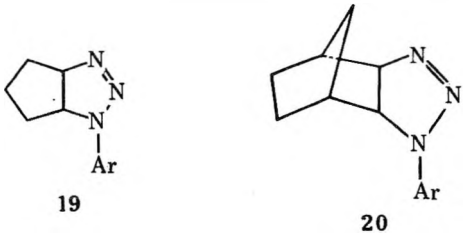
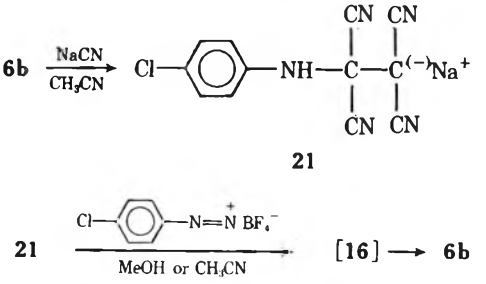


Table I. λ_{max} of the Charge-Transfer Bond in Ethereal Solutions of TCNE and Various Donors

Registry no.	Donor	λ_{max}, nm
785-86-4	1,3-Di-*p*-tolyltriazene (1a)	690
3470-39-1	1,3-Di-*p*-chlorophenyltriazene (1b)	590
62166-63-6	1-*p*-Chlorophenyl-1-methyl-3-*p*-tolyltriazene	640
62166-64-7	1-*p*-Tolyl-1-methyl-3-*p*-chlorophenyltriazene	670
106-49-0	*p*-Toluidine	705
106-47-8	*p*-Chloroaniline	610
932-96-7	*N*-Methyl-*p*-chloroaniline	650

decomposition of the cyclic triazenes 19 and 20 in methanol.[3]

In order to test if the azo derivative 16 may be also the precursor of 2 and 3, NaCN was added to the tricyanovinylaniline (6b), and *p*-chlorophenyldiazonium tetrafluoroborate was added to the sodium salt of the anion 21, previously separated and purified.



The only reaction product identified was the tricyanovinylaniline 6b; no trace of 2b or 3b was found. For this reason we believe that Scheme V accounts only for the formation of tricyanovinyl amino derivatives, and not the formation of 2 and 3.

The [2 + 3] cycloaddition mechanism (Scheme V, path A) is therefore probably the most satisfactory for explaining the products of Scheme I.

The rearrangement of 15 to the hydrazone (3) may be an example of aryl shift to an electron-deficient nitrogen. Unsuccessful attempts have been made to trap 15 by an ene reaction with a reactive double bond.

In the primary addition step the diazoamino derivative may behave as a 1,3 dipole with respect to the TCNE. No other examples of this behavior are reported in the literature; the only known cycloaddition of a triazene is the photochemically initiated [2 + 2] addition of the azo linkage of 1-phenyl-3,3-dimethyltriazene to diphenylketene.[4] In our case, a [2 + 2]

Scheme VI

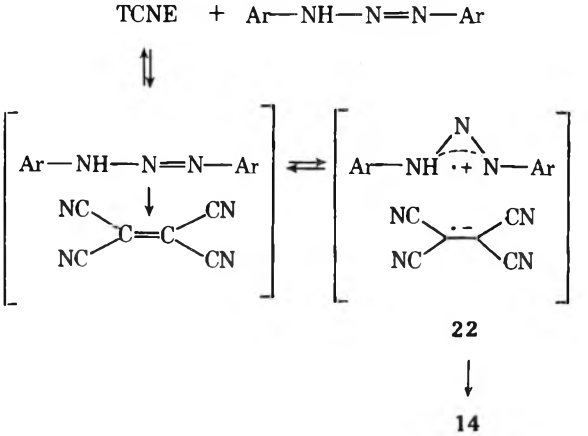


Table II. Physical Constants[a]

Compd	Mp, °C	Mass spectrum, *m/e*
2a	98–100	169, $C_{10}H_7N_3^{+\cdot}$ (base); 142, $C_9H_6N_2^{-\cdot}$; 91, $C_7H_7^+$
2b	136–138	189, $C_9H_4ClN_3^{+\cdot}$ (base); 163, $C_8H_4ClN_2^+$; 154, $C_9H_4N_3^+$; 137, C_7H_4ClN; 111, C_6H_4Cl
3a	168–170 dec	184, $C_{10}H_8N_4^{+\cdot}$; 157, $C_9H_7N_3^{+\cdot}$; 119, $C_7H_7N_2^+$; 106, $C_7H_8N^+$; 91, $C_7H_7^+$ (base)
3b	189–190 dec	204, $C_9H_5ClN_4^{+\cdot}$; 177, $C_8H_4ClN_3^{+\cdot}$; 139, $C_6H_4ClN_2^+$; 126, $C_6H_5ClN^+$; 111, $C_6H_4Cl^+$ (base)
4a	124–125	249, $C_{16}H_{15}N_3^{+\cdot}$; 248, $C_{16}H_{14}N_3^+$; 222, $C_{15}H_{14}N_2^{+\cdot}$; 143, $C_9H_7N_2^+$; 91, $C_7H_7^+$ (base)
4b	174–175	289, $C_{14}H_9Cl_2N_3^{+\cdot}$; 288, $C_{14}H_8Cl_2N_3^+$; 262, $C_{13}H_8Cl_2N_2^{+\cdot}$; 163, $C_8H_4ClN_2^+$; 111, $C_6H_4Cl^+$ (base)
7a	147–149	187, $C_{10}H_9N_3O^{+\cdot}$; 143, $C_9H_7N_2^+$ (base); 91, $C_7H_7^+$; 44, $CONH_2^+$
8a	237–238 dec	202, $C_{10}H_{10}N_4O^{+\cdot}$ (base); 185, $C_{10}H_7NO_3^{+\cdot}$; 157, $C_9H_7N_3^{+\cdot}$; 119, $C_7H_7N_2^+$; 105, $C_7H_7N^{+\cdot}$; 91, $C_7H_7^+$
8b	258–259 dec	222, $C_9H_7N_4OCl^{+\cdot}$ (base); 205, $C_9H_4N_3OCl^{+\cdot}$; 177, $C_8H_4N_3Cl^{+\cdot}$; 139, $C_6H_4N_2Cl^+$; 125, $C_6H_4NCl^{+\cdot}$; 111, $C_6H_4Cl^+$; 44, $CONH_2^+$
10b	187–188	316, $C_{15}H_{10}N_4Cl_2^{+\cdot}$; 315, $C_{15}H_9N_4Cl_2^+$
11	155–157	261, $C_{17}H_{15}N_3^{+\cdot}$; 234, $C_{16}H_{14}N_2^{+\cdot}$; 219$^+$; 208, $C_{15}H_{14}N^+$; 106, $C_7H_8N^+$ (base); 91, $C_7H_7^+$
12	130–131	234, $C_{16}H_{14}N_2^{+\cdot}$ (base); 219$^+$; 208, $C_{15}H_{14}N^+$; 91, $C_7H_7^+$
18	179–181	222, $C_{13}H_{10}N_4^{+\cdot}$ (base); 207, $C_{12}H_7N_4^+$; 196, $C_{12}H_{10}N_3^+$; 91, $C_7H_7^+$

[a] Satisfactory analytical data for all compounds in table (±0.4% for C, H, N, and for **b** series, Cl) were reported for all compounds except **2a** (N: calcd, 24.84; found, 23.90), **4b** (C: calcd, 57.93; found 57.28), **10b** (C: calcd, 56.78; found, 56.25), and **18** (C: calcd, 70.24; found, 69.72).

cycloaddition to the azo linkage of the aromatic triazene can be easily discounted by examining the results of the reaction with N-methylated triazenes, in which the products are not consistent with this kind of initial step (see Experimental Section). In addition, it must be noted that the triazaallyl anion[5] does not react with TCNE in this way.

An alternative pathway to the cycloadduct **14** may involve the solvation of an initial charge-transfer complex, giving a radical ion pair **22** that can collapse to **14** via an "aromatic" transition state (Scheme VI).

Initial formation of charge transfer complexes has been previously postulated for other cycloaddition reaction of TCNE.[6]

Experimental Section

The diaryltriazenes were synthesized in the usual way.[7] Reaction products were identified on the basis of elemental analysis and spectral data: 60-MHz NMR (JEOL C60HL), mass spectra (JEOL JMS D100), IR, or by comparison with authentic specimens prepared in an independent way.

Reactions between 1,3-Diaryltriazenes and TCNE. The triazene (0.01 M) was dissolved in 100 mL of the solvent (methanol, acetonitrile, or diethyl ether) and TCNE (0.01 M) was added under stirring at room temperature. In every case it developed an intense blue-green color (see Table I for λ_{max} in dry ether) that faded quickly in methanol (5 min) and more slowly in acetonitrile or ether (12 h in dry ether). The solvent was then evaporated and the residue was chromatographed on silica gel. The products reported below were separated by using *n*-pentane/ethyl ether gradient, with the exception of the amides **7** and **8** and of the tricyanovinylamines **6** and **18**, eluted with methanol. Table II reports analytical data and mass spectra for the separated compounds; elemental composition of fragment Ions are obtained from exact mass measurement, resolution 7500 (10% valley, mean error <5 ppm). NMR and IR data are consistent with the proposed structures. The symmetrical NMR spectrum obtained for the amidines **4a** and **4b** can be rationalized on the basis of the known tautomerism of this kind of compound.[8]

1a and TCNE in Methanol. Elution of the chromatographic column with *n* pentane/ether (90:10) gave 0.5 g of *N*-dicyanomethylene-*p*-toluidine (**2a**). The IR spectrum of this product ($CHCl_3$) shows characteristic bands at 2210 (m, cyano group), 1610 (m, >C=N– stretching), and 1530 cm^{-1} (s); NMR spectrum ($CHCl_3$) 2.40 (s, 3, CH_3), 7.25 ppm (AA′BB′, 4). Elution with *n* pentane/ether (50:50) gave N^1,N^2-di-*p*-tolylaminocyanoformamide (**4a**), 0.5 g. IR spectrum ($CHCl_3$) 3440 and 3350 (m, N–H stretching), 2230 (m, C=N), 1640 and 1615 cm^{-1} (s, >C=N– stretching). The literature reports similar absorption for N^1,N^2-substituted amidines. NMR ($CHCl_3$) 2.29 (s, 6, 2 CH_3), 7.0 (s, 8, aromatics), 7.2 ppm (broad singlet, 1, NH). Elution with ether gave 1.7 g of *p*-dicyanomethylenehydrazinotoluene (**3a**), identical with an authentic specimen synthesized from malononitrile and diazotized *p*-toluidine: IR ($CHCl_3$) 3270 (m, NH stretching), 2220 (s, –C≡N) 1605 (m), 1545 (s), 1460 cm^{-1} (s). Traces of *p*-toluidine were also detected in intermediate fractions by TLC (R_f and color reaction). Elution with methanol gave a mixture of products, then separated by a new chromatographic column. Using a continuous gradient ether/methanol were separated **7a** (traces) [IR ($CHCl_3$) 3510, 3400 (m, NH stretching), 2220 (w, CN), 1710 (s, amide I), 1565 cm^{-1} (s, amide II)]; **8a**, traces [IR ($CHCl_3$) 3510, 3400 (m, NH stretching), 2210 (s, –CN), 1665 (s, amide I), 1590 cm^{-1} (m, amide II)]; and *N*-tricyanovinyl-*p*-toluidine (**6a**), traces, identical with an authentic model prepared from *p*-toluidine and TCNE.

1a and TCNE in acetonitrile gave **2a**, 0.2 g; *N*-cyano-*p*-xylylene *p*-toluidine (**12**), 0.6 g [IR ($CHCl_3$) 2210 (m, C≡N), 1600 and 1565 cm^{-1} (s); NMR ($CDCl_3$) 2.40 (s, 3, $-CH_3$), 2.45 (s, 3, $-CH_3$), 7.22 (AA′BB′ multiplet, 4), 7.70 ppm (AA′BB′ multiplet, 4)]; α,α-dicyano-α-toluidino-*p*-xylene (**11**), 0.5 g [IR ($CHCl_3$) 3400 (m, NH stretching), 2240 cm^{-1} (w, CN); NMR ($CDCl_3$) 2.30 (s, 3, CH_3), 2.40 (s, 3, CH_3), 4.0 (broad s, 1, NH), 7.08 (AA′BB′ multiplet, 4), 7.58 ppm (AA′BB′ multiplet, 4); this product dissolved in methanol gives **12** and hydrogen cyanide]; **3a**, 0.7 g; **13**, traces.

1a and TCNE in dry ether gave **2a**, 1.3 g; **3a**, 1.4 g; **11**, 0.11 g; **12**, 0.1 g.

1b and TCNE in methanol gave *N*-dicyanomethylene-*p*-chloroaniline (**2b**), 0.1 g; *p*-dicyanomethylenehydrazinochlorobenzene (**3b**), 1.8 g; N^1,N^2-di-*p*-chloroanilinocyanoformamidine (**4b**), 0.7 g; *N*-tricyanovinyl-*p*-chloroaniline (**6b**), traces; **8b**, traces.

1b and TCNE in dry diethyl ether gave **2b**, 0.5 g; **3b**, 1.8 g; dicyanodi-*p*-chloroanilinomethane (**10**), traces; **4b**, 0.5 g. Using wet diethyl ether, no **10** was obtained.

1-*p*-Tolyl-1-methyl-3-*p*-chlorophenyltriazene (17) and TCNE in methanol gave **3b**, 1.5 g; *N*-methyl-*p*-toluidine, 0.6 g; **8b**, traces.

1-*p*-Tolyl-1-methyl-3-*p*-chlorophenyltriazene (17) and TCNE in acetonitrile gave *N*-methyl-*N*-tricyanovinyl-*p*-toluidine (**18**), 0.4 g, and unidentified tars.

1-*p*-Chlorophenylamino-2-*p*-chlorophenyldiazotetracyanoethane (16). To a suspension of sodium cyanide (1.1 g) in dry acetonitrile was slowly added at 0 °C a solution of *N*-tricyanovinyl-*p*-chloroaniline (5 g) in dry acetonitrile. Dry ethyl ether was then added to the homogeneous solution and the precipitate was filtered and washed with dry ether. The solid product (5.4 g) was completely free from *N*-tricyanovinyl-*p*-chloroaniline.

This compound (2.2 g) was then treated in acetonitrile and—separately—in methanol with 1.3 g of *p*-chlorobenzendiazonium tetrafluoroborate. From both reactions the only identified product was *N*-tricyanovinyl *p*-chloroaniline; no traces of **2b** or **3b** were detected by TLC.

***p*-Chlorophenylthio-*p*-chlorophenyldiimide and TCNE in Methanol.** To a solution of *p*-chlorophenylthio-*p*-chlorophenyldiimide (2.8 g) in methanol (100 mL) was added TCNE (2.3 g) and the reaction mixture was refluxed for 24 h. Column chromatography of the residue after evaporation of the solvent gave 4,4′-dichlorodiphenyl disulfide, (**3b**) and 1,1-dimethoxydicyanoethylene, identified by comparison with authentic specimens.

Registry No.—**2a**, 62166-65-8; **2b**, 62166-66-9; **3a**, 40257-94-1; **3b**, 946-76-9; **4a**, 58078-43-6; **4b**, 62166-67-0; **7a**, 62166-68-1; **8a**, 3665-

89-2; **8b**, 20931-91-3; **10b**, 62166-69-2; **11**, 62166-70-5; **12**, 31429-31-9; **18**, 62166-71-6; TCNE, 670-54-2.

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Rapid and Unequivocal Determination of Syn–Anti Stereochemistry for Toluenesulfonylhydrazones and Other Imine Derivatives via Carbon-13 Nuclear Magnetic Resonance Spectroscopy. A Synthetic Adjunct

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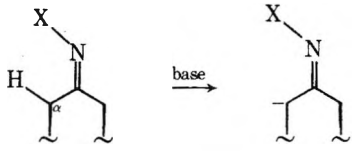
Measurement of the ^{13}C NMR chemical shift differences between the α carbons of ketone and imine derivatives (toluenesulfonylhydrazones, dimethylhydrazones, and oximes) provides a convenient and reliable means of assigning imine stereochemistry. It has been found that carbons syn to the imine "X" moiety are shifted to higher field (Δ syn α = 12–15 ppm) than are carbons anti to the imine "X" moiety (Δ anti α' = 3–6 ppm).

α-Metalated imine derivatives (**2a–c**), including dimethylhydrazones,[1] oximes,[2] and toluenesulfonylhydrazones,[3] are becoming increasingly important intermediates in organic synthesis. The deprotonation reactions of these imines (**1a–c**) exhibit a substantial preference for selective removal of α hydrogens which are syn to the imine X group (**1a–c** → **2a–c**).

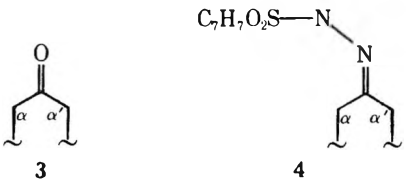


1a, X = $N(CH_3)_2$ 2a, X = $N(CH_3)_2$
b, X = OH b, X = O^-
c, X = $NHSO_2C_7H_7$ c, X = $N^-SO_2C_7H_7$

Utilization of this directing effect in a synthetically rational manner clearly requires an unambiguous method for the determination of syn–anti stereochemistry for imine derivatives of unsymmetrical ketones.

In connection with several synthetic projects in the area of tosylhydrazone chemistry,[3a,b] it became apparent that the traditional ^1H NMR spectral methods for assigning syn and anti isomers, such as differential solvent shifts[4a] (including benzene, a medium in which tosylhydrazones are only sparingly soluble) and lanthanide shift reagent studies,[4b,c] were neither uniformly unambiguous nor particularly convenient.

Several literature reports on the ^{13}C NMR spectra of hydrazones[5] and oximes[6] have indicated a substantial chemical shift difference between the syn and anti carbons α to the imine moiety. We have measured the ^{13}C NMR of a large number of imine derivatives (Tables I–V) based on the hypothesis that the major factor responsible for affecting chemical shift differences between syn and anti carbons is a steric compression effect,[7] which results in upfield shifts for syn α carbons. We have also measured the ^{13}C NMR of the parent ketone in each case. Comparison of the chemical shift differences between the ketone (**3**) and its imine derivative (**4**) *for each* α *carbon* readily shows that α carbons syn to the tosylhydrazone moiety are substantially shifted upfield (Δ syn α = 12–15 ppm) by comparison to the ketone, while α carbons



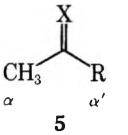
3 4

Δ syn α = (δ ketone **3** for C_α) − (δ hydrazone **4** for C_α)
Δ anti α' = (δ ketone **3** for $C_{\alpha'}$) − (δ hydrazone **4** for $C_{\alpha'}$)

anti to the tosylhydrazone moiety are shifted upfield only slightly (Δ anti α' = 3–6 ppm) (Tables I–IV).

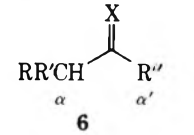
These observations can be qualitatively explained by postulating that the small upfield shift of the anti carbons is primarily due to an inductive effect resulting from the electronegativity difference between ketone and tosylhydrazone. The larger upfield shift of the syn α carbons results from a combination of the inductive effect *plus* a steric compression effect[6b,7] which, in turn, results in additional shielding. Use of this comparison of ketone and tosylhydrazone shifts allows the ketone to serve as an "internal standard"; therefore, the primary structural contributions to the chemical shift which are present both in the ketone and the tosylhydrazone tend to cancel out. The only major effect remaining is that which results from, and hence defines, the hydrazone stereochemistry.

Inspection of Tables I–IV for the structural types **5–11** demonstrates the validity of this approach. Table V indicates



5

a, R = Me
b, R = CH_2Cl
c, R = CH_2Br
d, R = CH_2OAc
e, R = Et
f, R = CH_2Ph
g, R = CH_2CO_2Me
h, R = CH_2CO_2tBu
i, R = *t*-Bu
j, R = Ph



6

a, R = H; R' = Me; R'' = Et
b, R = R' = Me; R'' = *i*-Pr
c, R = R' = Me; R'' = Ph
d, R = R' = Me; R'' = CH_2CO_2Et
e, R = H; R' = Et; R'' = CH_2CO_2Et
f, R = H; R' = Me; R'' = $CH(Me)CO_2Me$

Table I. Tosylhydrazones of Methyl Ketones, 5 (X = $NNHSO_2C_7H_7$)

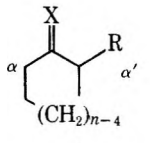
Registry no.	Hydrazone	δα	δα′	Δ syn α	Δ anti α′	Δ anti α	Δ syn α′
3900-79-6	**5a**[e] syn α	17.1	25.3	13.6	5.3		
	anti α	25.3	17.1			5.3	13.6
62460-87-1	**5b** syn α	13.6	48.0	13.4	1.0		
62460-88-2	**5c** syn α	14.2	35.5	12.9	−0.7		
62460-89-3	**5d** syn α	13.4	67.0	12.6	1.4		
62460-90-6	**5e**[a] syn α	15.6	32.0	13.8	4.9		
62460-91-7	anti α[d]	23.5	22.5			5.9	14.4
62460-92-8	**5f**[a] syn α	15.1	45.1	14.1	5.9		
62460-93-9	anti α	24.1	36.9			5.1	14.1
62460-94-0	**5g**[a] syn α	16.0	44.0	14.1	5.8		
62460-95-1	anti α	24.7	37.9			5.4	11.9
62460-96-2	**5h**[a] syn α	16.0	45.5	14.0	6.0		
62460-97-3	anti α	24.6	39.8			5.4	11.7
62460-98-4	**5i** syn α	11.8	38.8	12.9	5.5		
62460-99-5	**5j**[e] syn α	13.5	137.4	13.0	−0.2[b]		
62461-00-1	**11** syn α	15.5	c	14.7			

[a] Syn and anti isomers were obtained as unequal mixtures which allowed assignment of chemical shifts. The syn methyl isomer always predominated. [b] Included for completeness but not applicable in direct comparison. [c] Could not be determined from several peaks. [d] Due to the low percentage of this isomer, it was not possible to unequivocally assign δα and δα′. [e] Reference 5 reports **5a** (X = NNHPh) has δα = 15.1 ppm and δα′ = 24.8 ppm for syn α while **5j** (X = NNHPh) has δα = 12.5 ppm.

Table II. Tosylhydrazones of Acyclic Ketones, 6 (X = $NNHSO_2C_7H_7$)

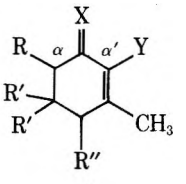
Registry no.	Hydrazone	δα	δα′	Δ syn α	Δ anti α′	Δ anti α	Δ syn α′
28495-72-9	**6a** syn α	22.7	29.4	12.8	6.8		
	anti α	29.4	22.7			6.1	12.8
17530-00-6	**6b** syn α	28.4	30.5	10.5	8.4		
	anti α	30.5	28.4			8.4	10.5
62461-01-2	**6c** anti α	36.4	132.4			−1.0	4.0[b]
62461-02-3	**6d** anti α	36.9	35.7			4.3	11.5
62461-03-4	**6e** anti α	40.3	37.5			4.6	11.9
62461-04-5	**6f**[a] syn α	21.7	46.7	13.0	5.8		
62461-05-6	anti α	27.5	41.2			7.2	11.3

[a] Syn and anti isomers were obtained as an unequal mixture with the anti α isomer predominating. [b] Included for completeness but not applicable in direct comparison.



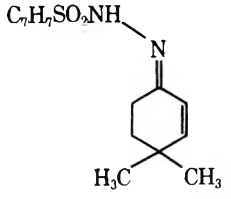
7

a, n = 6; R = H
b, n = 6; R = Me
c, n = 6; R = t-Bu
d, n = 6; R = CO_2Me
e, n = 5; R = H
f, n = 7; R = H
g, n = 8; R = H



8

a, R = R′ = R″ = H; Y = H
b, R = R″ = H; R′ = Me; Y = H
c, R = R′ = H; R″ = CO_2Et; Y = H
d, R = i-Pr; R′ = R″ = H; Y = H
e, R = R″ = H; R′ = Me; Y = OMe



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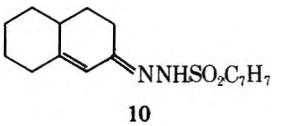

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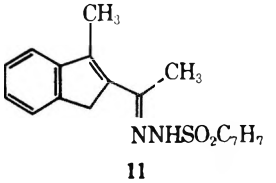
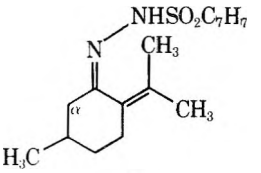


11

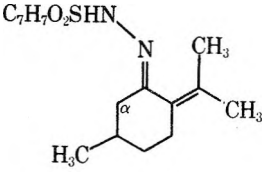
that the same procedure also appears to be generally applicable for oximes and dimethylhydrazones.

Verification of the accuracy of the method was provided by examination of tosylhydrazones **12** and **13**, whose stereochemistry has recently been established by x-ray crystallography.[3h] Consistent assignments were also obtained for other compounds including **1i** (X = $NHSO_2C_7H_7$),[4a] **1j** (X = $NHSO_2C_7H_7$),[8] and **8b** (X = NOH).[9]



12

(Δ syn α = 14.7 ppm)



13

(Δ anti α = 6.0 ppm)

The observed chemical shift effects do not seem to be universally applicable to phenyl ketones, i.e., the phenyl α carbons are shielded considerably less than aliphatic or vinyl carbons (vide supra) so that comparison of alkyl phenyl ketone imine derivatives (**5j** and **6c**) must be made with the alkyl portion.

Another limitation can occur in those occasional cases where difficulty is encountered in assigning the chemical shifts for the α carbons. Since the α carbons usually occur downfield of the potentially crowded aliphatic region for both the ketone and the imine derivatives, this situation seldom occurs. Furthermore, an imine derivative should yield a substantially

Table III. Tosylhydrazones of Cycloalkanones, 7 (X = $NNHSO_2C_7H_7$)

Registry no.	Hydrazone	δα	δα′	Δ syn α[a]	Δ anti α′	Δ anti α	Δ syn α′[a]
4545-18-0	**7a** syn α	26.9	35.2	≥15.0	6.7		
	anti α	35.2	26.9			6.7	≥15.0
63269-90-9	**7b** syn α	24.5	39.2	≥15.4	6.2		
63269-91-0	anti α	*b*	31.8				13.6
63269-92-1	**7c** syn α	24.8	54.1	≥19.5	6.2		
63269-93-2	7d syn α	26.8	50.9	14.8[c]	6.3[c]		
63269-94-3	anti α	33.3	41.7			8.3	15.5
61515-13-7	**12** syn α	36.2		14.7			
61515-14-8	**13** anti α	44.9				6.0	
17529-98-5	**7e** syn α	28.1	33.5	10.2	4.8		
	anti α	33.5	28.1			4.8	10.2
56382-69-5	**7f** syn α	30.4	37.0	≥13.5	6.9		
	anti α	37.0	30.4			6.9	≥13.5
2567-85-3	**7g** syn α	28.0	36.2	≥14.0	5.8		
	anti α	36.2	28.0			5.8	≥14.0

[a] Uncertainty in Δ syn values arises from ambiguity in chemical shift assignment of the respective carbon; however, the values assigned are the best guesses and are correct to within 3 ppm. [b] This isomer was <20% of the mixture and the α carbon signal was apparently hidden under the signals of the more predominant isomer. [c] This compound is a mixture of the enehydrazine form as well as syn and anti isomers. There is uncertainty in both δα and δα′. These values are correct to ±1.0 ppm.

Table IV. Tosylhydrazones of Cyclohexenones, 8 (X = $NNHSO_2C_7H_7$)

Registry no.	Hydrazone	δα	δα′	Δ syn α	Δ anti α′	Δ anti α	Δ syn α′
61530-89-0	**8a**[b] syn α	23.5	122.8	≤13.5[a]	4.0		
61530-88-9	anti α	31.4	113.5			≥5.6[a]	13.3
62505-87-7	**8b**[c] syn α	37.0	122.0	13.8	3.5		
62505-85-5	anti α	45.9	112.5			4.9	13.0
62461-11-4	**8c** syn α	20.9	125.4	13.4	3.1		
62560-50-3	**8d** anti α	45.9	113.0			5.7	13.9
62461-12-5	**8e**[b] syn α	38.3	*d*	13.9			
62461-13-6	anti α	46.7	*d*			5.5	
62461-14-7	**9** syn α	21.1	124.6	15.0	2.2		
62461-15-8	**10** syn α	22.8	121.0	≤15.2[a]	3.3		
62461-16-9	anti α	*e*	111.0				13.3

[a] Uncertainty arises from ambiguity in chemical shift assignment of the respective carbon atom; however, the values given are accurate within 2.0 ppm. [b] Syn and anti isomers were obtained as unequal mixtures with the syn α isomer predominating. [c] The anti α isomer could be obtained in >90% purity by fractional crystallization; however, equilibration occurred during data acquisition. [d] Due to ambiguity in the spectra of ketone (δ 142.8 and 148.5 ppm) we could not assign the chemical shifts of the hydrazone (δ 130.5 and 145.6 ppm for syn α and δ 131.5 and 145.7 ppm for anti α). [e] There were too many peaks to even make a good guess at the chemical shift.

Table V. Comparison of ^{13}C Chemical Shifts of Tosylhydrazones, Oximes, and Dimethylhydrazones[a,d]

Registry no.	Compd		δα	δα′	Δ syn α	Δ anti α′	Δ anti α	Δ syn α′
	5e (X = $NNHSO_2C_7H_7$)	syn α	15.6	32.0	13.8	4.9		
		anti α	23.5	22.5			5.9	14.4
	7a (X = $NNHSO_2C_7H_7$)	syn α	26.9	35.2	≥15.0[b]	6.7		
		anti α	35.2	26.9			6.7	≥15.0[b]
	8b (X = $NNHSO_2C_7H_7$)	syn α	37.0	122.0	13.8	3.5		
		anti α	45.9	112.5			4.9	13.0
10341-63-6	**5e** (X = NOH)	syn α	13.3	29.2	16.1	7.7		
10341-59-0		anti α	19.2	21.9			10.2	15.0
100-64-1	**7a** (X = NOH)	syn α	25.6	32.2	≤16.3[b]	9.7		
		anti α	32.2	25.6			9.7	≤16.3[b]
3968-96-5	**8b**[c] (X = NOH)	syn α	35.0	118.8	15.8	6.7		
3968-95-4		anti α	41.1	112.6			9.7	12.9
19885-65-5	**5e** (X = $NN(CH_3)_2$)	syn α	16.0	32.2	13.4	4.7		
62461-17-0		anti α	22.1	24.6			7.3	12.3
10424-93-8	**7a** (X = $NN(CH_3)_2$)	syn α	28.7	36.0	≥13.2[b]	5.9		
		anti α	36.0	28.7			5.9	≥13.2[b]
62461-19-2	**8b** (X = $NN(CH_3)_2$)	syn α	38.8	123.1	12.0	4.7		
62461-20-5		anti α	46.1	115.8			2.4	9.7

[a] Reference 5 reports that the semicarbazone of **5e** (syn α) gives δα = 15.3 and δα′ = 31.9 ppm. [b] Uncertainty is due to ambiguity in assigning respective carbon atoms. The values shown are correct within 3 ppm. [c] We were able to obtain a pure sample of the anti isomers by fractional crystallization, mp 100–102 °C (lit. 102–104 °C).[9b] [d] Syn and anti isomers were unequal mixtures with syn α isomer predominating.

different shift increment (Δ syn α and Δ anti α′ or Δ anti α and Δ syn α′) for each of two α carbons, making it possible to assign stereochemistry even in cases where only either δα or δα′ are known. For example, with enone derivatives, such as **10** (Table IV), there is great ambiguity in assignment of δα; however, the stereochemistry of the major isomer can be clearly established from the chemical shift (δα′ = 121.0, Δ anti α′ = 3.3) of the α′ carbon alone. Another obvious advantage is that only one isomer of the syn–anti pair is needed for comparison. The large body of empirical data in Tables I–V should be of substantial assistance in making subsequent stereochemical assignments for new imine derivatives.

It should be also noted that the five carbons of the toluenesulfonyl group fall within such a narrow range that assignment of other peaks in these areas should cause no problems (144.1–143.6, 136.1–135.4, 129.7–129.3, 128.4–128.7, and 21.7–21.5 ppm).[10]

Experimental Section

Natural abundance, ^{1}H-decoupled ^{13}C NMR spectra were obtained with a Varian CFT-20 instrument in $CDCl_3$ with Me_4Si as internal reference. Fourier transform spectra were obtained using 4000- and 5000-Hz spectral widths. A pulse angle of 45° was used with a pulse delay of 1 s. Chemical shift assignments of ketones were made by analogy to known systems.[11] Single frequency off-resonance ^{1}H-decoupled spectra were obtained when unambiguous assignment of resonances could not be made from the fully ^{1}H-decoupled spectrum.

The *p*-toluenesulfonylhydrazones **5–10** (X = $NNHSO_2C_7H_7$) were prepared by either of two general methods from the ketone **5–10** (X = O) and *p*-toluenesulfonylhydrazide.[12]

The following hydrazones (X = $NNHSO_2C_7H_7$) were prepared in ether:[13] **5a**;[14] **5b** (mp 123–125 °C dec); **5c** (mp 114–116 °C dec); **5d** (mp 106–107 °C); **5e**;[15] **5f**;[14] **5g** (mp 128–130 °C); **5h** (mp 115–118 °C); **5i** (mp 158–160 °C); **6a** (mp 101–103 °C); **6d** (mp 77–78 °C); **6e** (oil); **6f** (mp 91–93 °C); **8a** (mp 131–141 °C dec); **8d** (mp 111–113 °C);[16] **10** (mp 139–141 °C).

All others were prepared in ethanol:[14] **5j**;[14] **6b** (mp 78–95 °C);[16] **6c** (mp 105–108 °C);[16] **7a–c**;[17] **7d** (mp 129–132 °C); **7e–g**;[17] **8b**;[18] **8c** (mp 157–159 °C); **8e**;[19] **9**;[20] **12**; and **13**.[3h]

The dimethylhydrazones **5e**,[21] **7a**,[21] and **8b** (X = $NNMe_2$)[22] and oximes **5e**,[23] **7a**,[23] and **8b** (X = OH)[9b] were prepared by standard procedures.

Ketones **5c**,[24] **6f**,[25] **7d**,[25] **8e**,[19] **9**,[26] and **10**[27] (X = O) were prepared by published procedures. **11** and the corresponding ketone were graciously provided by Professor H. A. Morrison and Dr. F. Palensky of this department. All other ketones were obtained from commercial sources.

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Registry No.—**5b** (X = O), 67-64-1; **5c** (X = O), 598-31-2; **5d** (X = O), 592-20-1; **5g** (X = O), 105-45-3; **5h** (X = O), 1694-31-1; **5i** (X = O), 75-97-8; **6a** (X = O), 96-22-0; **6d** (X = O), 7152-15-0; **6e** (X = O), 3249-68-1; **6f** (X = O), 17422-12-7; **7d** (X = O), 41302-34-5; **8a** (X = O), 1193-18-6; **8c** (X = O), 487-51-4; **8d** (X = O), 89-81-6; **10** (X = O), 1196-55-0.

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Notes

Meerwein Arylation of Fluorinated Olefins

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The Meerwein arylation—copper-catalyzed addition of Ar and X from an arenediazonium halide to an "activated" olefin CH_2=CHZ (eq 1)—has been applied to olefins bearing diverse Z groups like aryl, vinyl, cyano, carbonyl, and chlorine.[1,2] Among the chlorine-activated olefins, chloroethene and 1,1-dichloroethene (vinyl and vinylidene chloride) give generally excellent yields of adducts. Trichloroethene and the geometrically isomeric 1,2-dichloroethenes give poorer results; tetrachloroethene fails to react.[3] Polychloroalkylalkenes like Cl_3CCH=CH_2 have not been tested. No examples have been noted where Z is one or more fluorine atoms. Where Z = CF_3, Failkov et al.[4] obtained 38–40% of adducts from *p*-nitrobenzenediazonium halides, X = Cl, Br.

$$ArN_2X + CH_2{=}CHZ \xrightarrow{CuX_2} ArCH_2CHXZ + N_2 \quad (1)$$

The present study aimed to determine whether a fluoroalkyl chain or several fluorine atoms could promote Meerwein arylation of an otherwise not activated olefin. The olefins selected for testing, **1**–**8**, are depicted in Chart I. The first two

Chart I

$HCF_2CF_2CR{=}CH_2$ + *p*-$YC_6H_4N_2Cl$

1, R = H

2, R = CH_3

$\longrightarrow HCF_2CF_2CRClCH_2C_6H_4Y$-*p*

9

$\xrightarrow{KOH} HCF_2CF_2CR{=}CHC_6H_4Y$-*p*

Y = NO_2, Cl, CO_2H

$H(CF_2)_4CF{=}CF_2$ (**3**) $CF_3(CF_2)_4CF{=}CF_2$ (**4**) *n*-$C_4H_9CF{=}CFCl$ (**5**)

$CF_2{=}CFCl$ (**6**) $CH_2{=}CF_2$ (**7**) $CF_2{=}CF_2$ (**8**)

are activated by electronegative fluoroalkyl groups, the third and fourth have three fluorines and one fluoroalkyl group on the double bond, the fifth has chlorine, alkyl, and two fluorines, and the sixth has chlorine and three fluorines. The last two have two or four fluorine atoms.

Olefins **1** and **2** react readily with diazonium salts bearing an electron-withdrawing substituent (Cl, NO_2, CO_2H), but not with 2,5-dimethoxybenzenediazonium chloride, under standard[1,2] Meerwein arylation conditions. Electron-releasing substituents, especially in the ortho position, often depress the yields of Meerwein adducts.[1,2] The products shown in Chart I and in Table I were obtained in 28–50% yields. In the cases studied, these were the Ar–Cl addition products **9**, not the hydrogen substitution products $ArCH{=}CHR_F$ which are often found. The latter may be prepared by dehydrochlorination of **9**.

The tetrasubstituted olefins **3**–**5** were not arylated under standard conditions. Most of the olefin was recovered, and the aryl group of the diazonium salt appeared as aryl halide and arene, by-products of the Sandmeyer and dediazoniation reactions which always accompany the Meerwein arylation.[1,2] Since these heavily fluorinated olefins are not very soluble in the aqueous acetone medium of the normal Meerwein arylation, a procedure was developed using acetone, a dry diazonium chloride or tetrafluoroborate, lithium trifluoroacetate as buffer, and aqueous cupric chloride to provide the copper catalyst and the small amount of water known to be essential for typical Meerwein arylations.[1,2] Using acrylonitrile as model olefin, reaction by this anhydrous procedure proceeded vigorously after a brief induction period to give 30–39% of the adduct *p*-$ClC_6H_4CH_2CHClCN$, which has been prepared in 37% yield under "standard" conditions.[5] However, the anhydrous procedure gave no detectable adduct with **4**. The induction period noted in all the experiments with the anhydrous procedure may reflect the time required to produce the cuprous chloride which some writers believe to be the only active catalyst in the Meerwein arylation.[1,2] However, in one attempt, use of cuprous chloride with **4** gave no better yield (zero) than did cupric chloride (also zero).

Chlorotrifluoroethylene reacted smoothly in an autoclave under otherwise standard conditions to yield the adduct $ArCF_2CFCl_2$ in 27% yield.[5] Since it could not be dechlorinated with zinc in refluxing methanol, the isomeric structure $ArCFClCF_2Cl$ is excluded. Since this olefin reacts, but tetrachloroethene does not,[3] the intermediate complex[1,2] evidently cannot form when the double bond is too heavily substituted by large groups. Two fluorines on one carbon are not too bulky, but two chlorines are. The regioselectivity observed here further supports the statement that the aryl radical becomes attached to the less hindered terminus of the olefin.[1,2] 1,1-Dichloro-2,2-difluoroethene was not available for testing.

Vinylidene fluoride (**7**) is less reactive toward *p*-chloro- and *p*-nitrobenzenediazonium chloride than are vinylidene chloride and **6**. Apparently the radical stabilization available in the structure Ar–C–Ċ–Cl is less important in Ar–C–Ċ–F. Most of the diazonium salt formed aryl chloride and azoarene, as well as a little ArH and phenol. About 10–15% (GC) formed the product $ArCH_2CF_2Cl$, and small amounts of telomers $Ar(C_2H_2F_2)_nCl$ were also present. Telomers are very rare in the Meerwein arylation.[1,2] Surprisingly, $ArCF_2CH_2Cl$ and $ArCH_2CF_2CF_2CH_2Cl$ were seen, showing that **7** is not nearly so regioselective in Meerwein arylations as other olefins. We have encountered such "inverse" products in radical telomerizations of R_FI with vinyl and vinylidene fluoride.[7]

Biaryls are not normally seen in Meerwein arylations. However, GC/MS detected several chlorobiphenyls in the product from *p*-chlorobenzenediazonium chloride and **7**; two were dichlorobiphenyls, one was a trichlorobiphenyl (isolated), and three were dichlorobiphenyls bearing $-CH_2CF_2Cl$ or related side chains. Except for the trichlorobiphenyl, none was formed in large amount.

This Meerwein arylation does not have preparative value under the conditions selected, partly because of the low yield, and partly because ArCl and $ArCH_2CF_2Cl$ boil very close together. However, the adduct could probably be dehydrochlorinated to $ArCH{=}CF_2$ which could be separated from ArCl.

The results with tetrafluoroethylene were less encouraging. From *p*-chlorobenzenediazonium chloride, the major products were again *p*-dichlorobenzene and 4,4′-dichloroazobenzene.

Table I. Properties of Products of Meerwein Arylation of Fluorinated Olefins p-$XC_6H_4CH_2C(R)ClCF_2CF_2H$ [a]

Registry no.	X	R	Mp or bp, °C (mm)	Recrystn solvent	Yield %[b]	Formula	Anal. Calcd, % C	H	Cl	Found, % C	H	Cl
62448-54-8	NO_2	H	33–34; 122–123 (1)[c]	MeOH	28	$C_{10}H_8ClF_4NO_2$	42.0	2.8	12.4	42.0	3.0	12.4
62448-55-9	NO_2	CH_3	95.5–97.5	EtOH	40	$C_{11}H_{10}ClF_4NO_2$	44.1	3.4		44.6	3.5	
62448-56-0	Cl	CH_3	134–135 (10)[c]		36	$C_{11}H_{10}Cl_2F_4$	45.7	3.5	24.5	45.9	3.6	24.9
62448-57-1	CO_2H	CH_3	199.8–201.6	EtOH; $PhCH_3$	50	$C_{12}H_{11}ClF_4O_2$[d]	48.4	3.4	11.9	48.5	4.0	11.6

[a] Satisfactory microanalyses were obtained for all the compounds reported in this table. [b] Yields are not corrected for recovered olefin. [c] Boiling point. [d] Neut equiv: calcd, 298; found, 298.

Perhaps 10% of the adduct $Ar(CF_2CF_2)_nCl$, $n = 1$, was formed, and decreasing amounts of the telomers $n = 2$ and 3 were also seen (GC/MS). Biaryls were not detected.

Experimental Section

Materials. The olefins 1 and 2 were prepared by vapor-phase pyrolysis (530–540 °C) of the acetates of the alcohols obtained by radical-catalyzed addition of ethanol or isopropyl alcohol to tetrafluoroethylene. They boiled at 27 and 52–53 °C, $n^{25}D$ 1.3028 and 1.3243, respectively. Olefins 3 and 4 were prepared by "dry distillation" of the sodium carboxylates $R_FCF_2CF_2COONa$, according to Hals et al.[8] They boiled respectively at 71–72 and 62–74 °C.[9] Olefin 5 was prepared from butyllithium and chlorotrifluoroethylene by the procedure of Dixon.[10] The fraction used boiled at 108.5–110 °C, $n^{25}D$ 1.3924. Chlorotrifluoroethylene was a commercial product.

General Procedure for Meerwein Arylation. The amine (0.1 mol) was diazotized conventionally with 25 mL of concentrated hydrochloric acid, 1 equiv of sodium nitrite, and ice. The filtered solution was added all at once to 0.1 mol of the olefin in 250 mL of reagent acetone, followed immediately by concentrated aqueous solutions of 0.1 mol of sodium acetate and 0.015 mol of cupric chloride. (The total volume of the aqueous solutions was 200 mL, hence the solvent was about 56% acetone.) In successful reactions, the homogeneous solution turned dark olive-green and began immediately to evolve nitrogen. In the unsuccessful reactions, the color remained clear light green. The mixture gradually reached about 33 °C, and nitrogen evolution ceased after about 0.5 h. After an additional 1 h, the mixture usually had separated into an upper dark-brown layer and a lower clear green layer.

The mixture was then distilled directly until the head temperature reached 90 °C. Unchanged olefin could be recovered from the distillate by diluting it with ice water. The residue was steam distilled, usually until 4 L had been collected. The distillate was extracted with 3 × 150 mL of methylene chloride, and the combined extracts were washed with dilute sodium hydroxide solution to remove any phenols, then with water, and then dried with potassium carbonate. In most cases, the steam-involatile material was discarded.

The extract was distilled through a small fractionating column to remove first solvent, then ArH (nitrobenzene or chlorobenzene), then ArCl (p-nitrochlorobenzene or p-dichlorobenzene) resulting from the Sandmeyer reaction, and finally the product. When the product was solid, it was crystallized from methanol or ethanol, as shown in Table I.

The procedure was modified for p-aminobenzoic acid. It was diazotized by the "inverse" method by dissolving it (0.1 mol) in sodium carbonate solution, adding sodium nitrite, and pouring the solution onto ice and hydrochloric acid. Since the extra mol of salt thus introduced impeded the solubility of the fluoro olefin 2, an extra 100 mL of water and 200 mL of acetone were added to achieve a homogeneous solution. Nitrogen evolution continued for 2.5 h, and a dark green, sticky solid precipitated. After removal of the acetone, the residue was steam distilled to remove benzoic acid (2.3 g). The residue was made strongly acidic, and the dark green solid became pale tan as the copper dissolved. The solid was collected, washed with dilute acid, then dissolved in sodium bicarbonate solution, filtered, and reprecipitated; 12.7 g was obtained. It was crystallized twice from alcohol and twice from toluene for analysis. Purification was difficult because the crude product was contaminated with p-chlorobenzoic acid.

In the unsuccessful experiments, most of the olefin was recovered with the acetone. The steam distillate contained little or nothing boiling higher than the Sandmeyer product, and almost no tar remained in the steam still.

Meerwein Arylation under Anhydrous Conditions. p-Chlorobenzenediazonium chloride and tetrafluoroborate were prepared from the corresponding salts of p-chloroaniline and 1 equiv of amyl nitrite in absolute ethanol, then precipitated with dry ether. A solution of lithium trifluoroacetate was prepared by stirring 10.0 g of lithium carbonate with 250 mL of acetone while adding 34.2 g (0.3 mol) of trifluoroacetic acid slowly. To this solution was added 0.1 mol of the dry diazonium chloride, 5.3 g (0.1 mol) of acrylonitrile, and 0.015 mol of cupric chloride in 5 mL of water. The diazonium salt did not dissolve completely. Slow nitrogen evolution began immediately. After 10 min, the reaction suddenly speeded up and the temperature reached 45 °C before it could be cooled. Some material was carried out the top of the condenser by the rapid escape of nitrogen. The standard workup procedure gave 20% of p-dichlorobenzene and 7.8 g (39%) of p-$ClC_6H_4CH_2CHClCN$, bp 169–173 °C (22 mm). Alternatively, the diazonium fluoroborate with 1 equiv of lithium chloride exhibited the same behavior, giving 32% of p-dichlorobenzene and 30% of arylation product.

Chlorotrifluoroethylene.[6] An aqueous acetone solution of 0.1 mol of p-chlorobenzenediazonium chloride containing 0.1 mol of sodium acetate was placed in an autoclave, which was then chilled and evacuated. Then 25.0 g (0.214 mol) chlorotrifluoroethylene was condensed into the autoclave from a cylinder. The vessel was warmed to room temperature, and the cupric chloride solution was sucked into the autoclave. The mixture was held for 15 min at room temperature, then heated for 1.5 h at 40–50 °C. The product was isolated by the general method; 7.1 g (27%) of p-$ClC_6H_4CF_2CFCl_2$ was obtained, bp 105–107 °C (20 mm). It was identified by its mode of formation, microanalysis, and by its failure to eliminate chlorine when refluxed with zinc dust in methanol.

Dehydrochlorination. The product 9 (X = NO_2; R = H) (4.3 g) was heated for 0.5 h with a solution of 1.5 g of potassium hydroxide in 50 mL of methanol. Dilution with water gave a yellow solid, 3.6 g, which was recrystallized from methanol, mp 89.9–90.4 °C, faintly yellow needles.

Anal. Calcd for $C_{10}H_7F_4NO_2$: C, 48.2; H, 2.8. Found: C, 48.6; H, 2.6.

The other products in Table I gave precipitates of potassium chloride when treated similarly, but the olefins were not isolated or characterized.

Vinylidene Fluoride and Tetrafluoroethylene. p-Chloroaniline (0.2 mol) in 83 mL of 6 N hydrochloric acid and 80 g of ice was diazotized with 0.2 mol of sodium nitrite at 0 °C. The filtered solution was charged to the shaker tube and frozen in a −80 °C bath. Then 125 mL of acetone, 13.6 g (0.1 mol) of sodium acetate trihydrate, and 5.2 g (0.03 mol) of cupric chloride dihydrate were added without agitation. The tube was sealed, further chilled, and evacuated. Then 0.4–0.5 mol of fluoro olefin was added by vacuum transfer. The tube was then heated to 25–30 °C and maintained there with shaking for 4 h. The pressure increased about 200 psig during this time, signaling loss of nitrogen from the diazonium salt.

The tube was vented and the two-phase dark green mixture was discharged. The acetone was removed on a rotary evaporator, and the organic material was taken up in methylene chloride, washed and dried, and again evaporated. The crude product was distilled at 0.5 Torr to pot temperature 200 °C; little tar remained. The distillate was examined by GC/MS.[11] The results are given in the text.

Isolation of Trichlorobiphenyl. The product from p-chloroaniline and vinylidene fluoride was fractionally distilled. The cut from 90–110 °C (0.3 Torr), 5.1 g, was crystallized twice from isopropyl alcohol, 1.1 g, mp 63.0–63.5 °C.

Anal. Calcd for $C_{12}H_7Cl_3$: C, 55.9; H, 2.7; Cl, 41.3. Found: C, 55.9; H, 2.5; Cl, 39.6; N, 1.6.

Since this material contained about 15% of 4,4′-dichloroazobenzene (GC), it should have the composition C, 56.1; H, 2.8; Cl, 39.4; N, 1.7. These values agree with those found.

Registry No.—1, 40723-71-5; 2, 57252-78-5; 3, 1767-94-8; 4, 355-63-5; 5, 367-36-2; 6, 79-38-9; *p*-chlorobenzenediazonium chloride, 2028-74-2; *p*-nitrobenzenediazonium chloride, 100-05-0; *p*-carboxybenzenediazonium chloride, 17405-00-4; *p*-dichlorobenzene, 106-46-7; p-$ClC_6H_4CH_2CHClCN$, 17849-64-8; p-$ClC_6H_4CF_2CFCl_2$, 62448-58-2; p-$NO_2C_6H_4CH{=}CHCF_2CF_2H$, 62448-59-3; *p*-chloroaniline, 106-47-8; vinylidene fluoride, 116-14-3; 4,4′-dichloroazobenzene, 1602-00-2; trichlorobiphenyl, 62461-62-5.

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(11) GC/MS analyses were performed by Mr. R. H. Weeks in this laboratory.

Metal–Ammonia Reduction of Fluorinated Aromatic Compounds

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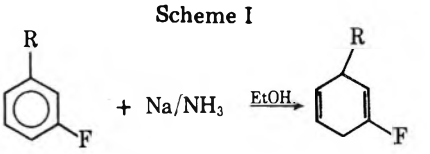
The acceptance of the hydrogenolysis of aryl carbon–halogen bonds (including fluorine) by alkali metals in liquid ammonia is evidenced by three major reviews.[1,2] Since direct metal–halogen exchange is not an attractive mechanism with fluorides,[3] and benzyne processes can be eliminated on other grounds,[4] the most likely pathway appears to be presented in eq 1.

$$ArF \xrightarrow{e^-} [ArF]^{-}\cdot \xrightarrow{-F^-} Ar\cdot \xrightarrow{e^-} Ar^- \xrightarrow{NH_3} ArH \qquad (1)$$

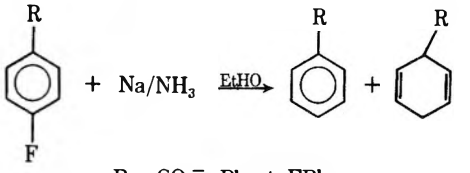
Thus, addition of an electron to the aromatic ring of ArF results in a radical anion which loses fluoride ion producing an aryl radical. This radical is expected to easily accept another electron to form an aryl carbanion which is rapidly protonated by ammonia. Depending on the nature of ArF and reaction conditions (metal supply, proton source, etc.), ArH may also be reduced to cyclohexadienes and related products.

In addition to the firm establishment of the aforementioned mechanism, our results indicate that under proper conditions, the Birch reduction can, in fact, provide an important synthetic pathway for the formation of fluorinated cyclohexadienes. As illustrated in Scheme I, compounds containing fluorine meta to an activating substituent[5] can be successfully reduced with retention of fluorine, whereas fluorine in the para position is lost.[6] Thus, this observed substituent effect rules out any direct electron transfer to the Ar–F bond and establishes electron addition to the ring as the first step. Loss of fluoride from this intermediate seems more attractive than a second electron addition, since dianions are generally not formed with benzene derivatives.[1,2] Protonation of the radical anion followed by a second electron addition and then loss of fluoride may also be ruled out since this would lead to a carbene intermediate which is not consistent with product analysis.

Scheme I



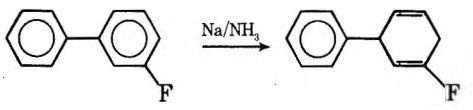
R = CO_2^-, Ph, 3-PPh, $(CH_3)_3Si$



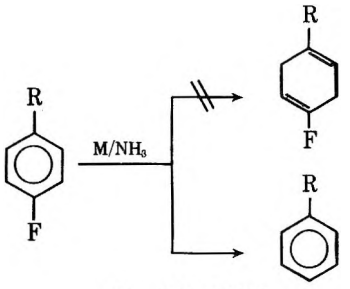
R = CO_2^-, Ph, 4-FPh

These transformations can be rationalized in terms of the electron density distribution in the intermediate radical anions.[7] Hence, as an oversimplification, if resonance structures 1 and 2 are considered as most important in their respective cases, the process for fluorine loss in 2 can be visualized. Alternatively, we may simply consider that fluorine is expected to be lost when attached to a carbon holding increased electron density in the intermediate anion, and, conversely, when fluorine is on a carbon with decreased electron density (such as 1) it may be retained. This generates particular interest in the biphenyl case, since electron density is distributed between two rings. Nonetheless, fluorine was lost from both 4-fluorobiphenyl and 4,4′-difluorobiphenyl while it was retained with 3-fluorobiphenyl and 3,3′-difluorobiphenyl. The

1 2



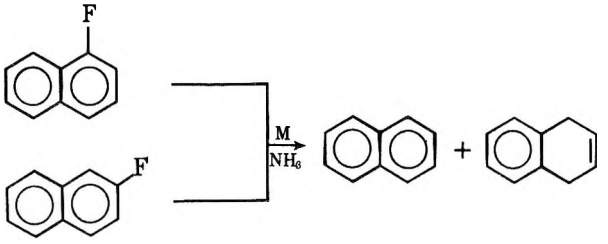
fact that 3-fluorobiphenyl reduces primarily in the fluorinated ring suggests that fluorine is an activating group[8] in metal/ammonia reduction, although not as activating as phenyl or trimethylsilyl in view of our present results. Since fluorine substitution is known to stabilize pyramidal or nonconjugated carbanions[8] but destabilize directly conjugated carbanions, this suggests that the effect of fluorine substitution in this position is largely inductive. However, the deactivating effect of a methyl or methoxy substituent presumably does not shift electron density away from the carbon bearing the fluorine in the intermediate, since the reduction of both *p*-fluorotoluene and *p*-fluoroanisole results in loss of fluorine.



R = CH_3, OCH_3

In principle, fluorinated polynuclear aromatic compounds might be reduced successfully, since the reduction of the

corresponding hydrocarbons often results in significant localization of the charge in the intermediate radical anions or dianions.[9] However, both 1- and 2-fluoronaphthalene afforded only naphthalene and its reduction products.



Experimental Section

General. Reductions were carried out by adding sodium or lithium metal to the fluoroaromatic compound in liquid ammonia with anhydrous ether as a cosolvent. In the case of polynuclear and biphenyl derivatives, solid ammonium chloride or water was used to quench the reaction whereas absolute alcohol was used with monobenzenoid compounds.

In cases where fluorine was lost (*p*-fluorobenzoic acid, 4-fluorobiphenyl, 4,4′-difluorobiphenyl, *p*-fluorotoluene, *p*-fluoroanisole, 1-fluoronaphthalene, and 2-fluoronaphthalene), the reduction products are identical with those resulting from reduction of the corresponding nonfluorinated derivatives, and these compounds have previously been characterized (i.e., 1,4-dihydrobenzoic acid, 1,4-dihydrobiphenyl, 2,5-dihydrotoluene, 2,5-dihydroanisole, and 1,4-dihydronaphthalene).[5] The absence of fluorinated reduction products in these cases was determined by GLC and/or NMR analysis. In addition, we have previously described the experimental procedure for the preparation of 3-fluoro-1,4-dihydrobenzoic acid.[10]

3,3′-Difluoro-1,4-dihydrobiphenyl. Sodium metal (10.4 mg-atoms) was added to 3,3′-difluorobiphenyl (5.2 mmol, 1 g) in 60 mL of anhydrous ether and 100 mL of anhydrous ammonia at −78 °C. After 20 min, solid ammonium chloride was added and the crude product isolated by ether extraction. The resultant oil was distilled, bp 135 °C (5 mm), to give 0.5 g (50%) of pure material: NMR ($CDCl_3$) δ 7.2 (m, 1 H), 6.9 (m, 3), 5.7 (m, 2, H_5 and H_6), 5.2 (d, 1, H_2), 4.1 (m, 1, H_1), 2.9 (d, 2, H_4).

Anal. Calcd for $C_{12}H_{10}F_2$: C, 74.99; H, 5.24; F, 19.77. Found: C, 74.75; H, 5.32; F, 19.70.

3-Fluorotrimethylsilylbenzene. A slight excess of *n*-butyllithium (1.1 equiv, 2 M in hexane) was added to 3-fluorobromobenzene (3 g, 17 mmol) in anhydrous ether at −78 °C. After stirring for 1 h, chlorotrimethylsilane (1 equiv, 1.8 g) was added and the solution was allowed to warm to room temperature (1.5 h). Water was then added followed by ether extraction resulting in an oil which was distilled, bp 60 °C (5 mm), to give pure material (1.2 g, 40%): NMR ($CDCl_3$) δ 7.3 (m, 4 H), 0.25 (s, 9).

Anal. Calcd for $C_9H_{13}FSi$: C, 64.26; H, 7.79; F, 11.30. Found: C, 63.95; H, 8.02; F, 11.55.

3-Fluoro-1,4-dihydrotrimethylsilylbenzene. Lithium wire (0.13 g, 18 mg-atoms) was added to 3-fluorotrimethylsilylbenzene (1.2 g, 7.2 mmol) in 60 mL of anhydrous ammonia containing 5 mL of absolute ethanol. After the blue color had disappeared, saturated ammonium chloride was added and the product was isolated by ether extraction. Distillation gave a colorless oil, bp 37 °C (5 mm), 0.5 g (40%): NMR ($CDCl_3$) δ 5.7 (m, 3 H), 2.8 (m, 2), 2.2 (m, 1), 0.05 (s, 9).

Anal. Calcd for $C_9H_{15}FSi$: C, 63.53; H, 8.88; F, 10.59. Found: C, 64.17; H, 9.05; F, 10.22.

3-Fluoro-1,4-dihydrobiphenyl. 3-Fluorobiphenyl[11] was reduced in the same manner as described above for 3,3′-difluorobiphenyl, to afford 3-fluoro-1,4-dihydrobiphenyl as the major reduction product together with minor products which could not be characterized. An analytical sample was trapped from the gas chromatograph. Structural assignment was based on the appearance of a vinyl proton shifted to higher field and exhibiting large (18 Hz) coupling from the adjacent ^{19}F. NMR ($CDCl_3$) δ 7.2 (m, 5 H), 5.7 (m, 2), 5.27 (d of m, 1), 4.2 (m, 1), 2.8 (d, 2).

Anal. Calcd for $C_{12}H_{11}F$: C, 82.73; H, 6.36; F, 10.90. Found: C, 82.68; H, 6.49; F, 10.75.

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Registry No.—Ammonia, 7664-41-7; 3,3′-difluoro-1,4-dihydrobiphenyl, 62476-43-1; 3,3′-difluorobiphenyl, 396-64-5; 3-fluorotrimethylsilylbenzene, 7217-41-6; 3-fluorobromobenzene, 1073-06-9; chlorotrimethylsilane, 75-77-4; 3-fluoro-1,4-dihydrotrimethylsilylbenzene, 62476-44-2; 3-fluorobiphenyl, 2367-22-8; 3-fluoro-1,4-dihydrobiphenyl, 62476-45-3.

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Steric Effects in Photochemical Intramolecular [$_\pi$2 + $_\pi$2] Ring Closure Reaction of Polycyclic Diolefins Leading to Strained Cage Molecules. Empirical Force Field Calculations

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The effect of ground state conformation on photochemical reactivity has rarely been studied[1] expect in the solid state reactions.[2] The [$_\pi$2 + $_\pi$2] cycloaddition, one of the most well-studied photochemical processes,[3] of polycyclic dienes leading to strained cage molecules provides an ideal material to probe the possible role of steric requirements. A variety of examples have already been accumulated wherein the steric environments with respect to the reacting double bonds differ considerably. In accordance with expected steric control, recorded yields of such reactions range between zero and quantitative (Table I). We are interested, from a rather practical standpoint, in studying how steric factors in the ground state influence the appalling difference in the yields.

Photochemical yields are also affected by other factors such as nearby substituents and side reactions including cycloreversions.[4] In order to reduce complications arising from these secondary factors to a minimum, we primarily limit our attention to sensitized irradiation of diolefins having no substituent. Diolefins carrying electron-deficient substituents not directly attached to the double bond are considered only for comparison purposes, while those carrying the substituents directly attached to the double bond are not considered except for a homologous series. The effects of side reactions will be discussed when the yield of expected product is poor.

Table I. Calculated Distance r and Orientation θ between Two Double Bonds in Polycyclic Diolefins and Strain Increase Accompanying Photochemical Ring Closure

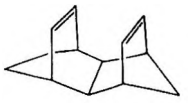
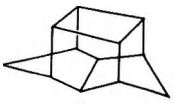
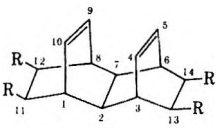
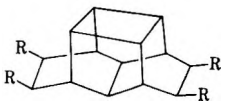
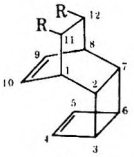
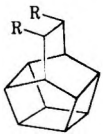
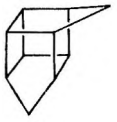
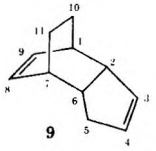
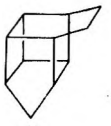
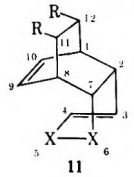
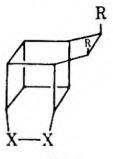
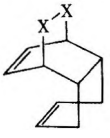
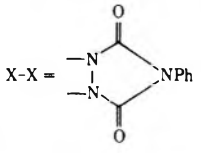
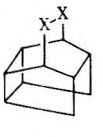
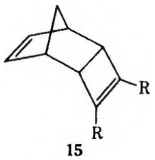
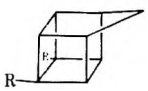
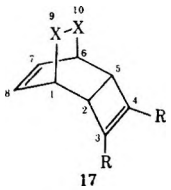
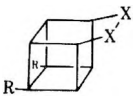
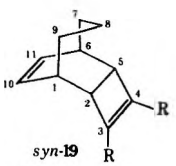
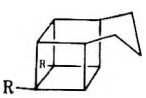
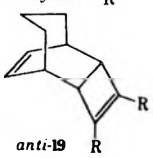
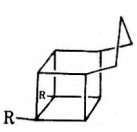
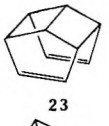
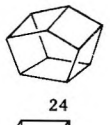
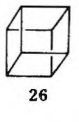
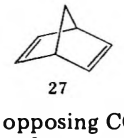
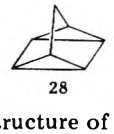
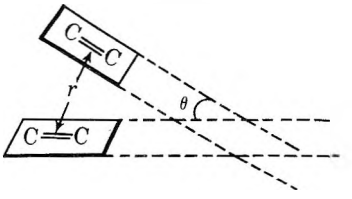
r, Å[a]	θ, deg[b]	Starting diene	Yield, %	Product	Δ_{strain}, kcal/mol[c]
2.94	0	 1	100[d]	 2	14.29[e]
2.80[f] 3.05[g]	0[f] 12.4[g]	 3	85[h]	 4	29.92[i] 26.31[j]
3.05[f] 3.07[g]	0 11.5[g]	 5	80,[h] 75[k]	 6	18.78[i] 18.26[j]
3.08	28.9	 7	61,[l] 31[m]	 8	52.28
3.04[f] 3.04[g]	21.6[f] 21.6[g]	 9	15[n]	 10	52.17[i] 54.45[j]
3.62[f] 3.01[g]	33.2[f] 40.0[g]	 11	Trace,[o] 63[p]	 12	51.61[i] 52.01[j]
2.93[f] 2.95[g]	0[f] 11.3[g]	 13	80,[q,r] 83[q]  i	 14	35.09[i] 34.95[j]
2.87	0	 15	—,[t] 80–85[u,v]	 16	65.13[e,w]
2.86[f]	0[f]	 17	5,[u] 20–25,[x] 58–62[y]	 18	72.64[e,i]
2.92[f]	0[f]	 *syn*-19	0[u]	 20	78.14[i]
2.92[f]	0[f]	 *anti*-19	0[u]	 20	77.05[i]

Table I
(*Continued*)

r, Å[a]	θ, deg[b]	Starting diene	Yield, %	Product	Δ_{strain}, kcal/mol[c]
2.77	0	 21	50[z]	 22	70.72
2.86	0	 23	0[aa]	 24	110.87[e]
3.05	0	 25	0[bb]	 26	71.88[e]
2.4[cc]	0[cc]	 27	95[dd]	 28	66.4[ee] 53.1[s]

[a] Distance between midpoints of opposing CC double bonds in minimum energy structure of the starting diene. [b] Dihedral angle between two planes containing four unsaturated carbon atoms in the minimum energy structure. [c] (Calculated strain energy of product) − (calculated strain energy of starting diene), according to Allinger 1971–1972 force field, 25°C, gas phase. The values refer to unsubstituted structures (R = H). See Tables II and III and ref 8a for individual strain energy values. [d] Reference 11. [e] For calculated strain of the product, see Table XII of ref 8a. [f] Eclipsed conformation. [g] Twisted conformation. [h] R, R = $(CO)_2O$, $(CN)_2$; ref 12. [i] Based on eclipsed starting diolefin conformation. [j] Based on twisted starting diolefin conformation. [k] R, R = $CH_3O_2CNNCO_2CH_3$; ref 13. [l] G. O. Schenck and R. Steinmetz, *Chem. Ber.*, **96**, 520 (1963); J. Blum, C. Zlotogorski, and A. Zoran, *Tetrahedron Lett.*, 1117 (1975). [m] Refers to corresponding 5-exo alcohol: W. L. Dilling and C. E. Reineke, *Org. Photochem. Synth.*, **1**, 85 (1971). [n] E. Osawa, Y. Fujikura, K. Aigami, Y. Inamoto, N. Takaishi, P. Grubmüller, and P. v. R. Schleyer, manuscript in preparation. [o] R = H; X = CH_2; ref 17. [p] R, R = $(CO)_2O$, $(CN)_2$; X–X = CH=CH; ref 12. [q] Reference 19. [r] X–X = *trans*-$CH(CO_2Et)$–$CH(CO_2Et)$. [s] Based on strain energies (norbornadiene 25.6, quadricyclane 78.7 kcal/mol) derived from combustion analysis: H. K. Hall, Jr., C. D. Smith, and J. H. Baldt, *J. Am. Chem. Soc.*, **95**, 3197 (1973). [t] R = H, yield not reported, ref 20. [u] R = $OSi(CH_3)_3$; X = CH_2; ref 14. [v] The ring closure reaction with an oxa analogue proceeds in 15–35% yield: W. Eberback and M. Perroud-Argüelles, *Chem. Ber.*, **105**, 3078 (1972). [w] Calculated heat of formation of homocubane reported in Table XII of ref 8a should read 99.03 kcal/mol. [x] R = $COOCH_3$; X = CH_2: W. G. Dauben, C. H. Schallhorn, and D. L. Whalen, *J. Am. Chem. Soc.*, **93**, 1446 (1971); R = H; X–X = benzo: L. A. Paquette, M. J. Kukla, and J. C. Stowell, *ibid.*, **94**, 4920 (1972); R = H; X–X = cyclobuteno: L. A. Paquette and M. J. Kukla, *J. Chem. Soc., Chem. Commun.*, 409 (1973). [y] R, R = $(CO)_2O$; X = CH_2: S. Masamune, H. Cuts, and M. G. Hogben, *Tetrahedron Lett.*, 1017 (1966); H. G. Cuts, E. N. Cain, H. Westberg, and S. Masamune, *Org. Photochem. Synth.*, **1**, 83 (1971); L. A. Paquette and J. C. Stowell, *J. Am. Chem. Soc.*, **93**, 2459 (1971). [z] Reference 24. [aa] Reference 25. [bb] References 26, 28. [cc] Reference 5, based on electron diffraction analysis: Y. Morino, K. Kuchitsu, and A. Yokozeki, *Bull. Chem. Soc. Jpn.*, **40**, 1552 (1967). [dd] Reference 31. [ee] Based on strain energies derived from heats of hydrogenation data. Schleyer's strain energy values [P. v. R. Schleyer, J. E. Williams, and K. R. Blanchard, *J. Am. Chem. Soc.*, **92**, 2377 (1970)] are to be corrected using a revised heat of formation of norbornane (Table IV). Revised enthalpies and strain energies (kcal/mol) are 55.7 and 30.7 for norbornadiene, and 79.6 and 97.1 for quadricyclane. Allinger and Sprague (ref 7b) give a slightly higher value (31.59 kcal/mol) for the strain of norbornadiene.

Steric factors considered include the midpoint distance r and the orientation θ between opposing double bonds, the



strain increase, Δ_{strain}, in the product relative to the starting diene.[5] These quantities can be estimated most readily and accurately by molecular mechanics calculations[6] based on Allinger 1971–1972 force field,[7] and summarized in Table I. The strain increase (Δ_{strain}) was obtained as the difference in strain energies of starting diolefin (Table II) and product (Table III). Table III includes corresponding energies obtained by using the Engler force field[8] for comparison. For those starting diolefins containing bicyclo[2.2.2]octane and bicyclo[3.2.2]nonane skeletons (**3, 5, 9, 11,** and **13**), twist as well as eclipse conformations are considered in view of the flexible nature of these systems.[9,10]

The criteria considered here appear to contribute more or less to the reactivity of diolefins listed in Table I. Most of the calculated distances r between opposing double bonds are in the vicinity of 3 Å, considerably shorter than the limiting distance of about 4 Å beyond which neither intra- nor intermolecular [$_\pi 2 + _\pi 2$] cycloadditions take place in solid state photochemical reactions.[2,5] Thus, the observed high yield of **2**[11] can be best explained by a remarkably small strain increase accompanying the ring closure, rather than the obvious close and parallel orientation of the double bonds in **1**. Close, parallel orientations of double bonds in **15, 17,** and **21** lead to poorer yields in the ring closure, indicating that the orientation factor does not always dominate. High-yield reactions **3** → **4**[12] and **5** → **6**[12,13] are also accompanied by only moderate Δ_{strain} values, although these examples are assisted by the electron-deficient substituents.

There appears to be essentially no difference between two reactions (**7** → **8** and **9** → **10**) as far as the three criteria, r, θ, and Δ_{strain}, are concerned. The poor yield of **10** should then be attributed to the lower reactivity of the bicyclo[2.2.2]octene type double bond of **9** relative to the norbornene type double bond of **7**, as suggested by Miller and Dolce.[14] The reactivity

Table II. Calculated Heats of Formation and Strain Energies of Polycyclic Diolefins and Monoolefins Based on Allinger 1971–1972 Force Field[a] (kcal/mol, 25 °C, Gas)

Registry no.	Diolefin		$\Delta H_f°$	Strain
1076-13-7	*endo,endo*-Tetracyclo[4.2.1.1^{3,6}.0^{2,7}]dodeca-4,9-diene (**1**)[b]		59.74	49.15
62415-10-5	*endo,endo*-Tetracyclo[6.2.2.2^{3,6}.0^{2,7}]tetradeca-4,9-diene (**3**, R = H)[c]	Eclipse	25.72	25.51
		Twist[d,e]	29.03	28.82
62415-15-0	*endo,endo*-Tetracyclo[6.2.2.0^{2,7}.0^{3,6}]dodeca-4,9-diene (**5**, R = H)[c]	Eclipse	88.61	78.02
		Twist[d,f]	89.13	78.54
1755-01-7	*endo*-Tricyclo[5.2.1.0^{2,6}]deca-3,8-diene (dicyclopentadiene, **7**)		42.48	27.58
54483-01-1	*endo*-Tricyclo[5.2.2.0^{2,6}]undeca-3,8-diene (**9**)[g]	Eclipse	31.20	21.49
		Twist[d,h]	28.92	19.21
62415-13-8	*endo*-Tricyclo[6.2.2.0^{2,7}]dodeca-3,9-	Eclipse	22.78	18.26
	diene (dicyclohexadiene, **11**, R = H; X = CH_2)[i]	Twist[d,j]	22.38	17.86
62447-34-1	*endo*-Tricyclo[6.2.2.0^{2,7}]dodeca-4,9-diene (**13**, X = CH_2)[k]	Eclipse	23.41	18.89
		Twist[d,l]	23.55	19.03
15564-45-1	*endo*-Tricyclo[4.2.1.0^{2,5}]nona-3,7-diene (**15**, R = H)[m]		76.42	56.33
55054-12-1	*endo*-Tricyclo[4.2.2.0^{2,5}]deca-3,7-diene (**17**, R = H; X = CH_2)[n]	Eclipse	61.65	46.75
		Twist[d,o]	61.73	46.83
62415-17-2	*syn,endo*-Tricyclo[4.3.2.0^{2,5}]undeca-3,10-diene (*syn*- **19**, R = H)[m]	Eclipse	54.52	44.81
	anti,endo-Tricyclo[4.3.2.0^{2,5}]undeca-3,10-diene (*anti*- **19**, R = H)[m]	Twist[d,p]	57.69	47.98
		Eclipse	55.61	45.90
		Twist[d,q]	55.55	45.84
30114-57-9	Tetracyclo[6.3.0^{4,11}.0^{5,9}]undeca-2,6-diene (homohypostrophene, **21**)[r]		49.97	34.19
34324-40-8	Tetracyclo[5.3.0.0^{2,6}.0^{3,10}]deca-4,8-diene (hypostrophene, **23**)[s]		89.43	68.46
20380-30-7	*syn*-Tricyclo[4.2.0.0^{2,5}]octa-3,7-diene (**25**)[t,u]		120.30	95.02

[a] Reference 7. [b] P. Buck, D. Thompson, and S. Winstein, *Chem. Ind. (London)*, 405 (1960); R. B. Turner, A. D. Jarrett, P. Goebel, and B. J. Mallon, *J. Am. Chem. Soc.*, **95**, 790 (1973); J. K. Stille and D. R. Witherell, *ibid.*, **86**, 2188 (1964). [c] See ref 12 for derivatives. [d] See footnote 10. [e] Twist angles: $C_1C_{10}C_9C_8$, 2.5°, $C_1C_{13}C_{14}C_8$, 8.6°; $C_1C_2C_7C_8$, 11.5°. [f] Twist angles: $C_1C_2C_7C_8$, 8.5°; $C_1C_{11}C_{12}C_8$, 6.0°; $C_1C_{10}C_9C_8$, 2.1°; $C_3C_2C_7C_6$, 6.5°; $C_3C_4C_5C_6$, 1.1°. [g] N. Takaishi, Y. Inamoto, K. Aigami, K. Tsuchihashi, and H. Ikeda, *Synth. Commun.*, **4**, 225 (1974). [h] Twist angles: $C_1C_2C_6C_7$, 9.6°; $C_1C_9C_8C_7$, 4.0°; $C_1C_{10}C_{11}C_7$, 8.9°. [i] Reference 17. [j] Twist angles: $C_1C_2C_7C_8$, 19.6°; $C_1C_{10}C_9C_8$, 5.3°; $C_1C_{11}C_{12}C_8$, 13.6°. [k] See ref 19 for derivatives. [l] Twist angles: $C_1C_2C_7C_8$, −10.9°; $C_1C_{10}C_9C_8$, −3.1°; $C_1C_{11}C_{12}C_8$, −7.8°. [m] See ref 14 for a derivative. [n] See ref 14 and references cited in footnotes *x* and *y* of Table I for derivatives. [o] Twist angles: $C_1C_2C_5C_6$, 1.4°; $C_1C_9C_{10}C_6$, 1.9°; $C_1C_8C_7C_6$, 0.7°. [p] Twist angles: $C_1C_2C_5C_6$, 0.7°; $C_1C_{10}C_{11}C_6$, 0.8°. [q] Twist angles: $C_1C_2C_5C_6$, 2.0°; $C_1C_{10}C_{11}C_6$, 0.5°. [r] Reference 24 and G. R. Underwood and B. Ramamoorthy, *Tetrahedron Lett.*, 4125 (1970). [s] Reference 25 and L. A. Paquette, R. F. Davis, and D. R. James, *Tetrahedron Lett.*, 1615 (1974). [t] Reference 27 and M. Avram, I. D. Dinulescu, E. E. Marica, G. Mateescu, E. Slim, and C. D. Nenitzescu, *Chem. Ber.*, **97**, 382 (1964). [u] Reference 28 for a permethyl derivative.

Table III. Calculated Heats of Formation and Strain Energies of Cage Hydrocarbons (kcal/mol, 25 °C, Gas)

Registry no.	Compd	$\Delta H_f°$		Strain	
		E[a]	A[b]	E[a]	A[b]
62415-11-6	Hexacyclo[6.4.2.0^{2,7}.0^{3,11}.0^{6,10}.0^{9,12}]tetradecane (**4**, R = H)[c]	11.04	13.12	53.16	55.43
62415-16-1	Hexacyclo[6.4.0.0^{2,7}.0^{3,6}.0^{4,12}.0^{5,9}]dodecane (1,1′-bishomopentaprismane, **6**, R = H)[c]	58.96	64.87	90.82	96.80
6707-86-4	Pentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decane (1,3-bishomocubane, **8**)[d]	48.33	52.24	75.87	79.86
62415-12-7	Pentacyclo[5.4.0.0^{2,5}.0^{3,11}.0^{4,8}]undecane (1,3-ethanomethanocubane, **10**)[e]	40.99	43.82	73.66	76.63
62415-14-9	Pentacyclo[6.4.0.0^{2,5}.0^{3,12}.0^{4,9}]dodecane (1,3-bisethanocubane, **12**, R = H; X = CH_2)[d,f]	31.65	38.87	69.45	69.87
4421-33-4	Pentacyclo[6.4.0.0^{2,7}.0^{3,11}.0^{6,10}]dodecane (**14**, X = CH_2)[g]	15.11	15.98	52.91	53.98
61304-39-0	Pentacyclo[5.4.0.0^{2,10}.0^{6,9}.0^{8,11}]undecane (**20**, R = H)	85.34	90.14	118.01	122.95
25107-14-6	Hexacyclo[6.2.1.0^{2,7}.0^{3,6}.0^{4,10}.0^{5,9}]undecane (homopentaprismane, **22**)[h]	69.64	78.17	96.37	104.91

[a] Engler force field, ref 8. [b] Allinger 1971–1972 force field, ref 7. [c] See ref 12 for derivatives. [d] Computational results for this molecule preliminarily reported in E. Ōsawa, P. v. R. Schleyer, L. W. K. Chang, and V. V. Kane, *Tetrahedron Lett.*, 4189 (1974). [e] E. Ōsawa, Y. Fujikura, K. Aigami, Y. Inamoto, N. Takaishi, P. Grubmüller, and P. v. R. Schleyer, manuscript in preparation. [f] Reference 18; K. Hirao, T. Iwakuma, M. Taniguchi, E. Abe, O. Yonemitsu, T. Date, and K. Kotera, *Chem. Commun.*, 691 (1974); T. Iwakuma, H. Nakai, O. Yonemitsu, and B. Witkop, *J. Am. Chem. Soc.*, **96**, 2564 (1974); T. Iwakuma, K. Hirao, and O. Yonemitsu, *ibid.*, **96**, 2570 (1974). [g] J. Dekker, J. J. Dekker, L. Fourie, and G. L. Wenteler, *J. S. Afr. Chem. Inst.*, **28**, 321 (1975); K. G. R. Pachler, P. L. Wessels, J. Dekker, J. J. Dekker, and T. G. Dekker, *Tetrahedron Lett.*, 3059 (1976). [h] Reference 24.

difference may be most readily understood in terms of the steric strain at these double bonds in the ground state, for which the strain energy difference between the alkene and corresponding alkane is proposed to be a good measure.[7b] This proposal is illustrated in Table IV for the parent systems, norbornene and bicyclo[2.2.2]octene, using experimental heats of formation as the basis of calculation. About 5 kcal/mol higher strain in the norbornene double bond relative to the bicyclo[2.2.2]octene double bond, which has virtually no extra strain compared to the ethylene double bond, is in accord with their known chemical and physical behavior.[15,16]

The failure of dicyclohexadiene (**11**, R = H; X = CH_2) to effect intramolecular ring closure[17] aroused some speculations.[17,18] The relatively large distance *r* (3.6 Å) of **11** is not likely to be an obstacle in view of the known examples in solid state photochemistry.[2] Strain increase in the reaction **11** → **12** is comparable to the reaction **9** → **10**. Therefore, from a steric standpoint, uncomfortable orientation of the double

Table IV. Alkene–Alkane Strain Energy Difference Based on Experimental Heats of Formation (kcal/mol, 25 °C, Gas)

		Strain		Difference	
	$\Delta H_f°$ (exptl)	S[g]	A[h]	S[g]	A[h]
Norbornene	20.7[a]	23.2	23.6		
	(21.1)[b]				
	(15.12)[c]			5.6	4.7
Norbornane	−12.42[d]	17.6	18.9		
	(−12.60)[a]				
Bicyclo[2.2.2]octene	4.88[e]	12.2[e]	13.0		
Bicyclo[2.2.2]octane	−23.67[e]	11.4[e]	13.7	0.8	−0.7
	(−23.75)[f]				

[a] Based on heat of hydrogenation data: H. K. Hall, Jr., C. D. Smith, and J. H. Baldt, *J. Am. Chem. Soc.*, **95**, 3197 (1973). [b] Based on equilibration between cyclopentadiene and ethylene: R. Walsh and M. Wells, *J. Chem. Thermodyn.*, 8, 55 (1976). [c] Combustion analysis by Hall et al. (footnote *a*). [d] Combustion analysis: P. v. R. Schleyer, J. E. Williams, and K. R. Blanchard, *J. Am. Chem. Soc.*, **92**, 2377 (1970). [e] Combustion analysis: S. S. Wong and E. E. Westrum, Jr., *ibid.*, **93**, 5317 (1971). [f] Combustion analysis: R. H. Boyd, S. N. Sanwal, S. Shary-Tehrany, and D. McNally, *J. Phys. Chem.*, **75**, 1264 (1971). [g] Based on Schleyer's group enthalpy increments (footnote *d*). [h] Based on Allinger's enthalpy increment scheme, ref 7b.

bonds (θ larger than 30°) appears responsible. The double bond isomer **13** having an ideal orientation undergoes the reaction with high yield,[19] albeit this example is assisted by electron-deficient substituents and moderate strain increase. The reaction **11** → **12** also proceeds smoothly when electron-deficient substituents are present in the molecule.[12]

A homologous series of fused cyclobutene derivatives, **15**, **17**, and **19**, provides a unique opportunity to test the effects of steric environments. Since only the first member (**11**, R = H) of the hydrocarbon series has been studied (without description of yield),[20] we first concentrate on the series of bis(trimethylsiloxy) derivatives (R = $OSiMe_3$). The reaction series **15** → **16**, **17** → **8**, **19** → **20** shows progressive and sharp decrease in the yield of ring closure product in this order.[14] Contrary to an earlier suggestion,[14] calculated distances *r* are invariably favorable 2.9 Å within the series. High yield in the reaction **15** → **16** despite a considerably large Δ_{strain} value will be the result of the high reactivity of the norbornene type double bond.[21] Sudden decrease in the yield of the reaction **17** → **18** is partly due to the lack of extra reactivity in the bicyclo[2.2.2]octene type double bond of **17** and partly due to an increase in Δ_{strain} by 7.5 kcal/mol. Complete inertness of **19** under irradiation must be attributed to the still higher Δ_{strain} value predicted for its ring closure reaction. The photochemical behavior of this series indicates that the maximum strain increase that can be overcome will be about 70 kcal/mol. In the presence of suitable substituents, the yield of **18** increases to a moderate range.[22,23]

The successful ring closure of homohypostrophene (**21**) to homopentaprismane (**22**)[24] provides an example of hydrocarbon reaction where a Δ_{strain} value of 70 kcal/mol is tided over. This reaction is undoubtedly assisted by an ideal juxtaposition of the double bond in **21**. In contrast, hypostrophene (**23**)[25] and tricyclo[4.2.0.$0^{2,5}$]octa-3,7-diene (**25**)[26,28] are inert under any photolytic conditions and their inertness has been attributed to the mixing effect of high-lying σ orbitals with π orbitals.[27,29] Nevertheless, we note here that an extremely large strain increase, which we predict to accompany the formation of pentaprismane (**24**) from **23**, could well be a key factor in the failure of this reaction. On the other hand, calculated Δ_{strain} arising from the formation of cubane (**26**) from **25** (72 kcal/mol) is comparable to that of homopentaprismane formation (**21** → **22**). Thus, the reaction (**25** → **26**) hs a good chance to proceed on steric grounds alone, especially if activating substituents are present.[30]

Finally, the high-yield conversion of norbornadiene (**27**) to quadricyclane (**28**)[31] under sensitized irradiation can be understood in terms of the shortest distance *r* among the diolefins in Table I, not unsurmountable Δ_{strain} (less than 70 kcal/mol) and expectedly high steric strain in the double bonds of **27**.

In conclusion, intramolecular [$_\pi$2 + $_\pi$2] photochemical ring closure reactions of polycyclic diolefins leading to strained cage products are recognized to be under the great influence of three steric criteria: *r*, θ, and Δ_{strain}. Although the higher limit of *r* could not be determined based on the available data, the limit of orientation factor θ appears to be near 35°. The maximum recorded Δ_{strain} that could be overcome among the known examples is about 70 kcal/mol. The norbornene type double bond is about 5 kcal/mol more strained than the usual double bonds and highly reactive in the cycloaddition reactions.

Rationale for the arguments presented above lies in Hammond's postulate.[32] Evaluation of relative contribution of steric factors to the overall activation process remains to be explored.

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Registry No.—**2**, 704-02-9; **3** (R,R = $(CO)_2O$), 24145-84-4; **3** (R,R = $(CN)_2$), 62415-18-3; **5** (R,R = $(CO)_2O$), 24147-34-0; **5** (R,R = $(CN)_2$), 62415-02-5; **5** (R,R = $CH_3O_2CNNCO_2CH_3$), 62415-03-6; **11** (R,R = $(CO)_2O$; X–X = CH=CH), 62415-00-3; **11** (R,R = $(CN)_2$; X–X = CH=CH), 62415-04-7; **12** (R = H; X–X = CH=CH), 62415-05-8; **13** (X–X = *trans*-CH(CO_2Et)CH(CO_2Et)), 41181-93-5; **13** (X–X = i), 41182-02-9; **14** (X–X = *trans*-CH(CO_2Et)CH(CO_2Et)), 41181-96-8; **14** (X–X = i), 62415-01-4; **15** (R = $OSi(CH_3)_3$), 39762-43-1; **16** (R = H), 452-61-9; **17** (R = $OSi(CH_3)_3$; X = CH_2), 39762-44-2; **17** (R = $COOCH_3$; X = CH_2), 62415-06-9; **17** (R = H; X–X = benzo), 27487-45-2; **17** (R = H; X–X = cyclobuteno), 62415-07-0; **17** (R,R = $(CO)_2O$; X = CH_2), 62415-08-1; **18** (R = H; X = CH_2), 5603-27-0; **18** (R = H; X–X = benzo), 29443-82-1; **18** (R = H; X–X = cyclobuteno), 62415-09-2; **19** (R = $OSi(CH_3)_3$), 39762-45-3; **24**, 4572-17-2; **26**, 277-10-1.

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(5) Similar and with respect to kinetic action of intermediates alternative treatment: G. Kaupp, *Justus Liebigs Ann. Chem.*, 844 (1973).
(6) Reviews: (a) N. L. Allinger, *Adv. Phys. Org. Chem.*, **13**, 1 (1976); (b) O. Ermer, *Struct. Bonding (Berlin)*, **27**, 161 (1976); (c) E. Osawa, P. v. R. Schleyer, and H. Musso, *Angew. Chem.*, in press.
(7) (a) N. L. Allinger, M. T. Tribble, M. A. Miller, and D. H. Wertz, *J. Am. Chem. Soc.*, **93**, 1637 (1971); (b) N. L. Allinger and J. T. Sprague, *ibid.*, **94**, 5734 (1972).
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(10) Bicyclic olefins are more resistant to twisting deformations compared to

saturated counterparts,[9] as indicated by small twist angles around the CC double bond in the energy minimum structures (Table II). For **17** and **19** having a fused cyclobutene ring as well as for *anti*-**29**, no energy minimum could be found for twist conformations, whereas twist forms of **15** and *syn*-**29** have well-defined energy minima.

(11) R. C. Cookson, E. Crundwell, R. R. Hill, and J. Hudec, *J. Chem. Soc.*, 3062 (1964).
(12) E. LeGoff and S. Oka, *J. Am. Chem. Soc.*, **91**, 5665 (1969).
(13) E. L. Allred and B. R. Beck, *Tetrahedron Lett.*, 437 (1974).
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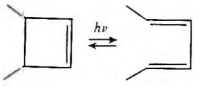
(16) If enthalpies obtained by Allinger force field calculations[7b] are used instead of experimental enthalpies, the double bond reactivity difference between norbornene and bicyclo[2.2.2]octene is greatly underestimated. Calculated alkene–alkane strain energy differences kcal/mol are as follows:

	Allinger[7b]	This work
Norbornene	5.72	3.58
Bicyclo[2.2.2]octene	4.30	4.60 (eclipse)
		3.30 (twist)

Recalculations of enthalpies using a different energy minimization scheme (pattern search method)[8] and taking the conformational flexibility of the bicyclo[2.2.2]octane skeleton[9] into account give essentially the same results as shown above. Comparison between experimental (Table IV) and calculated enthalpies revealed that our calculations overestimated the enthalpy of bicyclo[2.2.2]octene and underestimated those of bicyclo[2.2.2]-octane and norbornene, although the discrepancies were close to the known accuracy range of ±2 kcal/mol.[8a] For these reasons, we do not extend the alkene–alkane strain energy difference scheme to other systems like **7**, **9**, **15**, **17**, and **19** for which calculated enthalpy values must be used.

(17) D. Valentine, N. J. Turro, and G. S. Hammond, *J. Am. Chem. Soc.*, **86**, 5202 (1964).
(18) H.-D. Becker, *Justus Liebigs Ann. Chem.*, 1675 (1973).
(19) B. M. Jacobson, *J. Am. Chem. Soc.*, **95**, 2579 (1973).
(20) L. A. Paquette and J. C. Stowell, *J. Am. Chem. Soc.*, **92**, 2584 (1970).
(21) The effect of the trimethylsiloxy group is not clear.
(22) The ring closure reactions of bis(trimethylsiloxy) series **15**, **17**, and **19** occur only under direct irradiation, and not at all under sensitized conditions. In this context, the generality of conclusions obtained with this series may be limited.
(23) The possibility of cycloreversion is ruled out based on the logic that cycloreversion should have been most prominent, if it occurs at all, in **15**



where strain release accompanying the ring opening must be the largest. The observed high yield of ring closure in **15** indicates the practically negligible extent of the cycloreversion.

(24) (a) A. P. Marchand, T.-C. Chou, J. D. Ekstrand, and D. van der Helm, *J. Org. Chem.*, **41**, 1438 (1976); (b) P. E. Eaton, L. Cassar, R. A. Hudson, and D. R. Hwang, *ibid.*, **41**, 1445 (1976).
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(26) H. Iwamura, unpublished results quoted in ref. 27.
(27) H. Iwamura, K. Morio, and H. Kihara, *Chem. Lett.*, 457 (1973).
(28) Permethyl-**25** (Louis hydrocarbon) also does not undergo ring closure upon irradiation to the cubane skeleton: R. Criegee, *Angew. Chem., Int. Ed. Engl.*, **1**, 519 (1962); L. T. Scott, and M. Jones, Jr., *Chem. Rev.*, **72**, 189 (1972).
(29) W. Schmidt and B. Wilkins, *Tetrahedron*, **28**, 5649 (1972).
(30) Here again, cycloreversions do not appear to be the main obstacle. Although no detail has been published on the photolysis of **23**,[25] irradiation of **25** does not produce cyclooctatetraene: T. J. Katz and E. W. Turnblom, *J. Am. Chem. Soc.*, **92**, 6702 (1970).
(31) G. S. Hammond, N. J. Turro, and A. Fischer, *J. Am. Chem. Soc.*, **83**, 4674 (1961). For substituted cases: G. Kaupp and H. Prinzbach, *Chem. Ber.*, **104**, 182 (1971).
(32) D. Farcasiu, *J. Chem. Educ.*, **52**, 76 (1975).

A Synthesis of Terminal Arylacetylenes—an in Situ Generated Copper(I) Acetylide

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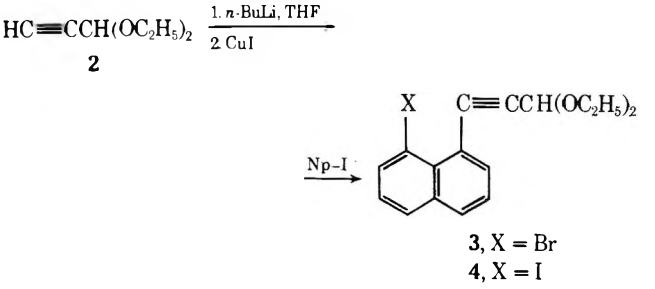
Terminal arylacetylenes can be prepared by several routes. Dehydrohalogenation of halogenated ethanes,[2-6] amine-induced decomposition of 5-aryl-3-nitroso-2-oxazolidones,[7] and pyrolysis of 4-aryl-1,2,3-selenadiazoles[8] are methods recently reported in the literature. Alternatively, the triple bond can be preformed with a protecting group attached to one end and then coupled at the unprotected end to a suitable aromatic ring, followed by removal of the protecting group.[9,10]

In connection with other studies, we required 1-ethynyl-8-halonaphthalenes. Because of the lability of the halogen atom in the 8 position, only the last method seemed a feasible preparative route. Curtis and co-workers[9] have reported using the Castro reaction[11] to couple 1-iodonaphthalene and copper(I) 3,3-diethoxy-1-propyne (**1**). Hydrolysis and deformylation of the coupled product gave 1-ethynylnaphthalene in moderate yield.

Our attempts to employ Curtis' method using 1,8-diiodonaphthalene[12] or 1-bromo-8-iodonaphthalene[13] gave the desired coupled product but in low yield. The lack of success of this method was apparently due to the difficulty in preparing and isolating **1**. Rather than isolate **1**, we generated and reacted **1** in situ. We have observed that **1** is soluble in THF and pyridine, unlike most other copper(I) acetylides.[11d] Soluble in situ generated copper(I) acetylides have been reported using *N*-ethylpiperidine as base. The yields of coupled products were low, however.[11e]

1,1-Diethoxy-2-propyne[15] (**2**) was dissolved in dry tetrahydrofuran (THF) and deprotonated with *n*-butyllithium. To this solution was added cuprous iodide, and the solution was allowed to stir until the CuI had dissolved. The desired naphthyl iodide was added and the solution refluxed for 12 h. Excellent yields of the coupled product were obtained after work-up. (Scheme I).

Scheme I

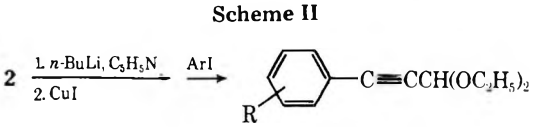


3, X = Br
4, X = I

Cuprous trimethylsilylacetylide proved too unstable to undergo coupling under our conditions.[14] Use of potassium *tert*-butoxide as the deprotonating base resulted in lower yields. 1-Bromonaphthalene and several substituted phenyl iodides failed to react when subjected to the same conditions.

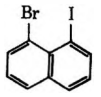
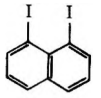
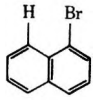
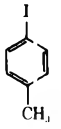
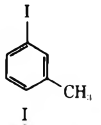
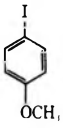
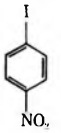
A number of substituted phenyl iodides did undergo coupling with **1** when the THF was replaced with dry pyridine and the reflux time extended to 48 h. The yields of the 1,1-diethoxy-3-aryl-2-propynes were lower but still useful. To achieve maximum yields the ratio of **2** to aryl iodide was 2:1. Variation of the ratio from 1:1 to 4:1 did not give any improvement in the yield (Scheme II). Our results are summarized in Table I.

Scheme II



5, R = H
6, R = *p*-CH_3
7, R = *m*-CH_3
8, R = *p*-OCH_3

Table I

Registry no.	Substrate	2/substrate	Yield
4044-58-0		1.1/1.0[c]	97, 98[a] (3)
1730-04-7		1.1/1.0[c]	90, 91[a] (4)
90-11-9		1.1/1.0[c]	0
591-50-4		2.0/1.0	68, 71[b] (5)
624-31-7		1.0/1.0	45[b] (6)
		2.0/1.0	50, 51, 57[a] (6)
		4.0/1.0	55[a] (6)
625-95-6		2.0/1.0	50[a] (7)
696-62-8		2.0/1.0	50, 55[b] (8)
636-98-6		2.0/1.0	0 (14)

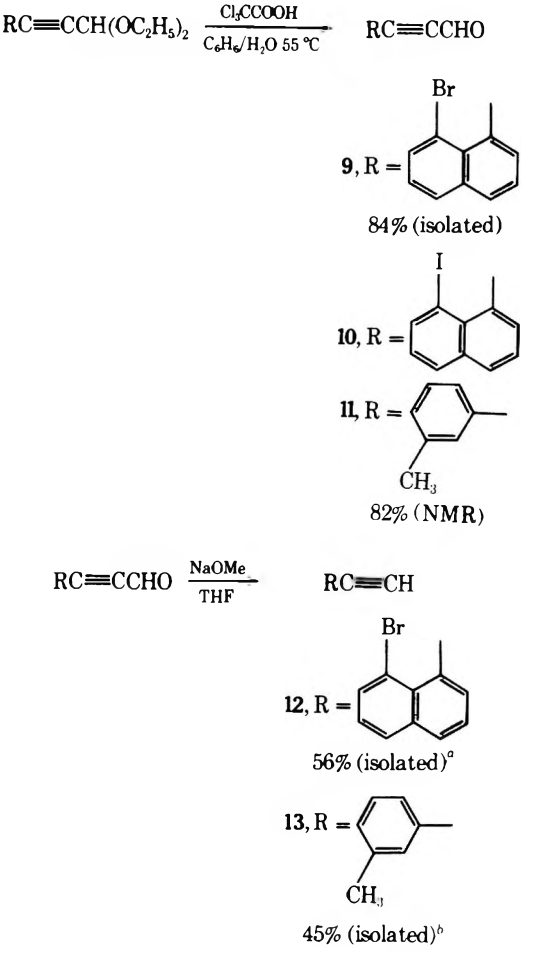
[a] Isolated yield. [b] NMR yield. [c] Run in THF; all others run in pyridine.

The diethyl acetal moiety protecting the terminal end of the triple bond is resistant to hydrolysis using dilute mineral acid, the usual hydrolysis method.[16] This problem has been noted earlier.[9,17] As expected, dilute mineral acid hydrolysis of 3 or 4 did not give satisfactory yields of the desired aldehydes. Use of trichloroacetic acid in benzene–water (150/1, v/v) at 55 °C gave good yields of the aldehydes with little contamination by the intractable tars produced in the mineral acid hydrolysis. 3-(8′-Bromo-1′-naphthyl)-2-propynal (9) could be purified by column chromatography. 3-(8′-Iodo-1′-naphthyl)-2-propynal (10) proved to be so unstable that attempts to purify it resulted in complete decomposition of the aldehyde. The phenyl-coupled product 7 could also be hydrolyzed by the same method to give 11 in good yield (Scheme III).

Deformylation of the aldehyde 9 or 11 to give the terminal acetylene was accomplished using sodium methylate in dry THF at room temperature. By this method the yield of acetylene is higher and less intractable tars are formed than in the sodium hydroxide–methanol deformylation procedure. The results of hydrolysis and deformylation are presented in Scheme III.

The present procedure is complementary to existing methods, giving comparable yields with good reproducibility. Many aryl iodides are easily accessible, making this procedure a reasonable synthetic route to terminal arylacetylenes. It is also noteworthy that this method gives ready access to aryl-α,β-acetylenic aldehydes.

Scheme III



[a] Yield from aldehyde. [b] Yield from acetal.

Experimental Section

NMR spectra were taken on a Varian A60-A spectrometer with Me_4Si as internal standard. Infrared spectra were taken on a Perkin-Elmer 137 spectrometer with polystyrene as a standard. Mass spectra were taken on a Finnigan 1015D GC–MS spectrometer at 70 eV. Before use, all glassware was oven dried, assembled hot, and cooled under a stream of dry nitrogen. All reactions were run under a nitrogen atmosphere. All column chromatography was performed with neutral activated (Alcoa F-20) alumina. Pyridine was distilled from KOH under N_2 and stored in brown bottles over 4-Å molecular sieves. THF was distilled as needed from benzophenone sodium ketyl under N_2. Melting points are uncorrected.

1,1-Diethoxy-3-(8′-bromo-1′-naphthyl)-2-propyne (3). In a 1-L single-necked round-bottom flask equipped with heating mantle, reflux condenser topped with an N_2 inlet, magnetic stirrer, and 1-in. Teflon-coated stir bar were placed 750 mL of THF and 4.5 mL (0.032 mol) of 2.[15] With stirring, 20.1 mL (0.032 mol) of 1.6 M *n*-butyllithium in hexane (Aldrich Chem. Co.) was added to the THF solution of 2 to give a pale-yellow solution. After allowing this solution to stir for several minutes, 6.13 g (0.032 mol) of CuI (Alfa Inorganic Ventron Inc.) was added and allowed to dissolve giving a green-yellow colored solution. To this green-yellow solution was added 9.75 g (0.029 mol) of 1-bromo-8-iodonaphthalene,[13] and the resulting yellow solution was refluxed for 12 h. The color of the solution changed to red-brown within a few minutes after reflux began. This red-brown solution was cooled and the THF removed in vacuo by the rotoevaporator to give a red-brown oil. This oil was dissolved in 200 mL of diethyl ether and 50 mL of H_2O added, causing a tan solid to precipitate. The solid was filtered from the ether and H_2O and washed with 4 × 100 mL of ether. All ether fractions were combined, washed with H_2O, dried ($MgSO_4$), and filtered, and the ether was removed in vacuo to give a brown oil. This oil was adsorbed on alumina and placed atop a 15 × 10 cm column of alumina. The product was eluted with 800 mL of hexane–ether (9/1, v/v). Removal of the hexane–ether gave 9.5 g (97%) of a yellow oil, 3, which was pure by TLC. A repeat of this reaction gave 9.6 g

(98%) of 3: IR (neat film, NaCl) 2230 (C≡C), 1150–1000 (C–O–C), 820 and 760 cm^{-1} (1,8-disubstituted naphthalene); NMR ($CDCl_3$) δ 1.30 (t, 6, $CH_2\mathbf{CH_3}$), 3.82 (m, 4, $\mathbf{CH_2}CH_3$), 5.59 (s, 1, $\mathbf{CH}(OC_2H_5)_2$), 7.44 (m, 6, ArH); MS (70eV) P^+ *m/e* 333, base peak *m/e* 152.

1,1-Diethoxy-3-(8′-iodo-1′-naphthyl)-2-propyne (4). The procedure employed for the synthesis of 4 was identical with that used for 3. The following amounts were used: THF, 175 mL; 2, 1.8 mL (0.013 mol); 1.6 M *n*-butyllithium, 8.1 mL (0.013 mol); CuI, 2.5 g (0.013 mol); 1,8-diiodonaphthalene,[12] 4.5 g (0.012 mol). The coupled product 4 was isolated in 91% yield (4.1 g). A repeat of the reaction on 5.19 g gave 4.7 g of 4 (90%): IR (neat film, NaCl) 2200 (C≡C), 1150–1000 (C–O–C), 820 and 750 cm^{-1} (1,8-disubstituted naphthalene). NMR ($CDCl_3$) δ 1.31(t, 6, $CH_2\mathbf{CH_3}$), 3.84 (m, 4, $\mathbf{CH_2}CH_3$), 5.62 (s, 1, $\mathbf{CH}(OC_2H_3)_2$), 7.75 (m, 6, ArH).

1,1-Diethoxy-3-(*m*-tolyl)-2-propyne (7). In a 500-mL single-necked round-bottom flask equipped with heating mantle, reflux condenser topped with an N_2 inlet, magnetic stirrer, and 1-in. Teflon stir bar were placed 500 mL of dry pyridine and 6.4 mL (0.045 mol) of 2 followed by 28.6 mL (0.0458 mol) of 1.6 M *n*-butyllithium in hexane giving an orange-red solution. To this solution was added 8.64 g (0.045 mol) of CuI and the solution was stirred until the CuI had dissolved; 5.0 g (0.023 mol) of *m*-iodotoluene was added to the solution and reflux begun. Several hours after refluxing began a brown solid began to precipitate from the red-brown pyridine solution. After 48 h, reflux was stopped and most of the pyridine was removed by the rotoevaporator in vacuo. The remainder (~100 mL) of the solution was poured into 200 mL of concentrated HCl and 500 g of ice and stirred vigorously, and the organics were extracted with 400 mL of ether (three portions). The ether extracts were combined, washed with H_2O, dried ($MgSO_4$), and filtered, and the ether was removed in vacuo to give a brown oil. This brown oil was filtered through a 3 × 1 cm column of alumina with 250 mL of hexane. Removal of the hexane gave an orange oil which was adsorbed on alumina and placed atop a 20 × 2 cm column of alumina, and the product was eluted with hexane after unreacted *m*-iodotoluene; 2.5 g (49.9%) of coupled product, 7, was obtained as a yellow oil which was TLC pure: IR (neat film, NaCl) 2220 (C≡C), 1150–1000 (C–O–C), 785 and 690 cm^{-1} (1,3-disubstituted phenyl ring); NMR ($CDCl_3$) δ 1.26 (t, 6, $CH_2\mathbf{CH_3}$), 2.30 (s, 3, $\mathrm{Ar}\mathbf{CH_3}$), 3.73 (m, 4, $\mathbf{CH_2}CH_3$), 5.48 (s, 1, $\mathbf{CH}(OC_2H_5)_2$), 7.20 (m, 4, ArH); MS (70 eV) P^+ *m/e* 218, 174, 146, 116 (base peak), 92.

1,1-Diethoxy-3-(*p*-tolyl)-2-propyne[18] (6). The procedure for 6 was identical with that used for 7 with the following amounts: 100 mL of dry pyridine in a 250-mL single-necked round-bottom flask; 2, 2.6 mL (0.0184 mol); 1.6 M *n*-butyllithium, 11.5 mL (0.0184 mol); CuI, 3.5 g (0.0184 mol); *p*-iodotoluene, 2.0 g (0.0092 mol). The cooled solution was poured directly into 200 mL of concentrated HCl and 500 g of ice and extracted with ether. The column chromatography was done on a 15 × 2 cm column; 1.15 g (57%) of 6 was obtained as a TLC pure pale-yellow oil. A repeat of the reaction on the same scale gave 1.00 g (50%) of 6: IR (neat film, NaCl) 2240 (C≡C), 1150–1000 (C–O–C), 820 cm^{-1} (1,4-disubstituted phenyl); NMR ($CDCl_3$) δ 1.22 (t, 6, $CH_2\mathbf{CH_3}$), 2.26 (s, 3, $\mathrm{Ar}\mathbf{CH_3}$), 3.71 (m, 4, $\mathbf{CH_2}CH_3$), 5.48 (s, 1, $\mathbf{CH}(OC_2H_5)_2$), 7.20 (m, 4, ArH); MS (70 eV) P^+ *m/e* 218, 174, 144, 116 (base peak).

1,1-Diethoxy-3-phenyl-2-propyne[19] (5). The procedure was the same as that used for 6 with the following amounts: pyridine, 100 mL; 2, 2.7 mL (0.019 mol); 1.6 M *n*-butyllithium, 12.3 mL (0.0196 mol); CuI, 3.7 g (0.0196 mol); phenyl iodide, 2.0 g (0.0098 mol). The crude product was filtered through a 6 × 2 cm column of alumina with hexane to give 1.75 g of a yellow oil which by Ir and NMR was a mixture of phenyl iodide and coupled product 5. NMR integration of the sample shows it to be 78 ± 3% 5 (total aromatic absorption vs. acetal proton). Yield of coupled product 5 is 68%. A repeat of the reaction on the same scale gave a yield of 5 of 71%: IR (neat film, NaCl) 2200 (C≡C), 1150–950 cm^{-1} (C–O–C); NMR ($CDCl_3$, integrations are vs. single acetal proton) δ 1.25 (t, 6, $CH_2\mathbf{CH_3}$), 3.69 (m, 4, $\mathbf{CH_2}CH_3$), 5.50 (s, 1, $\mathbf{CH}(OC_2H_5)_2$), 7.33 (m, 7, ArH) a 22% impurity of phenyl iodide inferred from integration of acetal proton vs. aromatic region.

1,1-Diethoxy-3-(*p*-anisyl)-2-propyne (8). The procedure was identical with that used for 6 with the following amounts: 100mL of dry pyridine; 2, 2.18 g (0.017 mol); CuI, 3.24 g (0.017 mol); 1.6 M *n*-butyllithium, 10.6 mL (0.017 mol); *p*-iodoanisole, 2.0 g (0.0085 mol). The purification was performed as described in 5 and gave 1.90 g of a mixture which was 55% 8 by NMR integration. Yield of 8 is 52% based on recovery and NMR: IR (neat film, NaCl) 2230 (C≡C), 1150–950 (C–O–C), 830 cm^{-1} (1,4-disubstituted phenyl); NMR ($CDCl_3$) δ 1.30 (t, 6, CH_2CH_3), 3.76 (m, 12.7, $\mathbf{CH_2}CH_3$ + $2\mathbf{OCH_3}$), 5.47 (s, 1, $\mathbf{CH}(OC_2H_5)_2$), 7.03 (m, 7.2, ArH). By integration of aromatics vs. acetal proton the sample is 55% 8 and 45% unreacted *p*-iodoanisole.

1,1-Diethoxy-3-(4-nitrophenyl)-2-propyne (14). The procedure was identical with that used for 6 with the following amounts: 100 mL of dry pyridine; 2, 2.3 mL (0.016 mol); 1.6 M *n*-butyllithium, 10.0 mL (0.016 mol); CuI, 3.05 g (0.016 mol); *p*-iodonitrobenzene, 2.0 g (0.008 mol). After work-up as in 6, no coupled product, 14, could be detected by NMR. Repetition of the reaction again yielded no detectable coupled product.

3-(8′-Bromo-1′-naphthyl)-2-propynal (9). Into a 1-L single-necked round-bottom flask equipped with water bath, magnetic stirrer, 1-in. Teflon-coated stir bar, and N_2 inlet were placed 750 mL of benzene and 5 mL of H_2O, and the solution was heated to 55 °C; 9.5 g (0.0285 mol) of 3 was added to give a yellow solution. With stirring, 4.6 g (0.0285 mol) of trichloroacetic acid was added. The temperature was maintained at 55 °C and as the reaction progressed the color changed from yellow to orange. The reaction was monitored by TLC (alumina plates eluted with benzene) and when completed (3–5 h) the solution was cooled, washed with 100 mL of dilute sodium bicarbonate solution, dried ($MgSO_4$), and filtered, and the benzene was removed by a rotoevaporator in vacuo (no heating was applied to the water bath) to give 7.2 g of a brown solid. By NMR, the solid contained no unreacted 3. The crude solid was chromatographed on silica gel (10 × 5 cm, Ventron 58 micron) with benzene–ether to give 6.2 g (84%) of 9 an orange solid, which was TLC pure. This solid was unstable at room temperature but could be stored indefinitely in a freezer: mp 77–79 °C; IR (KBr pellet) 2190 (C≡C), 1655 (C=O), 820 and 755 cm^{-1} (1,8-disubstituted naphthalene); NMR ($CDCl_3$) δ 7.62 (m, 6, ArH), 9.47 (s, 1, CHO); MS (70 eV) P^+ *m/e* 259, 231, 152 (base peak).

3-(8′-Iodo-1′-naphthyl)-2-propynal (10). The procedure for 10 was identical with that used for 9. The crude product was a brown oil which contained the desired acetylenic aldehyde by NMR and no unreacted 4. All attempts at purification resulted in complete decomposition to tars.

1-Ethynyl-8-bromonaphthalene (12). Into a 250-mL single-necked round-bottom flask equipped with magnetic stirrer, 1-in. Teflon-coated stir bar, and N_2 inlet were placed 100 mL of dry THF and 1.0 g (0.00386 mol) of 9 to give an orange solution. To this solution was added 0.24 g (0.0044 mol) of sodium methylate which caused the solution to darken quickly to a brown color. The solution was stirred for 1 h, and then the THF was removed by a rotoevaporator in vacuo with no heat on the water bath. The residue was dissolved in ether, washed with dilute NH_4Cl solution, dried (Na_2SO_4), and filtered, and the ether was removed in vacuo by a rotoevaporator (again no heat) to give an orange solid. This solid was adsorbed on alumina (placed atop 5 × 2 cm of alumina) and the acetylene was eluted with 750 mL of hexane–ether (20/1, v/v). Removal of the solvent yielded 0.5 g of a white solid (56%) which was TLC pure. At room temperature in room light the solid quickly turned brown but could be stored for approximately 1 week in the cold and dark without appreciable decomposition. The decomposed solid could be recrystallized from pentane–ethanol: mp 62–64 °C; IR ($CHCl_3$ solution cells) 3290 (≡CH), 2250 cm^{-1} (C≡C); NMR ($CDCl_3$) δ 3.59 (s, 1, C≡CH), 7.50 (m, 6, ArH); MS (70 eV)P^+ *m/e* 231, 152, 77 (base peak).

***m*-Methylphenylacetylene (13).**[20,21] Into a 50-mL single-necked round-bottom flask equipped with water bath, magnetic stirrer, 1-in. Teflon-coated stir bar, and N_2 inlet were placed 350 mL of benzene and 2 mL of H_2O, and this solution was heated to 55 °C. To this preheated solution was added 1.0 g (0.0046 mol) of 7 to give an orange-yellow solution followed by 0.75 g (0.0046 mol) of trichloroacetic acid. The solution was stirred at 55 °C for 10 h, at which time TLC showed no remaining 7. The solution was cooled, washed with dilute sodium bicarbonate solution, dried ($MgSO_4$), and filtered, and the benzene was removed by a rotoevaporator to give 0.66 g of an orange oil. This crude oil is the desired aldehyde 11 by NMR (82% by integration). Without further purification, the crude 11 was dissolved in 30 mL of dry THF and, with stirring, 0.25 g (0.0046 mol) of sodium methylate was added quickly. The color changed from orange to dark brown. This solution was stirred at room temperature for 6 h and then the THF was removed by a rotoevaporator. The brown solid which remained was dissolved in ether, washed with H_2O, and dried ($MgSO_4$), and the ether was removed by distillation under N_2. The remaining oil was purified by GLC (Varian 920 G.C., 5 ft × 0.25 in. 5% SE-30 on Chromosorb WAW 45/60 mesh with column temperature at 80 °C and injector and detector at 240 °C, 55 mL of He/min flow rate) to give 0.19 g (45%) of 13 as a clear oil: IR ($CDCl_3$ solvent cell) 3313 (≡CH), 2112 cm^{-1} (C≡C); NMR ($CDCl_3$) δ 2.39 (s, 3, $\mathrm{Ar}\mathbf{CH_3}$), 3.00 (s, 1, C≡CH), 7.20 (m, 4, ArH).

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Chemistry of Enolates. 8. Kinetics and Mechanism of Alkylation of Lithium Enolates[1]

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Alkylations of sodium and potassium ketone enolates exhibit second-order kinetics in ethereal solvents.[2] Although rates in Me_2SO are 10^4–10^6 times faster than in ethereal solvents and O/C product ratios are independent of metal cation for a given enolate and alkyl halide, the solvated cation is important in the transition state as shown by a pronounced effect on reaction rate.[3] In this paper, we describe similar second-order kinetics for the alkylation of lithium enolates by most halides but have observed surprisingly different behavior for alkylations by alkyl chlorides.

Alkylations of lithium enolates in Me_2SO by allyl chloride, alkyl bromides, and alkyl iodides exhibit good second-order kinetics over several half-lives regardless of whether rates are determined in excess halide or at moderate halide concentration (Figure 1). The usual order of reactivity for halides in bimolecular substitution (RI > RBr > CH_2=$CHCH_2Cl$) is shown in Table I.

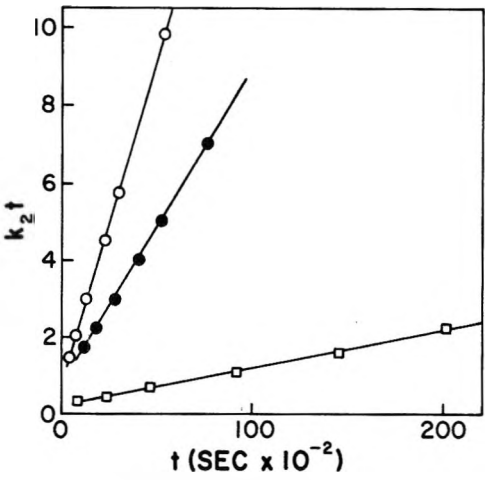

Figure 1. Alkylation of lithiobutyrophenone by *n*-propyl bromide (○), *n*-pentyl bromide (●), and allyl chloride (□).

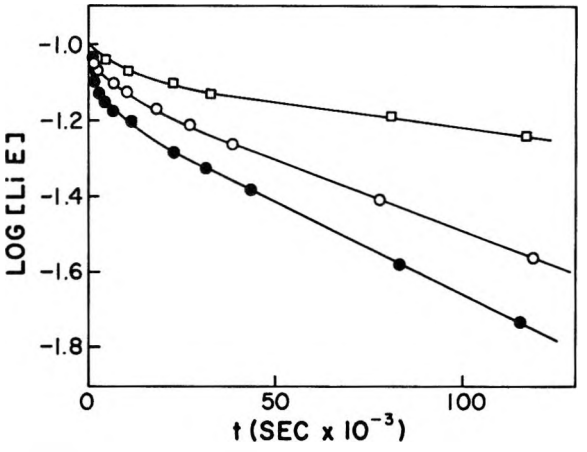

Figure 2. Alkylation of lithiobutyrophenone by *n*-pentyl chloride in Me_2SO (●); 0.074 M (○) and 0.66 M (□) LiCl added.

Table I. Second-Order Alkylations of Lithiobutyrophenone

Halide	$[RX]_0$, M	$[LiE]_0$, M	k_2 at 30 °C, s^{-1} M^{-1} × 10^4
n-C_3H_7Br	0.26	0.14	15.3
	0.50	0.14	14.0
n-$C_5H_{11}Br$	0.16	0.13	7.4
	0.29	0.13	7.7
	1.18	0.11	6.5
	1.85	0.09	6.0
	0.22	0.13	63.5[a]
	0.34	0.13	64.0[a]
n-$C_5H_{11}I$	0.26	0.13	88.5
	0.34	0.13	85.0
C_2H_5I	0.26	0.14	200
CH_2=$CHCH_2Cl$	0.44	0.13	1.2
	0.87	0.13	1.0

[a] At 50 °C.

For alkyl chlorides, a very rapid rate over the first 20–30% of the reaction is followed by a much slower rate for the remainder of the reaction. This second phase is first order in enolate but independent of the concentration of the alkyl chloride (Figure 2). Second-order plots show considerable curvature, whereas alkylations in which the ratio of initial concentrations $[RCl]_0/[E]_0$ is as low as 2.3 obey the first-order

Table II. First-Order Alkylations of Lithium Enolates

Registry no.	$C_6H_5C(O^-)=CRR'$ R	R'	RCl R	$[RCl]_0$, M	$[LiE]_0$, M	k_1 at 30 °C, $s^{-1} \times 10^5$
	H	C_2H_5	n-C_3H_7	1.50	0.10	1.5
			n-C_5H_{11}	0.30	0.13	1.0
				0.73	0.11	1.2
				1.04	0.10	1.2
				1.07	0.11	1.2
				1.06[a]	0.10	0.9
				0.68[b]	0.10	0.4
				0.64	0.14	3.8[c]
				1.42	0.12	3.9[c]
				0.60	0.13	14.8[d]
				1.30	0.12	15.0[d]
			i-C_4H_9	0.61	0.10	1.3
				1.32	0.08	1.2
				1.51	0.09	1.2
62416-34-6	CH_3	CH_3	n-C_5H_{11}	1.36	0.09	2.3
			i-C_4H_9	1.30	0.08	2.1
62416-35-7	C_6H_5	C_6H_5	n-C_3H_7	1.62	0.10	5.5

[a] $[LiCl]_0$ = 0.074 M. [b] $[LiCl]_0$ = 0.66 M. [c] At 40 °C. [d] At 50 °C.

law, and a threefold increase in alkyl halide concentration has no effect on the rate constant (Table II).

The initial, rapid reaction of lithiobutyrophenone and n-pentyl chloride was investigated in detail. Preferential O- or C-alkylation during this phase was ruled out by measuring O/C product ratios on each titrated aliquot. The mean O/C ratio for the first third of the reaction was 1.33 and for the second two-thirds, 1.30. When lithium chloride, a reaction product, was added in varying amounts to the enolate solutions prior to alkylation, the initial, rapid reaction was suppressed, and the subsequent reaction, although still independent of alkyl chloride concentration, was appreciably slowed (Figure 2).

These results suggest that a reactive enolate such as the free ion, ion pair, or its aggregate is converted to a less active species by complexing with lithium halide; for example

$$LiX(LiE)_n \underset{-LiX,\ k_{-1}}{\overset{+LiX,\ k_1}{\rightleftharpoons}} Li^+E^- \xrightarrow[k_2]{RX} RE + LiX$$

A steady-state treatment of Li^+E^- leads to first-order alkylation kinetics when $k_2[RX] \gg k_{-1}[LiX(LiE)_n]$ and the dissociation of the complex is rate determining. The second-order kinetics observed with more reactive alkyl halides requires that $k_{-1}[LiX(LiE)_n] \gg k_2[RX]$ or that the alkyl halide is sufficiently reactive to directly alkylate the complex. The former explanation is in line with the observation that LiBr and LiI are not as effective as LiCl in decreasing the reactivity of phenyllithium as a polymerizing agent,[5] while the latter explanation best accounts for the results with allyl chloride where the complex is identical with that from alkylation by alkyl chlorides.

From the ratio of lithium chloride formed in the initial alkylation phase to the lithium enolate remaining, a stoichiometric $LiCl(LiE)_3$ complex is indicated. Such a complex may resemble the tetrameric alkyllithiums, where four lithium atoms occupy corners of a tetrahedron with the anions on the faces.[7] Lithium halide complexes have been postulated to account for decreased anionic activity of phenyllithium[5] and lithium piperidide,[4] and stoichiometric LiRLiX complexes have been suggested to explain the stability of the relatively unreactive solid product obtained by the action of alkyllithium compounds on alkyl halides.[6]

Activation parameters were determined for both the first- and second-order substitutions. A plot of log k vs. $1/T$ for the alkylation by n-pentyl chloride was linear and gave $\Delta H^{\ddagger}$ = 26.4 kcal/mol and $\Delta S^{\ddagger}$ = +6.0 cal/mol K. Dissociation of a complex in the rate-determining step would be expected to have a positive activation entropy, although a higher positive value was anticipated. Perhaps transition-state solvation by the Me_2SO with its accompanying negative entropy change becomes a leveling factor in this solvent. For the second-order alkylation by n-pentyl bromide, $\Delta H^{\ddagger}$ = 20.4 kcal/mol and $\Delta S^{\ddagger}$ = −6.4 cal/mol K. The latter result may be compared with $\Delta S^{\ddagger}$ values ranging from −13 to −40 cal/mol K for alkylations of sodium enolates of alkyl phenyl ketones in ethereal solvents[8] and values of −8 to −12 cal/mol K for hydroxide displacement of bromide from n-alkyl bromides in aqueous Me_2SO.[9]

Experimental Section

Kinetic measurements were made at 30.00 ± 0.05 °C unless otherwise indicated. Vacuum-line techniques for preparation, storage, and transfer of methylsulfinyl carbanion and enolate solutions, as well as analytical procedures for kinetic and product studies, have been previously described.[3] Disappearance of alkylatable enolate species was followed by quenching 2.4-mL aliquots from a pneumatic sampling buret and titrating the resulting hydroxide ion to a phenolphthalein end point. For product analysis, infinity samples were quenched in 0.1 M sodium hydroxide solution and extracted with carbon tetrachloride. O-Alkyl products were detected in the infrared (Beckman IR-8) by broad peaks near 1063 cm^{-1}, and C-alkyl products in the carbonyl stretching region near 1675 cm^{-1}. Enol ethers were confirmed by a repeat analysis on a second sample of carbon tetrachloride extract after shaking with dilute acid. Absorption at 1063 cm^{-1} disappeared and that in the carbonyl region increased. Quantitative analyses of the extracts of all 12 aliquots from an alkylation by n-pentyl chloride were made by GLC at 170 °C on a 5 ft × 0.3 mm column packed with GE SF-96 phenylsilicon on 100–140 mesh Gas Chrom Z. The O/C ratio was essentially constant at 1.3, a value in agreement with the infinity samples from all alkylations of lithiobutyrophenone and n-pentyl chloride. No products other than enol ether, alkylated ketone, and original ketone could be detected.

Registry No.—Lithiobutyrophenone, 62416-33-5; n-C_3H_7Br, 106-94-5; n-$C_5H_{11}Br$, 110-53-2; n-$C_5H_{11}I$, 628-17-1; C_2H_5I, 75-03-6; $CH_2{=}CHCH_2Cl$, 107-05-1; n-C_3H_7Cl, 540-54-5; n-$C_5H_{11}Cl$, 543-59-9; i-C_4H_9Cl, 14753-05-0.

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Decarbalkoxylation of Isohexylmalonates

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A decade ago Krapcho reported that a geminal diester could be converted to the corresponding monoester by a novel one-step method.[1] The original procedure of sodium cyanide and dimethyl sulfoxide (Me_2SO) was subsequently extended to include other salts in wet Me_2SO or wet dimethylformamide (DMF),[2] and it was further discovered that even the salt was unnecessary in the case of phenylmalonates.[3,4] While the pioneering work of Krapcho and co-workers served to define the structural range of diesters,[1-3] there has been no systematic study of the other reagents. In fact, a variety of conditions has been reported: sodium cyanide in Me_2SO,[5] lithium iodide and sodium cyanide in DMF,[6] and lithium chloride or sodium iodide[7a] or tetramethylammonium acetate[7b] in hexamethylphosphoric triamide. Recently, cyclic secondary or tertiary amines in hydrocarbon solvents have also been utilized for decarbalkoxylations.[8]

In connection with studies related to the synthesis of the gypsy moth sex pheromone, we required 1-bromo-6-methylheptane.[9,10] As an alternative to the published procedures, we have explored a route which involved the following reaction.

$$\underset{\mathbf{1}}{Me_2CH(CH_2)_3CH(CO_2R)_2} \rightarrow \underset{\mathbf{2}}{Me_2CH(CH_2)_4CO_2R}$$

a, R = Me; **b**, R = Et

The present work was undertaken to define the scope of this decarbalkoxylation step. Esters **1a** and **1b** were obtained by malonic ester syntheses. Hydrolysis, decarboxylation, and esterification gave authentic samples of **2a** and **2b** for calibration purposes. A standardized procedure for decarbalkoxylation was utilized to assess the effects of different salts, concentration, reaction times, and ester groups. The analytical procedure involved GLC determination of **1** and **2**; the isolated yield of crude product was 65–95%. The results are shown in Tables I and II. It is clear that an added salt is necessary; best results were obtained with 1 equiv. Previous work established that wet Me_2SO was necessary.[3] In the present study, 2 equiv of water proved satisfactory. The more facile reaction of methyl esters compared to the corresponding ethyl esters was also observed by Krapcho, who has considered the mechanistic aspects.[11] Although the present study was not designed to elucidate reaction pathways, our results do establish that acid catalysis generated in situ is not operative.[12]

Table I. Decarbalkoxylation of 1a by Various Salts in Me_2SO

Salt	Salt, mmol	Water, mmol	Reflux time, h	**2a**, %[a]
LiCl	4	8	1	>99
	4	8	0.5	99
NaCl	4	8	1	99
	4	4	1	99
KCl	4	8	1	98
$CaCl_2 \cdot 2H_2O$	4	0	1	>99
	4	0	0.5	99
NaBr	4	8	1	96
$LiI \cdot H_2O$	4	0	1	>99
NaI	4	8	1	97
NaCN	4	8	1	>99
	4	8	0.5	>99
	4	4	1	>99
	4	0	1	>99
	2	8	1	95
$Na_2CO_3 \cdot H_2O$	4	0	1	96
$Na_3PO_4 \cdot 12H_2O$	0.8	0	1	98
None		8	1	10
None		0	1	11

[a] Purity was determined by GLC and is based on **1a** and **2a**; no additional substances were detected. Values are the average (±1%) of duplicate runs.

Table II. Decarbalkoxylation of 1b by Various Salts in Me_2SO

Salt	Salt, mmol	Water, mmol	Reflux time, h	**2b**, %[a]
LiCl	4	8	2	>99
	4	8	1	88
NaCl	4	8	2	99
	4	8	1	81
KCl	4	8	2	>99
	4	8	1	83
$CaCl_2 \cdot 2H_2O$	4	0	2	98
	4	0	1	91
NaCN	4	8	2	>99
	4	8	1	99
	4	8	0.5	85
	4	4	1	95
	4	0	1	75
	2	8	1	93
$Na_3PO_4 \cdot 12H_2O$	0.8	0	2	>99
	0.8	0	1	90
None		8	1	2
		0	1	5

[a] Purity was determined by GLC and is based on **1b** and **2b**; no additional substances were detected. Values are the average (±1%) of duplicate runs.

Experimental Section

Melting points and boiling points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 237B spectrophotometer and calibrated by a polystyrene film. Gas–liquid chromatography (GLC) was carried out on a Varian 1400 chromatograph with a 12 ft × 0.125 in. column of 10% Dow-Corning 710 on Chromosorb W, the helium flow rate was 30 mL/min, and the column was operated at 210 °C. Elemental analyses were obtained from the Analytical Services Laboratory, University of California, Berkeley.

Materials. Dimethyl sulfoxide (Me_2SO; Fisher Certified), 1-bromo-4-methylpentane (Chemical Samples Co.), and all salts (reagent grade) were used without further purification.

Dialkyl Isohexylmalonates (1). The reaction of 1-bromo-4-methylpentane with dimethyl sodiomalonate by the method of Adams and Kamm[13] gave 69% of **1a**: bp 85–87 °C (2 Torr); IR (neat) 1757 and 1736 cm^{-1}.

Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found: C, 61.04; H, 9.11.

Similarly, the reaction with diethyl sodiomalonate gave 64% of **1b:** bp 142–144 °C (10 Torr); IR (neat) 1751 and 1733 cm^{-1} [lit.[14] bp 136–139 °C (11 Torr)].

Alkyl 6-Methylheptanoates (2). Diester **1b** was converted by known procedures[15] to 6-methylheptanoic acid (**3**) in 95% yield, bp 85–88 °C (2 Torr); *p*-bromophenacyl ester, mp 67.5–67.6 °C [lit.[16] bp 128–129 °C (15 Torr); *p*-bromophenacyl ester, mp 67.7 °C]. Fischer esterification of **3** gave **2a:** bp 72.5–73.2 °C (11 Torr); IR (neat) 1745 cm^{-1} [lit.[17,18] bp 73 °C (10 Torr); IR (neat) 1739 cm^{-1}]. Similarly, **3** gave **2b** in 59% yield: bp 52–53 °C (2 Torr); IR (neat) 1739 cm^{-1} (lit.[19] bp 200.3 °C).

General Reaction Procedure. A. Analytical Scale. The following procedure was typical of that used for all experiments reported in Tables I and II.

To a 25-mL flask were added diester **1a** or **1b** (4.0 mmol), a salt (4.0 mmol), water (8.0 mmol), and Me_2SO (10 mL). The heterogeneous reaction mixture was refluxed for 1 h, cooled, transferred to a separatory funnel containing 100 mL of water, and extracted with three 15-mL portions of hexane. The combined hexane extract was washed once with water, dried (Na_2SO_4), filtered, and concentrated at reduced pressure on a rotary evaporator.

The residual oil was analyzed by GLC. Authentic samples of **1a, 1b, 2a,** and **2b** were used to calibrate the detector response and determine the retention times (in min): **2a,** 1.8; **2b,** 2.2; **1a,** 4.6; and **1b,** 6.6. It was established by control runs that the detectable limit of diester in a mixture of **1** and **2** was 0.8%. No peaks other than **1** and **2** were observed in the product mixture.

B. Preparative Scale. A mixture of **1a** (4.4 g, 0.020 mol), sodium cyanide (1.0 g, 0.020 mol), water (0.72 mL, 0.040 mol), and Me_2SO (50 mL) was refluxed for 1 h and worked up as above to give 2.3 g (72%) of **2a:** purity >99% by GLC.

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Registry No.—**1a,** 62337-57-9; **1b,** 39953-95-2; **2a,** 2519-37-1; **2b,** 62337-58-0; **3,** 929-10-2; **3** *p*-bromophenacyl ester, 62337-59-1; 1-bromo-4-methylpentane, 626-88-0; dimethyl sodiomalonate, 18424-76-5; diethyl sodiomalonate, 996-82-7.

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Eremofortin C. A New Metabolite Obtained from *Penicillium roqueforti* Cultures and from Biotransformation of PR Toxin

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Penicillium roqueforti is a fungal species of particular interest because of the toxic compounds recently isolated from the mycelium of this species. These compounds include the indole alkaloids[1,2] and the sesquiterpenoid metabolites such as PR toxin (**3**) and related compounds.[3,4] We report here the isolation and characterization of a new sesquiterpenoid compound, eremofortin C (**4**). This compound was obtained using two methods: direct isolation from *P. roqueforti* culture media and biotransformation of PR toxin and eremofortin A[4] (**1**) by liver mixed-function oxidases.[5,6]

Isolation and Characterization of Eremofortin C. Eremofortin C was isolated from the culture media of a *P. roqueforti* strain by chloroform extraction. The chloroform extract was chromatographed on silica gel and crystallized from ethyl ether. The structure **4** was assigned on the bases of spectral data and various chemical reactions. The spectral characteristics of the compound indicated that it was closely related to PR toxin (**3**) and eremofortin A (**1**).

The IR spectrum (KBr) showed a hydroxyl group (3420, 3350 cm^{-1}), an α,β-unsaturated ketone (1685 cm^{-1}), an isolated double bond (1650 cm^{-1}), and a conjugated double bond (1620 cm^{-1}). The mass spectrum of **4** showed a molecular ion at *m/e* 322. High-resolution mass spectral analysis indicated a molecular peak at *m/e* 322.14161 (calcd for $C_{17}H_{22}O_6$, 322.14163). The complex 250-MHz ^1H NMR spectrum appeared to be a superposition of the spectra of two acetylated compounds: δ CH_3COO 2.18 and 2.19 ppm, two multiplets centered at δ 5.18 and 5.25 (H-3), and two singlets at δ 6.02 and 6.44 (H-9).

The equilibrium suggested by these data was proved by variable temperature ^1H NMR studies. Ratios of the areas of the H-9 peaks were measured at different temperatures. That at δ 6.02 ppm was attributed to compound **4a** and that at δ 6.44 ppm to compound **4b** after comparison with values obtained for H-9 in compounds **1, 3,** and **6.**[3,4] Results are given in Table I. An increasing temperature seemed to promote the formation of compound **4b** (79% at 95 °C). A lowering of these temperatures resulted in the recovery of the initial ratio of the two compounds.

The structure was confirmed by the following chemical reactions. Sodium borohydride reduction of PR toxin (**3**) yielded a crystalline substance. Chromatographic behavior and spectroscopic data (IR, ^1H NMR, mass spectrum) showed that this compound was identical with naturally occurring eremofortin C(**4a** $\rightleftarrows$ **4b**). Acetylation of eremofortin C yielded a unique compound **2** which crystallized from ethyl ether. The structure of **2** was assigned on the bases of spectral data by comparison with the previously mentioned metabolites.[4]

In Vitro Metabolism of PR Toxin and Eremofortin A. Four metabolites were obtained during incubation of PR toxin and eremofortin A with the microsomal enzymes of rat hepatocytes. Their chemical structures are shown in Scheme I.

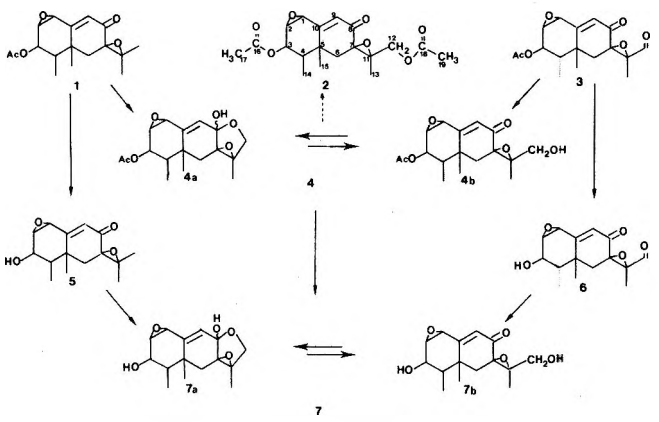
All the metabolites obtained from 10 mg of compounds **1** or **3** were isolated from the enzymatic reaction medium by

Table I. Effect of Temperature on Percent of Compound 4b in the Equilibrium 4a ⇄ 4b (in Pyridine-d_5)[a]

θ	20 °C	35 °C	50 °C	65 °C	80 °C	95 °C
% of 4b	61	67	69	73	77	79

[a] % 4b = (area of H-9 peak of 4b)/(area of H-9 peaks 4a + 4b) × 100.

Scheme I. Bioconversion of PR Toxin and Eremofortin A



Continuous lines: metabolic conversions
↓: metabolism not requiring $NADPH_2$
↘ ↙: metabolism requiring $NADPH_2$

Dotted lines ↓: chemical synthesis
⇄: chemical equilibrium

chloroform extraction. Reactions products were monitored by TLC and purified by silica gel column chromatography. Each metabolite isolated (a few milligrams) was crystallized and analyzed by mass spectroscopy and some by FT NMR spectroscopy (250 MHz). The structures were confirmed by chemical synthesis from known precursors.

Eremofortin C (4), eremofortin A alcohol (5), and PR alcohol (6), obtained from the enzymatic medium, were identified by direct comparisons with authentic specimens (chromatographic behavior, mass spectra, ^1H NMR spectra, and mixture melting points).

Eremofortin C Alcohol (7). The enzymatic product and saponification product from eremofortin C (4) showed similar chromatographic behavior. Low-resolution mass spectra were identical. The ^1H NMR spectrum (CD_3OD) showed an equilibrium between two compounds **7a** ⇄ **7b** measured on H-9 peaks: δ 5.95 ppm for **7a** and 6.42 for **7b**. Compound **7b** represented 75% of the mixture at 20 °C. Eremofortin C alcohol (7) was also obtained by sodium borohydride reduction of compound 6 and by enzymatic conversion of 5 and 6.

These results suggest an interesting biotransformation relationship between three compounds: eremofortin C (4), PR toxin (3) and eremofortin A (1). If similar relationships are found to exist during PR toxin biosynthesis by *Penicillium roqueforti* we could then hope to determine the biochemical pathway of *P. roqueforti* metabolites.

Experimental Section

Infrared spectra were obtained with a Perkin-Elmer 447 spectrometer, ^1H NMR spectra (250 MHz) were recorded with a Cameca spectrometer, variable temperature ^1H NMR spectra (90 MHz) with a Perkin-Elmer R-32 spectrometer, ^1H NMR spectra (60 MHz) with a Varian T-60 spectrometer, and ^{13}C NMR spectra (15, 1 MHz) with a JEOL FT 60 spectrometer.

Mass spectra were determined on an AEI Model MS 12 spectrometer for low resolution and MS 9 for high resolution (Laboratoire de Chimie Appliquée de l'Université de Bordeaux, 1 Bordeaux, France). Ultraviolet spectra were run on a Cary 11 spectrometer. A Perkin-Elmer 141 polarimeter was used for specific rotation. All melting points are uncorrected. Elemental microanalyses were carried out by the Centre de Microanalyse du CNRS, Thiais, France.

Isolation of Eremofortin C (4). NRRL 849, a *Penicillium roqueforti* strain, was grown in a culture medium containing 2% yeast extract and 15% sucrose. The culture flasks were incubated for 14 days at 25 °C in the dark without shaking. The mycelium was discarded and the culture medium extracted with chloroform. The dried, concentrated chloroform extract was chromatographed on a silica gel column. PR toxin and eremofortin C (4) were eluted with methanol–chloroform at proportion of 1:99 (v/v) and 2:98 (v/v), respectively. Each compound was monitored by TLC (elution solvent $CHCl_3$/MeOH, 95:5). Each was sprayed with a concentrated sulfuric acid reagent, examined with UV light at 365 nm, and then heated to 120 °C for 20 min.

Crystallization from ethyl ether gave a compound whose properties (IR, ^1H NMR) are described in the text: mp 122–126 °C; mass spectrum *m/e* 322 (M^+), 191, 177, 163, 149. Anal. Calcd for $C_{17}H_{22}O_6$ C, 63.34; H, 6.89. Found: C, 63.26; H, 6.92. The acetate of eremofortin C was prepared in acetic anhydride–pyridine solution at room temperature. 4 (140 mg) in 15 mL of solution gave 120 mg of pure acetate: mp 122–124 °C; $[\alpha]^{20}_D$ +161° (c 1.09, $CHCl_3$); UV λ_{max} 248 nm (ε 16 960); IR (KBr) 1745, 1740, and 1685 cm^{-1}; mass spectrum *m/e* 364 (M^+), 322, 291, 279, 205, 191, 177; ^1H NMR (60 MHz) δ ($CDCl_3$) H_3C-14 1.07 (d, 6.5 Hz), H_3C-13 1.4, H_3C-15 1.47, H_3C–COO 2.10 and 2.15, H-1 3.72 (d, 3 Hz), H-2 4 (m), H_2C-12 4.6, H-3 5.25 (m), H-9 6.55; ^{13}C NMR (15.1 MHz) ($CDCl_3$) δ (from Me_4Si) C-1 55.22 or 55.87 (d), C-2 55.22 or 55.87 (d), C-3 70.04 (d), C-4 41.84 (d), C-5 37.29 (s), C-6 42.36 (t), C-7 61.98 or 64.17 (s), C-8 192.96 (s), C-9 131.50 (d), C-10 161.39 (s), C-11 61.98 or 64.17 (s), C-12 65.36 (t), C-13 22.61 (q), C-14 10.39 (q), C-15 16.37 (q), C-16 and C-18 170.15 (s), C-17 and C-19 20.79 (q). Anal. Calcd for $C_{19}H_{24}O_7$: C, 62.62; H, 6.64. Found: C, 62.49; H, 6.63.

Reduction of PR Toxin. PR toxin (240 mg) was reduced with 17 mg of $NaBH_4$ in 40 mL of MeOH at −5 °C for 20 min. The crude extract was purified on a silica gel column and gave 120 mg of PR toxin and 100 mg of eremofortin C, crystallized from ether. All spectroscopic data are identical with those previously obtained for naturally occurring eremofortin C (IR, mass spectrum, ^1H NMR), mp 122–126 °C, mixture melting point unchanged with eremofortin C (4).

Microsomal Preparations. Male rats (Wistar strain) weighing about 250 g were used for the experiment. They received an ip injection of 3-methylcholanthrene (20 mg/kg dissolved in corn oil) once a day for 3 consecutive days before killing. Livers were homogenized in 3 volumes of ice-cold 150 mM KCl and centrifuged at 4 °C for 20 min at 15 000 *g*. The pellets were discarded and the post-mitochondrial supernatant was removed and centrifuged for 90 min at 200 000 *g* (Beckman Ti Rotor). The microsomal pellets were washed twice with the following medium: 10 mM Tris HCl, pH 7.4, containing 0.5 mM $MgCl_2$ and 0.25 M sucrose. Microsomes were resuspended in this buffer and stored in liquid nitrogen. The amount of protein in the microsomal fraction was determined by the method of Lowry et al.[8] using bovine serum albumin as a standard.

Incubation Procedure. Incubations were carried out in conical glass flasks open to the air at 37 °C with gentle shaking for 1 or 2 h. The reaction mixture in 100 mL of Tris HCl buffer (10 mM Tris HCl, pH 7.4, 0.5 mM Mg Cl_2, 0.25 M sucrose) contained 150 mg of microsomal proteins and in some experiments 150 μM $NADPH_2$ (Boehringer). PR toxin or eremofortin A (10 mg in 450 μL of methanol) was added just before incubation. The reactions were stopped by addition of cold chloroform and the metabolites were extracted with chloroform. The dried, concentrated chloroform extract was analyzed by TLC using the system previously described. The metabolites were isolated using a stepwise gradient mixture of MeOH (0:100 to 20:80). A typical experiment with 10 mg of PR toxin and 150 μM of $NADPH_2$ produced 0.5 mg of compound 5, 3 mg of compounds 4 and 3, and 5 mg of compound 7. Each metabolite isolated was crystallized in the appropriate solvent and submitted to mass spectrum analysis.

Eremofortin A alcohol was obtained from eremofortin A by an incubation procedure without $NADPH_2$. Saponification of eremofortin A (50 mg) was carried out in a 0.02 M solution of potassium hydroxide in methanol–water (4:1 v/v, 10 mL) at 37 °C for 2 h. The reaction mixture was diluted with water and extracted with chloroform. The crude extract was crystallized from ethyl ether–isopropyl ether mixture (25 mg): mp 128–130 °C; $[\alpha]^{20}_D$ +143° (c 1.04, $CHCl_3$); UV $CHCl_3$ λ 246 nm (ε 13 200); IR (KBr) 3570, 3510, 3380, and 1685 cm^{-1}; mass spectrum *m/e* 264 (M^+), 235, 177, 149; high-resolution mass spectrum M^+ 264.13598 (calcd for $C_{15}H_{20}O_4$, 264.13615); ^1H NMR (60 MHz) ($CDCl_3$) δ H_3C-14 1.09 (d, 6.5 Hz), H_3C-12 1.28,

H_3C-13 1.40, H_3C-15 1.52, H-1 3.7 (m), H-2 3.95 (m), H-3 4.12 (m), H-9 6.4, mixture melting point of the two compounds unchanged.

PR alcohol (6) was obtained from PR toxin by an incubation procedure without $NADPH_2$ and was chemically synthesized from **3** by the procedure described above. All spectroscopic data are in good agreement with the data previously reported:[3] mp 152–154 °C and mixture melting point unchanged. The melting point given in ref 3 (113.5–115 °C) is the only difference observed from literature data.

Eremofortin C alcohol (7) was prepared by saponification of eremofortin C according to the procedure described above (poor yield) or by $NaBH_4$ reduction of PR alcohol according to the procedure described for the chemical synthesis of eremofortin C (4). **6** (48 mg) yielded 11 mg of crystallized eremofortin C alcohol (**7**) (from ethyl acetate): mp 170 °C, dec; IR (KBr) 3460, 3390, 1685 cm^{-1}; ^1H NMR (CD_3OD) see text, mass spectrum *m/e* 280 (M^+), 237, 191, 177, 149, 121, 91; high-resolution mass spectrum 280.13149 (calcd for $C_{15}H_{20}O_5$, 280.13106). Anal. Calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.17; H, 7.36.

Acknowledgments. We thank A. Butryn for technical assistance, Dr. M. H. Loucheux for variable temperature NMR measures, Dr. G. Bourgeois for measurement of the mass spectra, and Dr. C. Berrier for ^{13}C NMR spectral analysis.

Registry No.—**1**, 62445-06-1; **2**, 62375-73-9; **3**, 56299-00-4; **4b**, 62375-74-0; **5**, 62375-75-1; **7b**, 62375-76-2.

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Monoterpene Halogenation by the Red Alga *Placamium oregonum*

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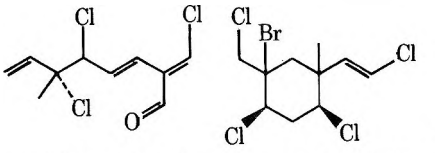
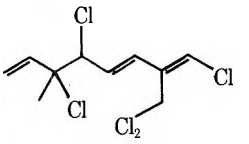
Several years ago we began to study the chemistry of the red seaweeds in the Plocamiaceae because extracts from some of its species were toxic to fish and insects.[1] This proved to be a rewarding venture in that several new natural products were characterized from the toxic extracts of *Placamium cartilagineum* (Dixon) and *Placamium violaceum* (Farlow) including cartilagineal (**1**),[1] plocamene A (**2**),[2] and plocamene B (**3**).[2a] Extending our work along a phyletic approach we discovered that *Placamium sandvicense* (J. Ag.) from Maui, Hawaii, was also a rich source of polyhalogenated monoterpenes including **4**.[3] Continuing our study of monoterpene halogenation by the Plocamiaceae we turned to *Placamium oregonum* (Doty) which ranges from the central California coast to the Pacific northwest. In the fall of 1975 we collected *P. oregonum* from Partridge Point, Whidbey Island, Wash., and, although its crude extract displayed very little toxicity in our bioassays, the GC/MS profile of semipure fractions did show several new polyhalogenated monoterpene constituents. Reported below are the structures of these metabolites along with evidence for their biogenesis.

Results and Discussion

Four major constituents could be observed in approximately equal amounts in the reconstructed GC/MS trace (RGC) of the total ions from the crude $CHCl_3$ extract of *P. oregonum*.

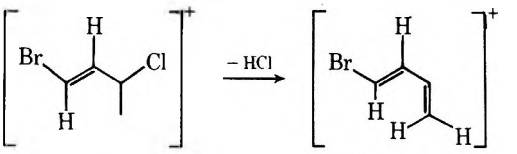


cartilagineal (**1**)[1] plocamene A (**2**)[2a] or violacene[2b] plocamene B (**3**)[2a]



4[3]

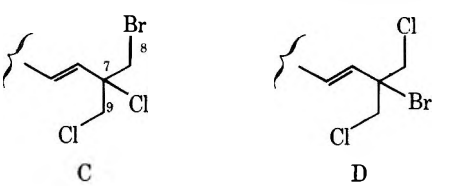
Comparison of this to the RGC for *m/e* 167 clearly showed that each of these components, along with a fifth minor one, contained a common C_4H_5ClBr structural unit A which fragmented to B by HCl loss. In addition, the mass spectra revealed that these five metabolites consisted of sets of isomers including two of formula $C_{10}H_{12}Cl_2Br_2$, two of formula $C_{10}H_{13}Cl_3Br_2$, and a single one of formula $C_{10}H_{12}Cl_4Br_2$. This



A [167/169/171] B [131/133]

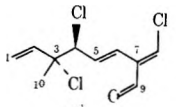
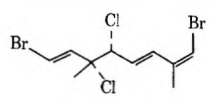
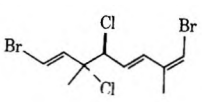
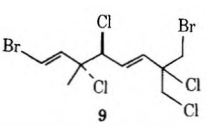
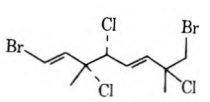
complex mixture was conveniently separated by HPLC on Porasil A, and the retention order on both HPLC and GLC was according to molecular weight.

The spectra of the lowest molecular weight isomers were consistent with structures **5** and **6** which were previously isolated from *Placamium cartilageineum*.[4] The highest molecular weight component did not show a mass spectral parent ion but it did show an $M^+ - Cl$ 395/397/399/401/403 ($C_{10}H_{12}Cl_3Br_2$) and $M^+ - Br$ 351/353/355/357 ($C_{10}H_{12}Cl_4Br$). It was concluded to have the gross structure of oregonene A (**9**) based upon the ^{13}C NMR spectrum, which showed four olefin carbons (Table I), and the ^1H NMR spectrum, which showed only a single methyl at δ 1.74 (s) and the trans vinyl AB at δ 6.49 (J = 14 Hz) associated with fragment A along with additional structural pieces including two $-CH_2X$ units at δ 3.76, 3.90 (AB, J = 11 Hz), 3.95 (s); and a XCHCH=CH– at 4.49 (d, J = 6 Hz), 6.02 (d, J = 16 Hz), 6.16 (m, J = 16, 6 Hz). While the presence of mass spectrum fragment A supported the placement of a Br at C_1 and a Cl at C_3, a combination of ^1H and ^{13}C NMR data was needed to unambiguously locate the remaining halogens. The ^{13}C chemical shift position for halogenated isostructural carbons is very sensitive to the type of halogen substituent. For example in *trans*-2-butenyl halide the $-CH_2Br$ appears 12 ppm higher than the $-CH_2Cl$.[5] Therefore, comparison of the δ values (Table I) for C_1, C_3, and C_4 of **9** vs. the same carbons in **1**, **5**, and **6** supported the assignment of a Br at C_1 and Cls at C_3 and C_4 in **9**. The remaining three halogens could then be placed as shown in C or D.



C D

Table I. 25.1-MHz ^{13}C NMR Chemical Shifts

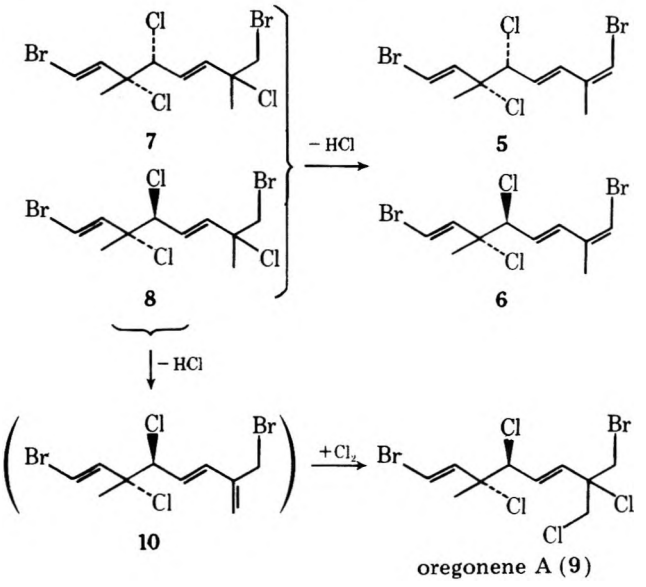
Carbon	 1[1]	 5	 6	 9	 7
1	116.3 (t)	110.5	110.0	110.6	110.6
2	122.5 (d)	128.5	127.9	130.6	127.6
3	71.5 (s)	71.9	71.6	71.3	
4	69.5 (d)	69.1	69.0	67.1	67.8
5	134.0 (d)	133.2	133.0	133.8	137.1
6	139.5 (d)	137.6	138.7	138.9	137.9
7	137.3 (s)		135.4	68.9	
8	143.9 (d)	108.2	108.0	37.1	41.5
9	189.3 (d)	19.1	19.5	49.5	27.8
10	24.6 (q)	28.4	25.4	24.9	28.0

Based upon the symmetry properties of these fragments, C_8 and C_9 are in an enantiotopic-like environment for D, whereas they are heterotopic for C. The observable proton $\Delta\nu_{av8-9}$ = 0.07 ppm is more consistent with the latter rather than the former arrangement. Similarly the $\Delta\nu_{8-9}$ = 12.4 ppm fits the expected shift difference for a C–Br vs. a C–Cl and is thus also consistent only with partial structure C. The relative *R,S* stereochemistry for the C_3–C_4 dichlorides was assigned by the empirical relationship developed below. The vicinal dichloride stereochemistry in **5** (*R,R*) and **6** (*R,S*) had previously been assigned based upon the difference in proton shifts for the C_3 methyls equal to 0.06 ppm (δ 1.79 vs. 1.73) and by a comparison to the methyl shift of a precursor to **6** whose structure had been established by x ray.[4] A much larger methyl shift difference equal to 3 ppm (δ 28 vs. 25) can be observed for the different vicinal dichloride stereochemistries in ^{13}C NMR as exemplified by compounds **1**, **5**, and **6** in Table I. Both the proton and carbon shifts for the **9** C_3 CH_3 support the dichloride stereochemistry shown in Table I.

The major component of the $C_{10}H_{13}Cl_3Br_2$ isomers was assigned structure **7**. Again ^{13}C data were invaluable for the difficult job of unambiguously establishing the halogen regiochemistry. Thus, a Br could be located at C_1 and Cls at C_3 and C_4 based upon the ^{13}C shifts and mass spectral data. The remaining Br could be easily located at C_8 based upon the shift of C_8 (41.5 ppm), vs. 37.1 ppm for the C_8 Br in **9**, with the difference being approximately equal to the expected 2–4 ppm shielding from the γ substituent in the latter.[6] While this work was in progress this same structure was reported from the digestive gland extract of the sea hare *Aplysia californica*; however, the halogen regiochemistry was deduced by a combination of biogenetic and mass spectral analogies.[7] Finally, a tentative assignment of the minor component as **8** was based upon GC/MS data and the discussion below.

The various halocarbons **5–9** isolated in this research are closely related from a biogenetic view. This is evident from both the gross halogenation pattern and the C_3–C_4 chlorine stereochemistry. For example, diastereomers **5** and **6** are undoubtedly each derived from **7** and **8** by a regiospecific loss of HCl as shown in Scheme I. Alternative loss of HCl from **8** from the other possible direction can lead to **9** after enzymatic addition of Cl_2 to an intermediate such as **10**.

Scheme I



Experimental Section

The NMR spectra were recorded on a JEOL PS 100 pulsed FT spectrometer operating at 100 MHz for ^1H and 25.1 MHz for ^{13}C. GC/MS data were recorded on a Finnigan 4000 system equipped with a 3 ft × 0.125 in. glass column packed with 3% OV-17 on Chromosorb G and temperature programmed from 120 to 190 °C at 6 min. Routine low-resolution mass spectral data were recorded on a Hitachi Perkin-Elmer RMU-6E mass spectrometer. High-performance liquid chromatography (HPLC) was done on a Waters ALC 201 using Porasil columns 0.375 in. × 8 ft. All solvents were reagent grade and distilled for HPLC use. Low-boiling petroleum ether was used in all instances. Spectral grade solvents were used for NMR (Me_4Si standard) determinations. The ^{13}C assignments (Table I) were made based on the data of compound **1** and expected additivity effects.[6b] Our earlier assignments of the ^{13}C NMR of **1** for carbons 2, 5, and 6 were revised based upon comparisons to the data for compounds **5** and **6**.

Collections and Extractions. *Plocamium oregonum* was collected from Partridge Point, Whidby Island, Wash., during Sept 2–4, 1975. The algae were kept frozen until extraction. All samples were cold extracted twice with $CHCl_3$ and once with ETOH (95%) over a period of 3–7 days. The combined extract was then chromatographed through silica gel (Grace grade 62, 60–200 mesh, activated) using petroleum ether followed by petroleum ether/benzene (1:1). The resulting semipurified oil was then subjected to HPLC using petroleum ether/benzene (90:10).

Isolations. Following the procedure above for compounds **5, 6,** and **7,** impure **8** and oregonene A (**9**) were isolated from the extraction of ca. 280 g (dry weight) of alga.

1,8-Dibromo-3,4-dichloro-3,7-dimethyl-1,5,7-octatriene (5) was obtained in HPLC fraction 8 (57 mg) as a clear, mobile oil. Its ^1H NMR [$CDCl_3$, i.e., methyl peaks at δ 1.78 (s) and 1.91, d, J = 2 Hz] and its mass spectrum [i.e., M^+ 360/362/364/366, ratio 32:100:86:26 (theory for Cl_2Br_2 38:100:90:32) for formula $C_{10}H_{12}Cl_2Br_2$] were identical with those in the literature.[4]

The dibromodichlorodimethyloctatriene 6 was obtained in HPLC fraction 9 (60 mg) as an oil. Its NMR [$CDCl_3$, i.e., methyl peaks at δ 1.74 (s) and 1.91, d, J = 2 Hz] and its mass spectrum were identical with those in the literature.[4]

1,8-Dibromo-3,4,7-trichloro-3,7-dimethyl-1,5-octadiene (7) was obtained in HPLC fraction 11 (43 mg) as a clear liquid. Its ^1H NMR ($CDCl_3$) showed two quaternary methyls δ 1.81 (s) and 1.86 (s); a $-CH_2X$ (s) 3.68; XCHCH=CH– (ABX) 4.43 (m, J = 7 Hz), 5.90 (m, J = 16 Hz), 5.98 (d, J = 16, 7 Hz); and a trans BrCH=CH– (AB) 6.45 (d, J = 14 Hz), 6.50 (d, J = 14 Hz). In benzene-d_6 the ABX for –C(Cl)HCH=CH– was clearly resolved: 4.0 (d, J = 7 Hz), 5.40 (d, J

= 16 Hz), 5.56 (dd, J = 16, 7 Hz). Its mass spectrum displayed no parent M^+ but showed fragments $M^+ - Cl$ 361/363/365/367, ratio 40:99:100:28 (theory for Cl_2Br_2 above); $M^+ - Br$ 317/319/321/323, ratio 48:100:68:16 (theory for Cl_3Br 51:100:65:18); 229/231/233; 193/195/197; 167/169/171; and 131/133.

The dibromotrichlorodimethyloctadiene 8 was obtained impure in HPLC fractions 12–13 (17 mg). It was tentatively identified by its GC/MS peak and its mass spectrum, which was identical with that above for **7**.

Oregonene A (9) was obtained as a clear oil in HPLC fractions 14–15 (50 mg). Its ^1H NMR ($CDCl_3$) is described in the text and in benzene-d_6 the H_5 and H_6 multiplet was simplified to a doublet (J = 16 Hz) and a doubled doublet (J = 16, 6 Hz). Its mass spectrum showed no parent M^+ but displayed fragments: $M^+ - Cl$ 395/397/399/401/403, ratio 33:87:100:41 (theory for Cl_3Br_2 32:92:100:50); $M^+ - Br$ 351/353/355/357, ratio 39:100:90:34 (theory for Cl_4Br 44:100:83:33), 315/317/319; 228/230/232; 167/169/171; 131/133.

Several attempts were made to dehalogenate the C_7 and C_8 positions. The reaction conditions ($NaCNBH_3$, HMPT, 70 °C, 2 h)[8] that successfully didebrominated 1,2-dibromo-1-methylstyrene in 83% yield in our hands gave no reaction with oregonene A (**9**). More forcing conditions caused decomposition.

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Registry No.—**5**, 57766-75-3; **6**, 57766-76-4; **7**, 62447-48-7; **8**, 62447-49-8; **9**, 62416-32-4.

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(4) J. S. Mynderse and D. J. Faulkner, *Tetrahedron*, **31**, 1963 (1975).
(5) For *trans*-2-butenyl chloride, $-CH_2Cl$ 45.5 ppm, and for *trans*-2-butenyl bromine, $-CH_2Br$ 33.3 ppm.
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Deoxygenation of *N*-Nitrosodibenzylamine with Aryl Azides

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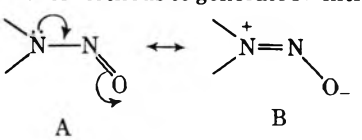
Recently a great deal of attention has been focused on *N*-nitrosamines because of their synthetic utility[1] as well as their carcinogenic[2,3] and carcinostatic[3] properties. The large contribution of dipolar form B to the structure of *N*-nitrosamines, clearly indicated by spectral data,[4] helps explain some of the chemistry of this class of compounds; thus, structure B suggests that *N*-nitrosamines may formally be regarded as *N*-oxides of *N*-nitrenes. These considerations coupled with our interest in novel methods to generate *N*-nitrenes,[5] led us

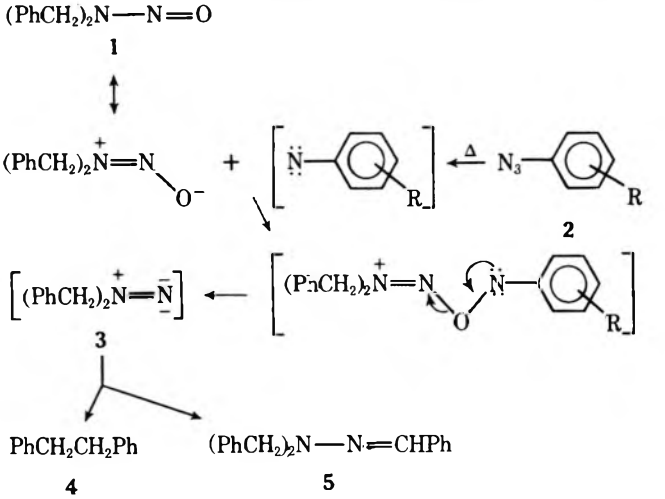


A B

to consider the "deoxygenation" of *N*-nitrosamines as a route to these reactive intermediates.

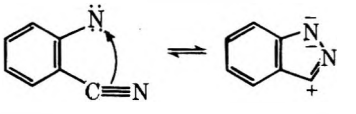
It was reported earlier[6] that the reaction of *N*-nitrosodibenzylamine (**1**) with iron pentacarbonyl resulted in the formation of products traceable to *N*-dibenzylaminonitrene (**3**). It was felt that electron-deficient species such as *C*-nitrenes should react with *N*-nitrosamines to yield *N*-nitrenes. This communication describes our results.

Since bibenzyl (**4**) and benzylidenedibenzylhydrazine (**5**) are known transformation products of *N*-dibenzylaminonitrene (**3**),[7] *N*-nitrosodibenzylamine (**1**) was selected as the substrate for our investigation. A solution of **1** in chlorobenzene was heated to reflux with a twofold excess of phenyl azide until nitrogen evolution ceased. Work-up of the reaction mixture gave 81.5% of recovered **1** along with trace amounts



of bibenzyl (**4**); thin-layer chromatography showed the presence of azoxybenzene.[8] Since the anticipated course of the reaction was predicated on the electron-deficient nature of the *C*-nitrenes, the reaction of **1** was carried out with aryl azides containing groups which should enhance the electron-deficient nature of the *C*-nitrenes derived from them.[9] 4-Nitrophenyl azide gave a 46% yield of bibenzyl (**4**), while only 48% of **1** was recovered. Similarly, 4-cyanophenyl azide afforded a 48% yield of **4**, although a much larger amount (93.7%) of **1** was recovered. Unexpectedly, *p*-chlorophenyl azide gave *no* bibenzyl, while 79.5% of **1** was unreacted. The anomalous effect of the chlorine was further confirmed by the reaction of 2-chloro-4-nitrophenyl azide with **1** in which only 14% of **4** (compared with 4-nitrophenyl azide) was obtained and **1** was recovered in 63% yield. 2,3-Dichlorophenyl azide gave **4** and **5**, albeit in low yield.[10]

With substituents in the 2 position, such as *o*-benzoyl and *o*-nitro, capable of reacting with the nitrene[11] to give stable compounds, little or no bibenzyl was obtained (see Table I, entries 8 and 9); 3-phenylanthranil and benzofuroxan were the major products, respectively. 2-Cyanophenyl azide provided a surprising contrast to the aforementioned azides; bibenzyl was isolated in as good a yield (47%) as those obtained from 4-nitro- and 4-cyanophenyl azides. This may be rationalized by the fact that the cyano group, being located ortho to the nitrene, may interact with and in a sense "store" the nitrene without forming a stable compound in contrast to the nitro and benzoyl groups (vide supra[11]). These data led to the



expectation that the synergistic effect of a cyano group in the 2 position coupled with that of a nitro group in the 4 position should result in providing us with a most efficient azide for

Table I. Reaction of *N*-Nitrosodibenzylamine (1) with Azides[a]

Registry no.	Azide	Recovered 1, %	$PhCH_2$-CH_2Ph, %	Other products
622-37-7	(1) Phenyl azide	81.5	Traces	*b*
1516-60-5	(2) 4-Nitrophenyl azide	48.5	46	
18523-41-6	(3) 4-Cyanophenyl azide	93.7	48	
31656-77-6	(4) 2-Cyanophenyl azide	66.5	47	
3296-05-7	(5) 4-Chlorophenyl azide	79.5	0	*c*
62416-01-7	(6) 2-Chloro-4-nitrophenyl azide	63	14	*d*
62416-02-8	(7) 2,3-Dichlorophenyl azide	0	1	*c, d*
16714-27-5	(8) 2-Benzoylphenyl azide	90	Traces	*e*
1516-58-1	(9) 2-Nitrophenyl azide	80	0	*f*
62460-41-7	(10) 2-Cyano-4-nitrophenyl azide	9.7	69.5	*d*
941-55-9	(11) Tosyl azide	>99	Traces	
1070-19-5	(12) *tert*-Butyl azidoformate	89	0	

[a] All reactions were carried out in enough chlorobenzene to give a homogeneous solution using 5 mmol of *N*-nitrosodibenzylamine and 10 mmol of the azides. The yields of bibenzyl are based on the amount of unrecovered nitrosamine. Other products such as the azo compounds and biphenyls were formed. [b] In this reaction, azoxybenzene was sought (see ref 8) and detected by thin-layer chromatography. [c] Trace amounts of benzylidenedibenzylhydrazine (5) were detected. [d] Benzaldehyde was identified as a by-product. [e] 3-Phenylanthranil was isolated in nearly quantitative yield. [f] Benzofuroxan was isolated in 32% yield.

the deoxygenation of **1**. That this expectation was fully warranted was shown by the fact that a 70% yield of bibenzyl was obtained with less than 10% of recovered *N*-nitrosamine. Our results indicated that aryl azides may be useful for the removal of semiionic oxygen in compounds such as *N*-oxides, azoxy compounds, and nitrones.

Experimental Section

Materials. *N*-Nitrosodibenzylamine was prepared according to the literature procedure.[12] The azides were obtained from the corresponding amines.[13] Three new azides were prepared by the same method.

2-Chloro-4-nitrophenyl azide (70% yield): mp 65–66 °C, pale yellow needles from a mixture of acetone–95% ethanol. Anal. Calcd for $C_6H_3ClN_4O_2$: C, 36.29; H, 1.52; N, 28.22. Found: C, 36.23; H, 1.71; N, 28.29.

2,3-Dichlorophenyl azide (76% yield): mp 61–62 °C, pale yellow needles from 95% ethanol. Anal. Calcd for $C_6H_3Cl_2N_3$: C, 38.33; H, 1.61; N, 22.35. Found: C, 38.54; H, 1.90; N, 22.50.

2-Cyano-4-nitrophenyl azide (17% yield): mp 107–108 °C, pale yellow needles from 95% ethanol. Since this azide deteriorates on standing, an elemental analysis was performed on its triphenylphosphine imine adduct, mp 247–248 °C (from benzene). Anal. Calcd for $C_{25}H_{18}N_3O_2P$: C, 70.92; H, 4.25; N, 9.93. Found: C, 71.09; H, 4.35; N, 9.87.

Typical Procedure. A solution of 1.14 g (5 mmol) of *N*-nitrosodibenzylamine and of 2-cyano-4-nitrophenyl azide (1.89 g, 10 mmol) in 40 mL of chlorobenzene was purged with nitrogen for 30 min. The solution was then heated to reflux for 48 h with stirring in a nitrogen atmosphere. After careful evaporation of the solvent, the residue was chromatographed on silica gel (60–200 mesh, 50 g) using hexane, varying mixtures of hexane–benzene, and finally benzene.

All products reported were characterized by direct comparison with an authentic sample by at least one of the following methods: IR, NMR, mixture melting point, and TLC retention time.[14]

Acknowledgment. The support of this work by the National Institutes of Health (GM 13689-10) is acknowledged with gratitude.

Registry No.—**1**, 5336-53-8; $PhCH_2CH_2Ph$, 103-29-7; 2-cyano-4-nitrophenyl azide triphenylphosphine imine adduct, 55210-55-4.

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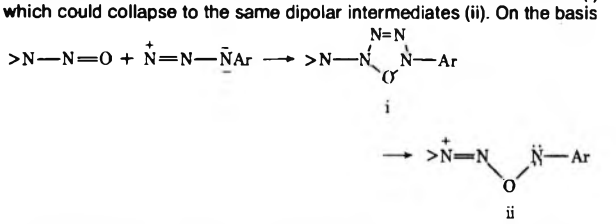
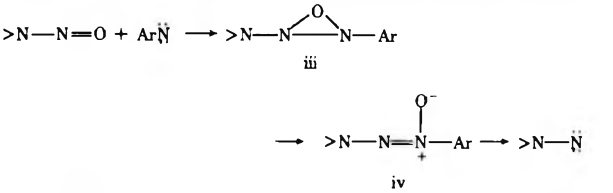
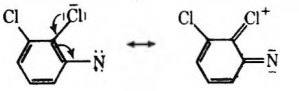
(9) R. A. Abramovitch and E. P. Kyba, "Chemistry of the Azido Group", S. Patai, Ed., Interscience Publishers, New York, N.Y., 1971, p 270. It is also possible to rationalize the results via the formation of unstable oxatetrazolines (i) which could collapse to the same dipolar intermediates (ii). On the basis



of the present data, we favor the nitrene mechanism. In the same context, the *C*-nitrenes could react with the nitroso group to give oxadiaziridines (iii) which could then open to triazene *N*-oxides (iv) which are known to



fragment to the *N*-nitrenes (M. Koga and J.-P. Anselme, unpublished results).
(10) While the inductive effect of a chloro substituted at any position would be expected to make the nitrene *more* electron deficient, in the ortho and para positions the chlorine may act as an electron-donating group to render the nitrene *less* electron deficient. Thus, if this putative resonance stabilization and concomitant deactivation of the nitrene by a chloro substituent could be inhibited, then deoxygenation of **1** should be possible. This hypothesis seems to be supported by the results from the reaction of 2,3-dichlorophenyl azide with **1**. Presumably in this case, steric inhibition of resonance,



such as shown, allows the chlorine in the ortho position to exert only its inductive effect. See Y. T. Struckhov and S. L. Solenova-Sidorova, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 93 (1960); S. L. Chien and R. Adams, *J. Am. Chem. Soc.*, **56**, 1787 (1934); see also J. March, "Advanced Organic Chemistry", McGraw-Hill, New York, N.Y., 1968, p 123.
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(14) See footnote *a* of Table I.

2-Methyl-3-butyn-2-ol as an Acetylene Precursor in the Mannich Reaction. A New Synthesis of Suicide Inactivators of Monoamine Oxidase[1]

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The propargylamines, *N*-[3-(2,4-dichlorophenoxy)propyl]-*N*-methyl-2-propynylamine (clorgyline, **1a**) and L-

N,α-dimethyl-*N*-2-propynylphenethylamine (L-deprenyl, **1b**) have been shown to be selective irreversible inhibitors of the isoenzymes of monoamine oxidase (MAO) type A and B, respectively.[2,3] Another propargylamine of this type, *N*-methyl-*N*-2-propynylbenzylamine (pargyline, **1c**), a more general MAO inhibitor, has been used therapeutically as an antihypertensive agent.[4]

In our studies of the metabolic fate of suicide enzyme inactivators of MAO A and B, we required a synthetic sequence which could be used to label the methylene carbon of the propargyl group of clorgyline (**1a**) and deprenyl (**1b**) with either radioactive (^{14}C or ^{11}C) or stable (^{13}C) isotopes of carbon. The introduction of isotopic carbon at this position using labeled formaldehyde in the Mannich reaction with acetylene and the appropriate secondary amine formally represented a sequence which could be used to yield the appropriately labeled propargylamines. However, the inconvenience and potential hazards associated with the use of acetylene as well as the formation of disubstituted by-products prompted us to investigate an alternative synthesis of **1a** and **1b**. 2-Methyl-3-butyn-2-ol (bp 104 °C) appeared to offer an attractive alternative to the use of acetylene in the Mannich reaction since it has been reported to act as an active hydrogen compound in the presence of cuprous catalysts,[5] and it is well known that acetylenic carbinols undergo KOH-catalyzed decomposition to the acetylene and carbonyl compound.[5,6]

We report here the synthesis of **1a–c** via the Mannich reaction with 2-methyl-3-butyn-2-ol followed by KOH-catalyzed elimination of acetone from the acetylenic carbinols **3a–c** (Scheme I). This reaction sequence has been used to synthesize ^{14}C-labeled **1a** and **1b**.[7]

In summary, this two-step reaction results in the formation of propargylamines in moderate yields (33–48%). The overall transformation is that of the Mannich reaction of acetylene without the hazards and inconvenience of using acetylene or the formation of complex mixtures of products by the substitution of both active hydrogen atoms on acetylene.

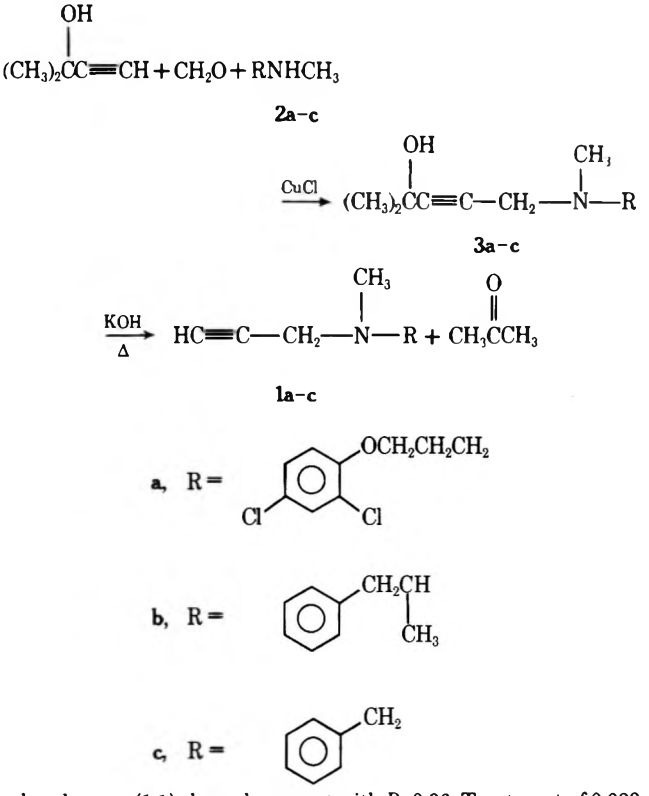
Experimental Section

Melting points are uncorrected. NMR spectra were run on a JEOL JNM-MH-100 using Me_4Si as an internal standard. Optical rotations were obtained using a Rudolf Research automatic polarimeter (Model 26202).

***N*-[3-(2,4-Dichlorophenoxy)propyl]-*N*-methyl-2-propynylamine (Clorgyline, 1a).** To 0.048 g (0.177 mmol) of 3-(2,4-dichlorophenoxy)-*N*-methylpropylamine hydrochloride[8] (**2a** HCl) in 0.2 mL of H_2O was added 0.0144 mL (0.177 mmol) of 37% CH_2O in 0.2 mL of H_2O. This was warmed slightly and 9 mg of CuCl added. The mixture was adjusted to pH 8 with 0.2 mL of 7.5% $NaHCO_3$ and 0.0172 mL of 2-methyl-3-butyn-2-ol in 0.6 mL of dioxane. The mixture was heated (110 °C) and stirred for 3 h and allowed to cool to room temperature, and 0.6 mL of ammonium hydroxide (concentrated) was added. The mixture was extracted with ether, the extracts were dried (K_2CO_3), and the solvent was removed to yield 0.050 g (86%) of **3a** a pale yellow oil having NMR ($CDCl_3$) δ 7.46–6.76 (m, 3 H, aromatic H), 4.06 (t, 2 H, *J* = 6 Hz, $-OCH_2-$), 3.34 (s, 2 H, $-C{\equiv}CCH_2N<$), 2.60 (t, 2 H, *J* = 7 Hz, $>NCH_2CH_2$), 2.30 (s, 3 H, $>NCH_3$), 1.96 (p, 2 H, *J* = 7 Hz, $-CH_2CH_2CH_2-$), 1.50 [s, 6 H, $(CH_3)_2C-$]. The compound was used in the next step without further purification.

To a film of KOH (0.2 mL of 1 M KOH, lyophilized on the bottom and sides of a test tube with a vacuum adapter and heated under vacuum for 2 min at 150 °C) was added an ethereal solution of **3a** (0.050 g). This was evaporated to dryness using a stream of N_2, a cold finger attached, and the residue heated under vacuum (1 mm) at 150 °C for 1 min. The material adhering to the cold finger was dissolved in ether–hexane (1:1) and passed over a 4 × 0.5 cm silica gel column and eluted with ~3 mL of the same solvent. The solvent was removed leaving 0.023 g (48% based on **2a**) of **1a**, a pale yellow oil, having NMR ($CDCl_3$) δ 7.46–6.76 (m, 3 H, aromatic H), 4.04 (t, 2 H, $-OCH_2-$), 3.32 (d, 2 H, *J* = 2 Hz, $HC{\equiv}CCH_2-$), 2.60 (t, 2 H, *J* = 7 Hz, $>NCH_2CH_2-$), 2.30 (s, 3 H, $>NCH_3$), 2.18 (t, 1 H, *J* = 2 Hz, $HC{\equiv}C-$), 1.96 (p, 2 H, *J* = 7 Hz, $-CH_2CH_2CH_2-$). The NMR spectrum was identical with that of an authentic sample of clorgyline.[9] TLC on silica gel in ether–hexane (1:1) showed one spot with R_f 0.36. Treatment of 0.023 g of **1a** in dry ether with HCl produced 0.025 g of **1a** HCl, mp 97–99 °C (lit.[8] mp 98.5–100 °C).

Scheme I



L-*N*,α-Dimethylphenethylamine (2b). To 1.6 g (0.0098 mol) of L-*N*-formyl-1-phenyl-2-aminopropane (prepared from L-amphetamine according to the procedure of Cavallito and Gray[10]) in 15 mL of ether at 0 °C was added dropwise 8 mL of $LiAlH_4$ solution (1 M in ether). The mixture was stirred at 25 °C for 8 h and decomposed with 1.25 mL of 3% NaOH. The mixture was filtered and the filtrate extracted with 1 N HCl. Addition of NaOH to the HCl solution followed by extraction with ether gave 0.63 g (43%) of a colorless oil. The NMR ($CDCl_3$) showed δ 7.50–7.14 (m, 5 H, aromatics), 3.02–2.54 (m, 3 H, $-CH_2CH<$), 2.42 (s, 3 H, $>NCH_3$), 1.34 (s, 1 H, $-NH-$), 1.06 (d, 3 H, *J* = 6 Hz, $CH_3CH<$). Treatment of an ethereal solution of the amine with HCl produced **2b** HCl which had mp 168–171 °C (lit.[11] 170–171 °C) and α^{25}_D −12.6° (c 16.1, H_2O) (lit.[11] α^{22}_D −14.8°).

L-*N*,α-Dimethyl-*N*-2-propynylphenethylamine (L-Deprenyl, 1b). Using the same general procedure described above, 0.033 g (0.178 mmol) of **2b** HCl was allowed to react with formaldehyde and 2-methyl-3-butyn-2-ol at 110 °C for 4 h to yield 0.037 g of a pale yellow oil which NMR showed to contain 71% of **3b** (60% yield). The NMR ($CDCl_3$) showed δ 7.42–7.06 (m, 5 H, aromatics), 3.42 (s, 2 H, $-C{\equiv}CCH_2N<$), 3.14–2.90 (m, 2 H, $-CH_2C_6H_5$), 2.52–2.22 (m, 1 H, $>NCH<$), 2.38 (s, 3 H, $>NCH_3$), 1.52 [s, 6 H, $(CH_3)_2C<$], 0.96 (d, 3 H, *J* = 6 Hz, $CH_3CH<$). This compound was used in the next step without further purification.

Pyrolysis of **3b** as described above yielded 11 mg of **1b** (33% based on **2b**), a colorless oil having NMR ($CDCl_3$) δ 7.4–7.04 (m, 5 H, aromatics), 3.42 (d, 2 H, *J* = 2 Hz, $HC{\equiv}CCH_2-$), 3.16–2.84 (m, 2 H, $-CH_2C_6H_5$). 2.56–2.32 (m, 1 H, $>NCH<$), 2.40 (s, 1 H, $>NCH_3$), 2.22 (t, 1 H, *J* = 2 Hz, $HC{\equiv}C-$), 0.96 (d, 3 H, *J* = 6 Hz, $CH_3CH<$). The NMR spectrum was identical with that of an authentic sample of deprenyl[12] and showed no other signals. Treatment of **1b** (0.011 g) in dry ether with HCl followed by crystallization from methanol–ether gave 0.0095 g of **1b** HCl, mp 141–142 °C (lit.[13] mp 141 °C), α^{25}_D −10.8° (c 6.48, H_2O) (lit.[13] α^{20}_D −11.2°).

***N*-Methyl-*N*-2-propynylbenzylamine (Pargyline, 1c).** The reaction of **2c** HCl (0.028 g. 0.178 mmol) with CH_2O and 2-methyl-3-butyn-2-ol at 110 °C for 8 h as described yielded 0.032 g of **3c** (83%), a pale yellow oil having NMR ($CDCl_3$) δ 7.45–7.21 (m, 5 H, aromatics), 3.57 (s, 2 H, $C_6H_5CH_2N<$), 3.31 (s, 2 H, $>NCH_2C{\equiv}C-$), 2.32 (s, 3 H, $>NCH_3$), 2.28 (s, broad, 1 H, $-OH$), 1.55 [s, 6 H, $(CH_3)_2C<$].

To 0.2 mL of 1 M KOH was added **3c** (0.032 g) in 0.2 mL of MeOH. The mixture was evaporated (1 mm), leaving a residue which was pyrolyzed and purified as described previously to yield 8 mg (41% based on **2c**) of **1c**, a colorless oil having NMR ($CDCl_3$) δ 7.44–7.16 (m,

5 H, aromatics), 3.58 (s, 2 H, $C_6H_5CH_2N<$), 3.32 (d, 2 H, J = 2 Hz, $>NCH_2C{\equiv}C-$), 2.33 (s, 3 H, $>NCH_3$), 2.25 (t, 1 H, J = 2 Hz, $HC{\equiv}C-$). The NMR spectrum was identical with that of authentic pargyline.[14] Treatment of **1c** in dry ether with HCl followed by crystallization from MeOH–ether gave 0.007 g of **1c** HCl, mp 158.5–159 °C (lit.[15] mp 154–155 °C).

Acknowledgment. The author is grateful to Richard Ehrenkaufer, Brian Gallagher, David Lloyd, Robert MacGregor, and Alfred Wolf for helpful discussions and suggestions.

Registry No.—**1a,** 17780-72-2; **1a** HCl, 17780-75-5; **1b,** 14611-51-9; **1b** HCl, 14611-52-0; **1c,** 555-57-7; **1c** HCl, 306-07-0; **2a** HCl, 62505-88-8; **2b,** 33817-09-3; **2b** HCl, 826-10-8; **2c** HCl, 13426-94-3; **3a,** 62505-89-9; **3b,** 62505-90-2; **3c,** 62505-91-3; 2-methyl-3-butyn-2-ol, 115-19-5; L-*N*-formyl-1-phenyl-2-aminopropane, 62532-67-6.

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α-Alkylation and Michael Addition of Amino Acids—a Practical Method

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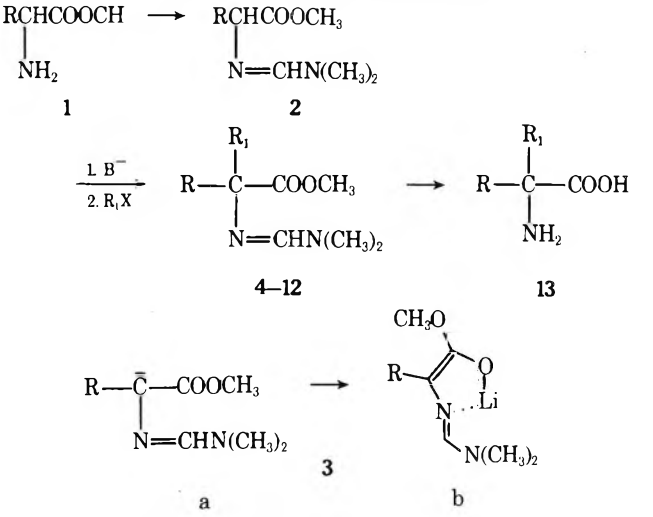
In recent years various methods have been developed to effect alkylation of amino acid derivatives at their α carbon.[1] One of the more versatile variants is the alkylation of deprotonated α-isocyano esters developed by Schöllkopf.[1a] Yet most of these procedures—the latter one included—suffer from the drawback of a multistep procedure necessary to sequentially protect carboxylic acid and amine functions in order to prepare a derivative suitable for α-deprotonation. We here wish to report a new and practical approach which is general for *all* α-amino acids and obviates the need for a laborious sequential protection.

The treatment of carboxylic acids in general and N-protected amino acids in particular with the acetals of dimethylformamide is known as an efficient and high-yielding method to prepare the corresponding esters.[2-6] Aminolysis of these reagents, on the other hand, particularly with primary aromatic amines, leads to substituted formamidines.[7-9] The simultaneous application of these two reactions for the conversion of a free amino acid into its α-formamidine methyl ester has not been used previously for preparative synthetic purposes.[10] Our results indicate that such ester formamidines are ideally suited as intermediates for α-alkylations.

By refluxing any α-amino acid **1** in 2–2.5 equiv of dimethylformamide dimethyl acetal (cf. ref 10) for 1–6 h, an essentially quantitative conversion to the distillable and reasonably stable[11] amidino esters **2** is achieved.[12] As we have discovered



independently, the conditions for deprotonation to **3** as well as its reactivity are very similar to those recently reported by Stork[1b] for the benzylidene derivative of glycine ethyl ester. Deprotonation can be achieved either with lithium diisopropylamide in THF at temperatures ranging from 0 to −70 °C or in certain instances with potassium *tert*-butoxide in CH_3OH. The anion **3** is sufficiently reactive toward alkylating agents such as alkyl iodides, allylic halides and even epoxides to give the products **4–12** in good to excellent yields[13] (see Table I). We have reason to believe that deprotonation of **2** initially leads to **3a** which readily tautomerizes to the lithium enolate **3b,** highly favored by the chelating effect of the unshared pair of electrons of the amidine nitrogen. In the case of the phenylglycine derivative **2c** (R = C_6H_5), low-temperature (−78 °C) deprotonation by LDA produces an intense red-orange color, characteristic of stabilized benzylic anions, gradually fading to a light orange-yellow. The infrared spectrum of the anionic species **3** (in CH_3CN) indicates no ester absorption but instead a strong band at 1630 cm^{-1} (C=N and C=C).[14]

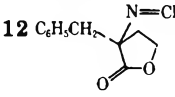
The high degree of chelation in **3** appears to be the reason for its unusually soft character (cf. ref 1b): in sharp contrast to the reactivity of the α-isocyano esters,[15,16] **3** does not react with ketones (benzophenone), and only sluggishly with benzaldehyde. This reactivity pattern is ideal for 1,4-additions which indeed occur readily either in aprotic or protic solvents (cf. ref 1b) (see Table I). Hydrolysis of the products **4–12** can be achieved in refluxing concentrated hydrochloric acid to produce the amino acids **13–15.** Unlike the imine functionality (cf. ref 1b), the dimethylformamidine moiety appears to be remarkably stable toward dilute mineral acids at room temperature.

Thus, we have outlined a practical method which permits the effective α-alkylation of any α-amino acid in a total of three steps: (1) simultaneous protection of both functional groups with dimethylformamide dimethyl acetal, (2) α-alkylation (or Michael addition), (3) acidic hydrolysis.

Experimental Section

The physical data were obtained as follows: melting points in a Thomas-Hoover melting point apparatus (uncorrected); IR spectra on a Perkin-Elmer 521; mass spectra on a AEI MS 902 by direct in-

Table I

Compd	(±)-Amino acid 1 R	Amidino ester 2[13] Yield, %	Amidino ester 2[13] Bp, °C (mmHg)	Electrophile	Product[13] R_1	Isold yield, %	Mp or bp, °C (mmHg)
a	H	80	71 (0.4)	Cinnamyl bromide	4 $C_6H_5CH{=}CHCH_2$	65	118[a]
				Dimethyl *p*-chlorobenzalmalonate	5 *p*-$ClC_6H_4CH(CO_2CH_3)_2CH$	63[b]	128
				Nitrostyrene	6 $C_6H_5CHCH_2NO_2$	(90)[c]	
b	$CH_3SCH_2CH_2$	94	128 (0.55)	*p*-Chlorobenzyl chloride	7 *p*-$ClC_6H_4CH_2$	84[d]	124
c	C_6H_5	86	128 (0.55)	Methyl iodide	8 CH_3	83	130 (0.4)
				Methyl acrylate	9 $CH_2CH_2CO_2CH_3$	88	61
d	$C_6H_5CH_2$	90	124 (0.6)	Methyl iodide	10 CH_3	84	130 (0.2)
				n-Propyl iodide	11 $CH_3CH_2CH_2$	80	135 (0.2)
				Ethylene oxide	12 	60[e]	178

[a] Isolated as fumarate salt. [b] Crude yield of diastereomeric mixture is >95%; 63% is of pure major isomer. [c] Crude yield as judged by NMR; product is unstable. [d] As CH_3SO_3H salt. [e] As cyclohexylsulfamic acid salt.

sertion; NMR spectra on a Varian A-60 using Me_4Si as internal standard. The following abbreviations are used: (b) broad, (w) weak, (ex) exchangeable with D_2O, (s) singlet, (d) doublet, (t) triplet, (q) quartet, (m) multiplet.

***dl*-Methyl *N*-(Dimethylaminomethylene)phenylglycinate (2c).** A suspension of 15.1 g (0.1 mol) of *dl*-α-phenylglycine in 75 mL (0.55 mol) of dimethylformamide dimethyl acetal was refluxed under N_2 for 3.0 h. Excess reagent was removed in vacuo. The residue was dissolved in ether and filtered through Celite. The oil from the ether was distilled to give 19.0 g (86.4%) of **2c**: bp (0.55 mm) 128–131 °C; NMR ($CDCl_3$) δ 2.88 (s, 6 H), 3.68 (s, 3 H), 4.93 (s, 1 H), 7.20–7.63 (m, 6 H); IR (CH_3CN) 1740, 1640 cm^{-1}.

Anal. Calcd for $C_{12}H_{16}N_2O_2$: C, 65.43; H, 7.32; N, 12.72. Found: C, 66.52; H, 7.37; N, 12.62.

Analogously, reaction of 11.3 g (0.15 mol) of glycine with dimethylformamide dimethyl acetal gave 17.2 g (79.6%) of **2a**: bp (0.4 mm) 71–74 °C; NMR ($CDCl_3$) δ 2.88 (s, 6 H), 3.69 (s, 3 H), 4.01 (s, 2 H), 7.30 (s, 1 H).

Reaction of 29.8 g (0.2 mol) of *dl*-methionine with dimethylformamide dimethyl acetal gave 40.8 g (93.6%) of **2b**: bp (0.55 mm) 124–128 °C; NMR ($CDCl_3$) δ 1.91–2.22 (m, 2 H), 2.06 (s, 3 H), 2.33–2.67 (m, 2 H), 2.86 (s, 6 H), 3.66 (s, 3 H), 3.70–3.98 (m, 1 H), 7.28 (s, 1 H).

Reaction of 16.5 g (0.1 mol) of *dl*-β-phenylalanine with dimethylformamide dimethyl acetal gave 21.0 g (89.7%) of **2d**: bp (0.6 mm) 124–126 °C; NMR ($CDCl_3$) δ 2.77 (s, 6 H), 2.80–3.39 (m, 2 H), 3.66 (s, 3 H), 3.71–4.02 (m, 1 H), 6.99 (s, 1 H), 7.20 (s, 5 H); IR (CH_2Cl_2) 1738, 1643 cm^{-1}.

Anal. Calcd for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74; N, 11.96. Found: C, 66.99; H, 7.85; N, 11.71.

Methyl 2-(Dimethylaminomethyleneamino)-5-phenyl-4-pentenoate (4). To a solution of 8 mmol of LDA (lithium diisopropylamide) in 10 mL of dry THF [prepared by adding dropwise 5 mL (8 mmol) of a 1.6 M *n*-butyllithium solution in hexane to 1.5 mL of diisopropylamine in 10 mL of dry THF at 0 °C under N_2] cooled to −70 °C under N_2 was added dropwise a solution of 1.04 g (7.2 mmol) of amidino ester **2a** in 3 mL of dry THF. After 1.25 h at −70 °C a solution of 1.7 g (8.6 mmol) of cinnamyl bromide in 3 mL of dry THF was added. After 3.0 h at room temperature the reaction mixture was partitioned between ether and ice-cold diluted Na_2CO_3 solution. The ether was washed with basic (Na_2CO_3) brine, dried, and evaporated to give 1.89 g of **4** as an oil: NMR ($CDCl_3$) δ 2.52–2.68 (m, 2 H), 2.80 (s, 6 H), 3.66 (s, 3 H), 3.70–3.95 (m, 1 H), 5.78–6.60 (m, 2 H), 7.0–7.35 (m, 6 H). This oil was dissolved in acetone and treated with 1 equiv of fumaric acid, to give 1.76 g (65.2%) of **4** fumarate salt: mp 116–119 °C dec; IR (Nujol) 1750, 1708, 1655, 1595 cm^{-1}; MS *m/e* 260 (M^+).

Anal. Calcd for $C_{15}H_{20}N_2O_2{\cdot}C_4H_4O_4{\cdot}H_2O$: C, 57.86; H, 6.64; N, 7.10. Found: C, 57.47; H, 6.52; N, 7.20.

Dimethyl 2-(Dimethylaminomethyleneamino)-3-(4-chlorophenyl)-4-(methoxycarbonyl)pentanedioate (5). To a solution of 55 mmol of LDA in 125 mL of dry THF at −70 °C under N_2 was added a solution of 7.2 g (50 mmol) of amidino ester **2a** in 25 mL of dry THF dropwise. After 1 h at −70 °C a solution of 12.8 g (50 mmol) of dimethyl *p*-chlorobenzalmalonate in 20 mL of dry THF was added at a fast drop rate. After 18 h at room temperature, the reaction mixture was partitioned between ether and ice water. The ether layer was washed with basic (NaOH) brine, dried, and evaporated to give 20 g of compound **5** as an oily diastereomeric mixture. Crystallization from ether afforded 12.5 g (62.7%) of a pure major isomer: mp 128–129 °C; NMR ($CDCl_3$) δ 2.88 (s, 6 H), 3.49 (s, 6 H), 3.66 (s, 3 H), 3.90–4.13 (m, 3 H), 7.24 (s, 4 H), 7.35 (s, 1 H); IR (Nujol) 1748, 1721, 1646 cm^{-1}.

Anal. Calcd for $C_{18}H_{23}N_2O_6Cl$: C, 54.21; H, 5.81; N, 7.02. Found: C, 54.51; H, 5.93; N, 6.71.

Methyl 2-(Dimethylaminomethyleneamino)-4-nitro-3-phenylbutanoate (6). To a solution of 11 mmol of LDA in 25 mL of dry THF at −70 °C under N_2 a solution of 1.45 g (10 mmol) of amidino ester **2a** was added dropwise. After 1 h a solution of 1.5 g (10 mmol) of ω-nitrostyrene in 10 mL of dry THF was added. After 1 h at −70 °C, 1 mL of acetic acid was added and the reaction mixture partitioned between ether and ice-cold $NaHCO_3$ solution (twice). The ether layer was dried and evaporated to give 2.8 g (95%) of compound **6**, an unstable oil: NMR ($CDCl_3$) δ 2.82 (s, 6 H), 3.53 (s, 3 H), 3.95–4.21 (m, 2 H), 4.80–5.16 (m, 2 H), 7.25 (s, 1 H), 7.29 (s, 5 H). Yield as judged by NMR is 90%.

***dl*-2-(4-Chlorobenzyl)-*N*-dimethylaminomethylene Methionine Methyl Ester (7).** To a solution of 24 mmol of LDA in 30 mL of dry THF at −70 °C under N_2 atmosphere was added dropwise a solution of 4.71 g (21.6 mmol) of amidino ester **2b** in 10 mL of dry THF. After 1 h at −70 °C, 4.2 mL (24.5 mmol) of hexamethylphosphoric triamide (HMPT) was added dropwise. After 15 min a solution of 3.85 g (24 mmol) of α-*p*-dichlorotoluene in 10 mL of dry THF was added. After 18 h at room temperature the reaction mixture was partitioned between ether and cold diluted Na_2CO_3 solution. The ether layer was washed with basic(Na_2CO_3) brine, dried, and evaporated to give 7.35 g of **7** as an oil: NMR ($CDCl_3$) δ 1.80–2.24 (m, 2 H), 2.05 (s, 3 H), 2.35–2.70 (m, 2 H), 2.79 (s, 6 H), 2.97–3.12 (m, 2 H), 3.67 (s, 3 H), 7.15 (s, 4 H), 7.33 (s, 1 H). This oil was dissolved in acetone and treated with 1 equiv of methanesulfonic acid to give 7.93 g (83.7%) of **7** methanesulfonate salt: mp 125–128 °C; IR (Nujol) 1740, 1697 cm^{-1}.

Anal. Calcd for $C_{16}H_{23}ClN_2O_2S{\cdot}CH_4O_3S$: C, 46.51; H, 6.20; N, 6.38. Found: C, 46.43; H, 6.37; N, 6.17.

2-(4-Chlorobenzyl)methionine (15). A solution of 1.3 g (3.8 mmol) of **7** in 25 mL of 2.0 N HCl was refluxed for 72 h. The reaction mixture was decanted from a small amount of insoluble gum and cooled in an ice bath. Neutralization with concentrated NH_4OH followed by filtration of the crystalline solid gave 690 mg (66.4%) of **15**: mp 245–248 °C dec; IR (Nujol) 2030, 1625, 1600 cm^{-1}; MS *m/e* 274 (M^+).

Anal. Calcd for $C_{12}H_{16}ClNO_2S$: C, 52.64; H, 5.89; N, 5.11. Found: C, 52.57; H, 5.41; N, 4.72.

Methyl 2-(Dimethylaminomethyleneamino)-2-phenylpropionate (8). To a solution of 8.0 mmol of LDA in 8 mL of dry THF at − 70 °C under N_2 was added a solution of 1.58 g (7.2 mmol) of amidino ester **2c** in 5 mL of dry THF dropwise. After 10 min at −70 °C the reaction mixture was warmed to 0 °C and 1.53 g (10.8 mmol) of methyl iodide added neat. After 1 h at room temperature the reaction mixture was partitioned between ether and basic (NaOH) brine

(twice). The ether layer was dried and evaporated and the residue distilled to give 1.4 g (83.3%) of compound **8**: bp (0.6 mm) 130–135 °C; NMR ($CDCl_3$) δ 1.70 (s, 3 H), 2.88 (s, 6 H), 3.65 (s, 3 H), 7.13–7.67 (m, 6 H); IR (film) 1721, 1634 cm^{-1}.

Anal. Calcd for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74; N, 11.96. Found: C, 66.39; H, 7.79; N, 11.89.

Dimethyl 2-(Dimethylaminomethyleneamino)-2-phenylpentanedioate (9). To a solution of 2.2 g (10 mmol) of amidino ester **2c** in 30 mL of anhydrous MeOH at room temperature under N_2, 300 mg (2.5 mmol) of potassium *tert*-butoxide was added. After 15 min 1.72 g (20 mmol) of methyl acrylate was added and the solution refluxed for 24 h. The solvent was removed in vacuo and the residue dissolved in ether, dried, and filtered through Celite. The oily residue crystallized from ether/hexane to give 2.69 g (87.9%) of compound **9**: mp 61–63 °C; bp (0.7 mm) 166–169 °C; NMR ($CDCl_3$) δ 2.19–2.45 (m, 4 H), 2.89 (s, 6 H), 3.59 (s, 3 H), 3.68 (s, 3 H), 7.19–7.60 (m, 6 H); IR (CH_2Cl_2) 1720, 1633 cm^{-1}.

Anal. Calcd for $C_{16}H_{22}N_2O_4$: C, 62.72; H, 7.24; N, 9.14. Found: C, 63.04; H, 7.38; N, 9.19.

Methyl 2-(Dimethylaminomethyleneamino)-2-methyl-3-phenylpropionate (10). To a solution of 27.5 mmol of LDA in 50 mL of dry THF at −70 °C under N_2 was added dropwise a solution of 5.85 g (25 mmol) of amidino ester **2d** in 50 mL of dry THF. The reaction mixture was warmed to 0 °C and 5.3 g (37.5 mmol) of methyl iodide added neat. After 1 h at room temperature, the reaction mixture was partitioned between ether and basic (NaOH) brine (twice). The ether layer was dried and evaporated. The residue was distilled to give 5.2 g (84%) of compound **10**: bp (0.2 mm) 130 °C; NMR ($CDCl_3$) δ 1.29 (s, 3 H), 2.81 (s, 6 H), 3.08 (s, 2 H), 3.67 (s, 3 H), 7.20 (s, 6 H); IR (film) 1721, 1638 cm^{-1}.

Anal. Calcd for $C_{14}H_{20}N_2O_2$: C, 67.71; H, 8.12; N, 11.28. Found: C, 67.66; H, 7.88; N, 11.17.

Methyl 2-Benzyl-2-(dimethylaminomethyleneamino)pentanoate (11). To a solution of 16.5 mmol of LDA in 30 mL of dry THF at −70 °C under N_2 was added a solution of 3.5 g (15 mmol) of amidino ester **2d** in 30 mL of THF. The reaction mixture was warmed to 0 °C and 3.83 g (22.5 mmol) of *n*-propyl iodide added neat. After 6 h at room temperature the reaction mixture was partitioned between ether and basic (NaOH) brine (twice). The ether layer was dried and evaporated and the residue distilled to give 3.32 g (80%) of compound **11**: bp (0.2 mm) 135–140 °C; NMR ($CDCl_3$) δ 0.70–1.95 (m, 7 H), 2.74 (s, 6 H), 3.01–3.11 (m, 2 H), 3.64 (s, 3 H), 6.98 (s, 1 H), 7.11 (s, 5 H); IR (film) 1723, 1638 cm^{-1}.

Anal. Calcd for $C_{16}H_{24}N_2O_2$: C, 69.53; H, 8.75; N, 10.14. Found: C, 69.40; H, 8.62; N, 10.14.

α-Propylphenylalanine (13). A solution of amidino ester **11** (1.38 g, 5 mmol) in 10 mL of concentrated HCl was refluxed for 24 h. On cooling, the hydrochloride salt of **13** crystallized from the solution. Filtration afforded 1.1 g (90.2%), mp 235 °C dec.

Anal. Calcd for $C_{12}H_{17}NO_2 \cdot HCl$: C, 59.14; H, 7.44; N, 5.74. Found: C, 59.51; H, 7.67; N, 6.08.

2-Benzyl-2-(dimethylaminomethyleneamino)butyrolactone (12). To a solution of 24 mmol of LDA in 40 mL of dry THF at −70 °C under N_2 was added a solution of 5.04 g (21.6 mmol) of amidino ester **2d** in 20 mL of dry THF. After 1 h at −70 °C the solution was saturated with ethylene oxide, and the bath removed and stirred at room temperature. After 2 days the solvent was removed in vacuo. The residue was dissolved in ether, decolorized with charcoal, dried, and filtered through Celite. The filtrate was evaporated to give 4.18 g of **12** as an oil: NMR ($CDCl_3$) δ 2.03–2.17 (m, 2 H), 2.91 (s, 6 H), 2.96–3.02 (m, 2 H), 3.91–4.13 (m, 2 H), 7.09 (s, 5 H), 7.51 (s, 1 H). This oil was dissolved in acetone and treated with 1 equiv of cyclohexylsulfamic acid to give 5.42 g (60%) of **12**, cyclohexylsulfamate salt: mp 178–180 °C; IR (Nujol) 1768, 1705 cm^{-1}.

Anal. Calcd for $C_{14}H_{18}N_2O_2 \cdot C_6H_{13}NO_3S$: C, 56.46; H, 7.34; N, 9.88. Found: C, 56.31; H, 7.55; N, 9.89.

2-Amino-2-benzylbutyrolactone (14). A solution of 3.63 g (14.7 mmol) of **12** in 25 mL of *p*-dioxane and 25 mL of 5 N HCl was refluxed for 18 h. The reaction mixture was concentrated to one-half volume and extracted with ether (twice). The aqueous layer was further concentrated yielding 950 mg (28.5%) of compound **14** HCl: mp 251–254 °C dec; ir (Nujol) 2010, 1775 cm^{-1}; MS *m/e* 192 ($M^+ + 1$).

Anal. Calcd for $C_{11}H_{13}NO_2 \cdot HCl$: C, 58.02; H, 6.20; N, 6.15. Found: C, 58.01; H, 6.43; N, 6.02.

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Registry No.—**1a**, 56-40-6; **1b**, 59-51-8; **1c**, 2835-06-5; **1d**, 150-30-1; **2a**, 62448-39-9; **2b**, 62448-40-2; **2c**, 62448-41-3; **2d**, 62448-42-4; **4**, 62448-43-5; **4** fumarate, 62448-44-6; **5** isomer a, 62460-38-2; **5** isomer b, 62448-45-7; **6**, 62448-46-8; **7**, 62448-47-9; **7** methanesulfonate, 62448-48-0; **8**, 62448-49-1; **9**, 62448-31-1; **10**, 62448-32-2; **11**, 62448-33-3; **12**, 62448-34-4; **12** cyclohexylsulfamate, 62448-35-5; **13**, 62448-36-6; **14**, 62448-37-7; **15**, 62448-38-8; dimethylformamide dimethyl acetal, 4637-24-5; cinnamyl bromide, 4392-24-9; fumaric acid, 110-17-8; dimethyl-*p*-chlorobenzalmalonate, 52927-44-3; ω-nitrostyrene, 102-96-5; α-*p*-dichlorotoluene, 104-83-6; methanesulfonic acid, 75-75-2; methyl iodide, 74-88-4; methyl acrylate, 96-33-3; *n*-propyl iodide, 107-08-4; ethylene oxide, 75-21-8.

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Electronic Structure and Nitrogen Hybridization in β-Aminovinylphosphonium Salts by Carbon-13 Nuclear Magnetic Resonance

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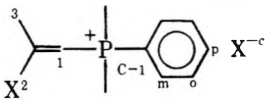
We have previously examined the ^{13}C NMR for a number of β-vinyl substituted phosphonium salts.[1] Current synthetic work in this laboratory has dealt with β-aminovinylphosphonium salts, and thus, a more detailed study of their spectra was undertaken. The following is a report on that study.

Compounds **2–7** were prepared by addition of the corresponding amine to 2-propynyltriphenylphosphonium bromide. The ^{13}C chemical shifts and ^{13}C–^{31}P nuclear couplings of these compounds are listed in Tables I and II, respectively, and their ^1H NMR spectra in Table III. Assignments of the carbons and the stereochemistry of the compounds were made by analogy with previous work.[1] In all cases, the *E* form (as shown) was indicated.

Table I. Carbon-13 Chemical Shifts of β-Substituted Vinylphosphonium Salts[a]



Compd	X	^{13}C chemical shift, ppm 1	2	3	4	5	6	C-1	o	m	p
2		80.7	175.8	22.2	28.6			120.3	133.2	130.5	134.7
3		54.3	164.1	17.5	51.5, 52.2	14.6		123.2	132.9	130.1	133.9
4		57.2	162.7	22.1	49.5	25.5, 24.9		123.4	132.9	130.1	133.8
5		59.3	163.7	22.3	48.5	25.5	23.5	123.3	132.9	130.2	134.0
6	$(H_3C)_2N-$	58.4	165.2	21.9	41.4			123.3	132.9	130.1	133.9
7	H_3C-N-	54.1	166.0	21.8	30.1			123.5	132.9	130.0	134.0
8[b]	H_3C-	102.4	172.0	24.8	29.9			119.4	133.2	130.6	134.8
9[b]	H_3C-H_2CO-	76.5	178.9	20.6	66.1	14.0		120.9	133.0	130.0	134.2

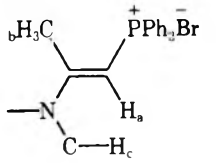
[a] The chemical shifts are referenced to internal Me_4Si. The numbering systems for the propenyl and triphenylphosphonium moieties are shown above Table I; the numbering for the substituent X is shown beside its corresponding number. All samples were run in $CDCl_3$. [b] Reference 1. [c] $X^- = Br^-$ for compounds 2–7 and 9; $X^- = Cl$ for 8.

Table II. ^{31}P–^{13}C Coupling Constants for β-Substituted Vinylphosphonium Salts[a]

Compd	$^1J(^{31}P-^{13}C)$, Hz 1	2	3	4	C-1	o	m	p
2	106	10.4	3.7		91.6	9.8	12.2	*
3	125.7	13.4	3.7		92.2	10.4	12.8	2.4
4	122.7	14.0	4.9		91.6	10.4	12.8	2.4
5	121.5	14.0	6.7		91.6	10.4	12.8	2.4
6	122.1	14.7	6.1		91.6	10.4	12.8	2.4
7	122.7	13.4	3.7	18.6	91.6	10.4	12.2	2.4
8	89.4	1.2	7.7		89.5	10.6	12.8	2.4
9	96.4	3.0	12.2		92.2	11.0	13.4	3.0

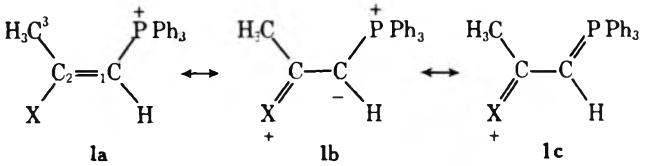
[a] The number system is identical with that used for Table I. The digital resolution was ±0.6 Hz. No coupling from phosphorus was observed beyond the carbons numbered. An asterisk indicates that the coupling was less than the resolution capable.

Table III. Proton Chemical Shifts of β-Substituted Vinylphosphonium Salts



Compd	^{1}H chemical shift, ppm a	b	c
2	5.31	1.87	2.55
3	3.68	1.70	∿4.40
4	3.73	1.92	∿3.6
5	4.05	1.95	∿3.6
6	3.78	1.90	3.23
7	3.73	1.89	2.98

The preceding work[1] has provided support for the mesomeric structures **1a–c** (X = NHR, OEt, CH_3). Thus, for example, support for mesomer **1b** is seen by the high shielding of carbon 1 when X = NHR or OEt relative to X = CH_3.[1] Likewise, mesomer **1c** is supported by an increased $^1J(^{13}C-^{31}P)$ which may be attributed to a greater electron density on carbon 1.[1]



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

A cursory examination of the present work provides additional support for these proposals. A closer examination, however, discloses an incongruity between the vinylaziridine **2** and the vinylamines **3–7**. In particular, carbon 1 of **2** is deshielded by 21.4–26.6 ppm from **3–7**, and the $^1J(^{13}C-^{31}P)$ is smaller in **2** by 16–20 Hz than that found for **3–7**. Indeed, the data for **2** are curiously closer to those of the vinyl ether **9** than to the other vinylamines.

This large deshielding of carbon 1 in **2** relative to **3–7** was also reflected in the ^{1}H NMR. Inspection of Table III shows that proton H_a is deshielded in **2** by 1.26–1.63 ppm from those found for **3–7**. Similar effects in NMR spectra of other systems have been reported.[2,4]

Presumably, the variations in carbon and proton chemical shifts and $^{13}C-^{31}P$ coupling in going from **2** to **3–7** arise from differential n–π interaction between the nitrogen lone pair and the olefinic double bond. Since the nitrogen inversion barrier is larger (due to angle strain) in the smaller polymethyleneimines, they are expected to exhibit planar nitrogens less readily[3] and, therefore, poorer π-donating lone pairs in conjugated systems.[8] In addition, calculations and spectroscopic data[5] have indicated that as the C–N–C angle of an amine decreases, the lone pair molecular orbital acquires more s character, becoming a poorer π donor. Similar angle strain arguments have been invoked by Truce and Gorbaty[2] to explain variations in the chemical shifts of β-vinyl protons in various *N*-vinylaziridines.

Assuming similar geometries (aside from ring size) for adducts **2–7**, from the above reasoning one would expect a smooth trend in chemical shifts and coupling. It is apparent from the data in Tables I, II, and III, however, that we are not dealing with a continuous function. A tempting interpretation is that a gross change in ground-state nitrogen geometry from

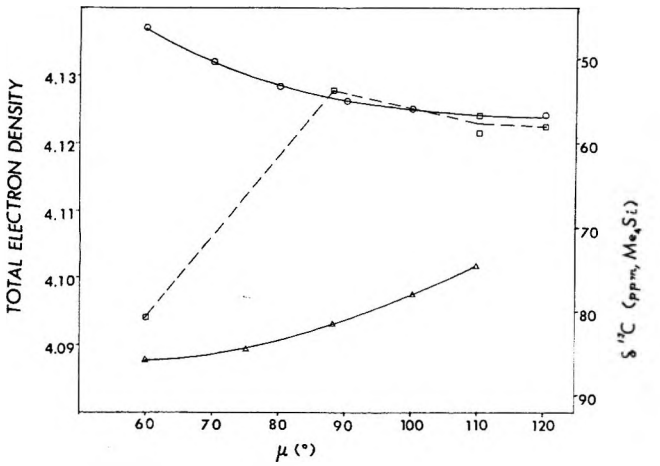


Figure 1. Variance of total electron density on the β carbon of vinylamine as a function of the HNH angle, μ, for ⊙ planar nitrogen, and △ pyramidal nitrogen. The dotted line shows the variance of ^{13}C chemical shift of carbon 1 in **2**–**6** as a function of μ.

pyramidal (sp^3) in **2** to essentially planar (sp^2) in **3**–**7** is being observed. Some support for this idea is provided by the work of Kamlet et al.[4] on *N*-(4-nitrophenyl)polymethylenimines. In that system, they found a pattern in the NMR for the ortho protons very similar to that mentioned in this paper, with supporting data from ultraviolet spectra and pK_a values.

In order to give further evidence for this notion, INDO SCF–MO calculations[7] were performed on a model system, vinylamine. Two functions were varied: (1) μ, the HNH angle, reflecting different ring sizes, and (2) θ, the angle between the HNH plane and the plane of the olefinic bond. Since ^{13}C chemical shifts are generally considered to correlate better with total electron density,[6] the latter vaues for the β carbon were plotted against μ for $\theta = 0$ (planar nitrogen) and $\theta = 54.7$ (~tetrahedral nitrogen). The two lines which resulted are shown in Figure 1. Also shown is a plot of the ^{13}C chemical shifts for **2**–**6** vs. μ (the dotted line).[9] From these data it is apparent that the deshielding of carbon 1 in **2** relative to **3**–**7** probably stems, in large part, from a pyramidal nitrogen. Deshielding of carbon 1 in **2** may also arise in part from angle strain rehybridization; however, the relative contribution of this effect is difficult to estimate from these calculations.

In conclusion, ^{13}C and ^1H spectra of the β-aminovinylphosphonium salts **3**–**7**, in conjunction with INDO SCF–MO calculations on vinylamine, seem to indicate structures with considerable enamine conjugation and essentially planar nitrogen atoms. Aziridine **2** appears to have considerably less enamine conjugation than **3**–**7** (albeit more conjugation than **8**) and a pyramidal nitrogen. The nearly planar azetidine nitrogen, though observed previously in other systems,[4] is still quite surprising. The chemistry of these interesting compounds, in particular, derivatives of **2**, is presently under investigation and will be reported in a later publication.

Experimental Section

Carbon-13 spectra were obtained on a Bruker HFX-90 spectrometer equipped for Fourier transform pulsed NMR with a Nicolet 1085 data system. The ^{13}C data were taken at an operating frequency of 22.63 MHz. The ^{13}C chemical shifts are reported as referenced to Me_4Si. All samples were run in approximately 0.05 M solutions of $CDCl_3$ at 32 °C with broad band ^1H decoupling (except compound **2**, which was run at −5 °C). The proton spectra were obtained on either a Perkin-Elmer R-12 or Varian A-60A spectrometer and were referenced to Me_4Si. Concentrations used for the proton spectra were similar to those used for the ^{13}C spectra. The ^1H spectrum of compound **2** was taken at −10 °C; all others were taken at normal probe temperatures (~30–40 °C).

Acknowledgments. The authors would like to thank Stevan Evans for his help with the INDO SCF–MO calculations and David L. Dalrymple for taking the ^{13}C spectra.

Registry No.—**2**, 62460-44-0; **3**, 62460-45-1; **4**, 62460-46-2; **5**, 62460-47-3; **6**, 62460-48-4; **7**, 62460-49-5; 2-propynyltriphenylphosphonium bromide, 2091-46-5; aziridine, 151-56-4; azetidine, 503-29-7; pyrrolidine, 123-75-1; piperidine, 110-89-4; dimethylamine, 124-40-3; methylamine, 74-89-5.

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(8) Cf. M. Dewar, "The Molecular Orbital Theory of Organic Chemistry", McGraw-Hill New York, N.Y., 1969, p 408.
(9) The values of μ vs. $\delta^{13}C$ are 60° for aziridine [B. Bak and S. Skaaryp, *J. Mol. Struct.*, **10**, 385 (1971)], 88° for azetidine [V. S. Mastryukov, O. V. Dorofeeva, and L. V. Vilkov, *J. Chem. Soc., Chem. Commun.*, 772 (1973)], 110° for the five- and six-membered rings, and 120° for the dimethylamine derivative.

An Improved Synthesis of Bicyclo[4.2.1]nonan-2-one

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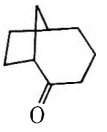
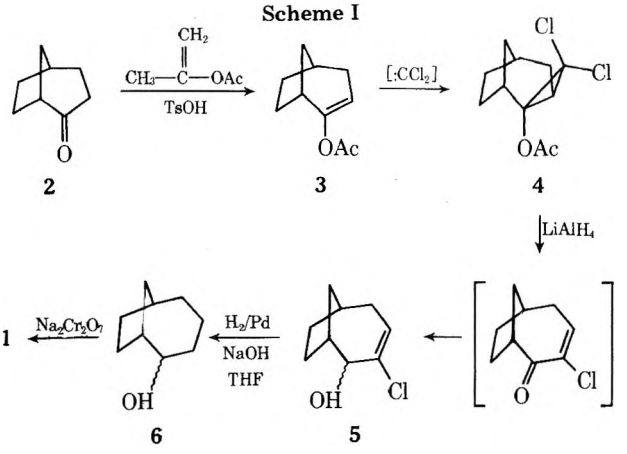
Our interest in the Favorskii rearrangement of bicyclic halo ketones[1] has prompted us to investigate the synthesis of bicyclo[4.2.1]nonan-2-one (**1**). Of the published routes to this



1

bicyclic ketone,[2–6] the method of Kraus et al.[6] is the only simple one. This involves treatment of bicyclo[3.2.1]octan-2-one[7] (**2**) with isopropenyl acetate and *p*-toluenesulfonic acid (TsOH) (Scheme I) to give bicyclo[3.2.1]oct-2-en-2-yl acetate (**3**). Dichlorocarbene addition to **3** yields 3,3-dichloro-*exo*-tricyclo[4.2.1.$0^{2,4}$]non-2-yl acetate (**4**), which undergoes re-

Scheme I



ductive fragmentation with lithium aluminum hydride in ether to give a mixture of exo and endo alcohols **5**. Hydrogenation and hydrogenolysis to alcohol **6** is routine and oxidation gives the desired ketone **1**.

A problem we encountered in the synthesis was the conversion of enol acetate **3** into cyclopropyl acetate **4**. Kraus stated that chloroform and 50% aqueous sodium hydroxide with catalytic amounts of benzyltriethylammonium chloride according to Makosza's procedure[8] gave a 67% yield of adduct **4**. He also mentioned that enol acetate **3** does not react with dihalocarbenes if they are generated from potassium *tert*-butoxide and trihalomethanes or from sodium trihaloacetates. This is probably due to the electron-deficient nature of the carbon–carbon double bond of **3**.

We have been unable to reproduce the addition of dichlorocarbene to acetate **3** by this procedure. Only nonvolatile products were obtained. However, use of Seyferth's reagent, (bromodichloromethyl)phenylmercury ($PhHgCCl_2Br$),[9] has been known for some time to be a mild method of generating dichlorocarbene.[10,11] Excess acetate **3** heated with this reagent in refluxing benzene for 4 h gives cyclopropyl adduct **4** in 57% yield and some **3**, easily separable by vacuum distillation, for a total recovery of 90%. The recovered enol acetate can be reused in the same reaction. The necessity of using excess **3** was not investigated, but a 1:1 stoichiometry has been found to be satisfactory for all but the least reactive olefins.[10] This change in the method of generating the dichlorocarbene makes bicyclo[4.2.1]nonan-2-one readily available through large-scale preparation.

Experimental Section

Melting and boiling points are uncorrected. Gas chromatography was performed on an SE-30 column at 190 °C.

3,3-Dichloro-*exo*-tricyclo[4.2.1.$0^{2,4}$]non-2-yl Acetate (4). Bicyclo[3.2.1]oct-2-en-2-yl acetate (**3**, 90% pure by GC, 24.39 g, 0.147 mol) and (bromodichloromethyl)phenylmercury (32.41 g, 0.0735 mol) were magnetically stirred and refluxed for 4 h with dry benzene (150 mL) under nitrogen. After the mixture was cooled, the phenylmercuric bromide (mp 275–280 °C, lit.[11] mp 283–285 °C) was suction filtered and washed with petroleum ether (bp 30–60 °C, 100 mL). The solvents were rotary evaporated and the yellow oil was vacuum distilled. The first fraction had bp 50–90 °C (0.12–0.18 mm) and was identified as enol acetate **3** (15.02 g, 0.0905 mol). The second fraction distilled as a colorless liquid with bp 93–108 °C (0.15–0.20 mm) and was found to be 3,3-dichloro-*exo*-tricyclo[4.2.1.$0^{2,4}$]non-2-yl acetate [**4**, 10.37 g, 0.0416 mol, 57%, lit.[6] bp 96 °C (0.5 mm)]: IR (neat) 3070 (cyclopropyl C–H), 2990 and 2930 (C–H), 1765 (C=O), 1445 (CH_2), 1355, 1200 (C–O), 1150, 1120 (C–O), 1015, 810 cm^{-1} (C–Cl); NMR (CCl_4) δ 3.0–3.2 (m, 1, $CHCCl_2$), 2.03 (s, 3, CH_3COO), 1.0–2.4 (m, 10). The starting material **3** plus product **4** represents a total recovery of 90%.

Acknowledgment. The author wishes to thank the University of Wisconsin—Eau Claire Research Fund for partial support of this work.

Registry No.—**1**, 3850-55-3; **3**, 37678-33-4; **4**, 37678-34-5; $PhHgCCl_2Br$, 3294-58-4.

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Synthesis of the Torsionally Strained Monocyclic Polythiaether 1,4,7-Trithiacyclononane

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In a previous paper, we had reported convenient synthetic methods[1] for macrocyclic polythiaether ligands, which were subsequently exploited in our continuing investigation of macrocyclic polythiaether coordination chemistry with copper and mercury.[2] In the course of current crystallographic studies of the metal complexes as a function of ring size and sulfur atom donor number, we required the 1,4,7-trithiacyclononane **2** ligand. Whereas the oxa, aza, and the mixed oxa–aza–thia nine-membered cyclic ligand syntheses have been reported[3] by methods analogous to those illustrated in Scheme I, often in excellent yields, the corresponding trithia ligand **2** in our hands proved to be frustratingly inaccessible.

Compound **2** had been reported in 1920 by Ray as a by-product from the synthesis of ethanedithiol by the reaction of ethylene bromide in alcoholic potassium hydrogen sulfide.[4] We have reinvestigated this reaction and found that the main cyclic product is *p*-dithiane **1**, without the slightest trace of **2** being detectable by analytical high-pressure liquid chromatography.

We had previously reported the absence of **2** from the cyclization of sodium mercaptides of either 3-thiapentane-1,5-dithiol with ethylene bromide or 1,2-ethanedithiol with 1,5-dichloro-3-thiapentane in butanol media at 60 °C.[1] Rather, in both of these reactions, the major direct cyclization product was the hexathia macrocycle **4** along with *p*-dithiane **1** and the tetrathia macrocycle **3**, both of the latter being formed by intrachain cyclization. The absence of **2** was reasonably rationalized by the prohibitive torsional ring strain of the cyclononane structure.[5] Analysis of the structure with CPK space-filling models reveals that the most stable conformation of **2** requires nearly completely eclipsed conformations of the ethylene bridges.

However, when we reacted the sodium dimercaptide of 3-thiapentane-1,5-dithiol with ethylene chloride in ethanol media below 5 °C, the desired product **2** was isolated in 0.04% yield from a preparative scale reaction. This low yield was not

Scheme I

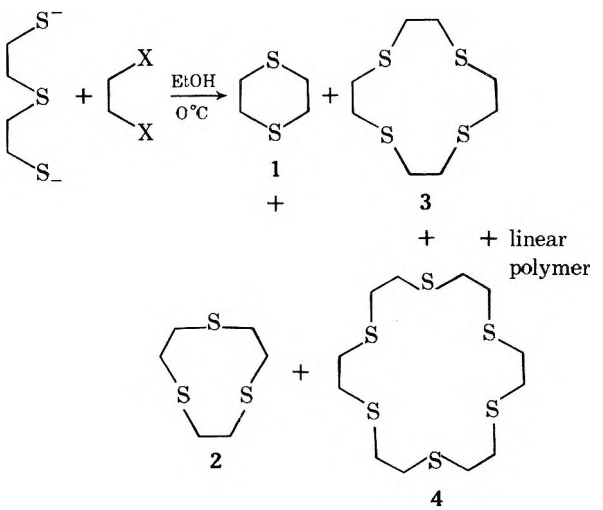

Table I. Product Yields and Direct vs. Intrachain Cyclization Ratios

Leaving group X	Yield % product[a] 1	2	3	4	Ratio (1 + 3/2 + 4)
Br	14.83	0	3.09	2.42	7.46
Cl	7.92	Trace	0.88	4.31	2.05

[a] Based on direct addition of 0.5 M ethylene halide–ethanol solution to 0.5 M 3-thiapentane-1,5-dimercaptide–ethanol solution under nitrogen. Reactants maintained below 5 °C for reaction duration; column chromatographic isolation.[1]

conveniently improved by use of high dilution conditions, which were investigated over a 50-fold dilution range.

The change in reaction course from a slight modification of reactants and conditions is consistent with our earlier observations[1] that leaving group, solvent polarity, and temperature could have a critical effect on intrachain cyclization, by which 1 and 3 arise, in competition with direct cyclization leading to the intended products 2 and 4. The results in Table I illustrate the effect of leaving group on cyclization. The intrachain cyclization process is enhanced by better leaving group, by virtue of lower nucleophilicity of the chain-interior thia function relative to the ω-mercaptide function which affords direct cyclization. Thus the lesser polarizability of chloro relative to bromo leaving group could represent the boundary at which the enthalpy of nucleophilic displacement by mercaptide and thia functions, respectively, is sufficiently differentiated as to significantly diminish the difference in total enthalpy for formation of the six- and nine-membered ring systems.

However, two additional observations suggest that formation of 2 might in fact be due to a fortuitous solvation effect of ethanol media at a particular stage in the two-step cyclization process. The reaction of 1,5-dichloro-3-thiapentane with the dimercaptide of ethanedithiol should give rise to the same intermediate, and therefore 2, as could be postulated in the present experimental design. As previously noted, 2 was not observed from these reactants in butanol media,[1] nor when subsequently investigated in ethanol media. Secondly, the use of less polar butanol media was found in all previous cases to inhibit intrachain cyclization and enhance direct cyclization relative to linear polymerization with better leaving groups than chloride. This observation also held true when chloride was displaced from 1,11-dichloro-3,6,9-trithiaundecane by 3-thiapentane-1,5-dimercaptide to yield macrocycle 4.[1] Thus the results in Table I are anomalous with respect to the usual solvent effect.

Experimental Section

General. Nuclear magnetic resonance spectra were obtained on a Varian Associates T-60 NMR, Me_4Si as internal reference. Infrared spectra were recorded on a Perkin-Elmer 283 infrared spectrometer. Molecular weights were determined with a Hitachi Perkin-Elmer 115 vapor pressure osmometer. Column chromatography was performed on Baker's Analyzed silica gel (60–200 mesh) and HPL chromatography was carried out with a Waters Associates 660 solvent programmable chromatograph. Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. All other general experimental details were as reported earlier.[1]

1,4,7-Trithiacyclononane (2). To a sodium ethoxide solution generated and maintained under a nitrogen atmosphere by dissolving sodium (8.0 mol) in 4 L of ethanol was added all at once 605.2 g (3.93 mol) of 3-thiapentane-1,5-dithiol.[1] The solution was allowed to equilibrate for 1 h, then cooled and maintained below 5 °C for the duration of the reaction. To the mercaptide solution was added 385.1 g (3.93 mol) of ethylene chloride in dropwise fashion. After 3 days of efficient stirring, the reaction mixture was filtered cold and filtrate concentrated. The filter cake was air dried, powdered, loosely packed in a 8 × 30 cm column, and leached by elution of 5 L of hexane–ethyl acetate, 80:20 volume ratio solvent. The leaching concentrates and original reaction filtrate concentrates were combined as a 1-L solution of methylene chloride, washed with two 500-mL portions of 5% sodium hydroxide, dried with sodium sulfate, and reconcentrated to yield 87.5 g of white solid residue. TLC analysis by comparison to authentic samples on silica gel H with 4% ethyl acetate–hexane revealed in descending order *p*-dithiane 1, traces of unreacted dithiol, substantial quantities of 1,4,7,10,13,16-hexathiacyclooctadecane (4), and finally higher polymers. The 1,4,7,10-tetrathiacyclododecane (3) is highly insoluble and may be leached directly from the filter cake as previously described.[1] Only at very high plate loading could an additional component be detected immediately following unreacted dithiol. The 87.5 g of residue was dispersed on 400 g of sand and loaded onto a 6 × 70 cm silica gel column. Elution with hexane yielded all of 1 and a portion of the unreacted dithiol in the first 2.6 L of eluent. The first traces of 4 did not appear until an additional 2.8 L of hexane was eluted. This void fraction was concentrated and yielded 0.630 g of oil. TLC analysis established the oil to be only unreacted dithiol and the presumed trithia macrocycle 2. No additional 2 in the presence of 4 could be detected in further column aliquots. The 0.630 g oil residue was taken up in 150 mL of hexane and filtered hot with three consecutive 0.3-g portions of charcoal. Cooling overnight at −20 °C deposited 283 mg (0.04%) of fine white crystals, mp 81–82 °C.[6] Further recrystallizations from hexane had no effect on the melting point. The data obtained are consistent with the structure assigned 2: NMR ($CDCl_3$) s, δ 3.08 (500-Hz sweep width) and in expansion mode m, $J \sim 0.2$ Hz (25-Hz sweep width); mol wt (in benzene), calcd 180.35, found 178 ± 1; IR (KBr) (s) 2922, (s) 2896, (w) 2805, (s) 1455, (m) 1408, (s) 1414, (s) 1420, (m) 1295, (s) 1283, (w) 1183, (s) 1135, (w) 1125, (m) 920, (s) 875, (m) 837, (s) 822, (w) 669, (w) 617, (w) 410.

Anal. Calcd for $C_6H_{12}S_3$: C, 39.95; H, 6.71; S, 53.33. Found: C, 39.60; H, 6.75; S, 53.55.

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Registry No.—1, 505-29-3; 2, 6573-11-1; 3, 25423-56-7; 4, 296-41-3; 3-thiapentane-1,5-dithiol, 3570-55-6; ethylene chloride, 107-06-2; ethylene bromide, 106-93-4.

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Convenient and General Method for Aliphatic and Aromatic Selenonester and N-Mono- and N,N-Disubstituted Selenoamide Synthesis

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Received October 12, 1976

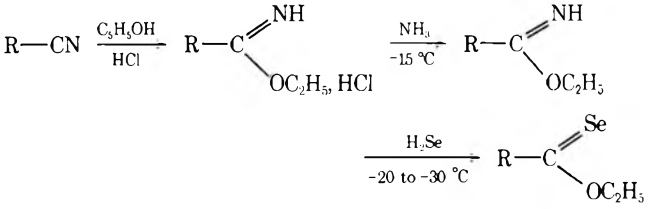
Selenonesters have been prepared by the treatment of arylethynylselenoate salts with alcohols,[1] or by addition of hydrogen selenide to imidoester or its hydrochloride,[2,3] or a less direct method.[4] These preparations are either not general, or require restrictive conditions or, in some cases, reagents that

Table I. Aliphatic and Aromatic Selenonesters R-CSeOC$_2$H$_5$

Registry no.		R	Bp, °C	Yield, %
62448-73-1	1	CH_3[a]	129	26
62448-74-2	2	C_2H_5[a]	147	34
62448-75-3	3	$CH_3CH_2CH_2$[a]	46[10]	46
62448-76-4	4	$(CH_3)_2CH$[a]	41[8]	48
62448-77-5	5	$CH_3(CH_2)_3$[a]	60[9]	57
62448-78-6	6	$CH_3(CH_2)_4$[a]	66[10]	60
57444-31-2	7	$C_6H_5CH_2$	105[2]	80
57701-22-1	8	C_6H_5	106[9]	86
62448-79-7	9	p-$CH_3C_6H_4$[a]	105[8]	90

[a] New compounds.

are not readily available. We wish to describe a method for the preparation of aliphatic and aromatic selenonesters via the imidoesters, which, in turn, are conveniently prepared from addition of ethanol to different nitriles.[5]



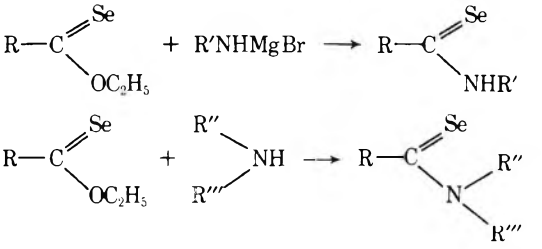
Initially, aliphatic and aromatic nitriles were converted to their imidoester salts by treatment with 2 equiv of ethanol and anhydrous hydrochloric acid in diethyl ether at 0 °C. After 5 days in refrigeration, simple treatment of these imidoester salts with anhydrous ammonia gave the desired imidoester bases. The addition of hydrogen selenide to these later compounds at −20 to −30 °C in the presence of pyridine–triethylamine affords respective selenonesters.

The IR spectra of the selenonesters (Table I) showed a selenocarbonyl absorption band at 1250–1220 cm^{-1}. The NMR spectra of all aliphatic and aromatic selenonesters prepared (Table I) showed a shift of the $-CH_2-$ of the ethoxy group at 4.5–4.7 ppm.

The overall advantage of the synthesis of the selenonesters described is that the procedure is straightforward and employs readily available starting materials.

The aliphatic selenonesters are yellow liquids; the aromatic esters are deep-red oils. The aromatic selenonesters are more stable than aliphatic ones; however, after 2 or 3 days, they begin to deposit elemental selenium, but in refrigeration there is no change after a few months.

The availability of the selenonesters has permitted the preparation of a series of selenoamides, which are little-studied compounds. A few examples have been prepared by the reaction of phosphorus pentaselenide with tertiary amines such as *N*,*N*-dimethylbenzylamine.[6] Yalpani and Malek-Yazdi have been able to obtain mono- and disubstituted selenoamides by reacting 5-unsubstituted 1,2,3-selenadiazoles with various amines.[7] We now wish to describe the synthesis of selenoamides from the corresponding selenonesters. Aliphatic selenonesters with various primary alkylamide magnesium bromides in diethyl ether give N-monosubstituted selenoamides, whereas direct addition of secondary amines to selenonesters after 15 days afford N,N-disubstituted selenoamides. With primary amines, formation of the imido ester and H_2Se was a significant side reaction.

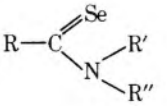


R = alkyl; R′ = alkyl, aryl; R″, R‴ = alkyl

The structures were determined by elemental analyses and spectroscopic data. The NMR spectra of all substituted selenoamides prepared (Table II) showed $-CH_2N$ proton signal at 3.60–4.70, $-CH_2C{=}Se$ proton signal at 2.28–3.72, and $-CHC{=}Se$ proton signal at 3.04–3.30.

The N-mono- and N,N-disubstituted alkyl aliphatic selenoamides are liquids and the N-monosubstituted aromatic ones are solids. Substituted selenoamides are more stable than

Table II. Substituted Selenoamides



Registry no.		R	R′	R″	Bp, °C (mm) (mp, °C)	Yield, %
62448-80-0	10	CH_3	p-BrC_6H_4	H[a]	(156)	82
62448-81-1	11	CH_3	p-$CH_3C_6H_4$	H[a]	(132)	85
62448-82-2	12	CH_3CH_2	p-$C_2H_5OC_6H_4$	H[a]	(93)	74
62448-83-3	13	CH_3CH_2	CH_3CH_2	CH_3CH_2	122 (7)	70
62448-84-4	14	$(CH_3)_2CH$	p-$CH_3C_6H_4$	H[a]	(99)	83
62448-85-5	15	$(CH_3)_2CH$	p-$CH_3OC_6H_4$	H[a]	(82)	75
62448-86-6	16	$(CH_3)_2CH$	CH_3CH_2	CH_3CH_2[a]	110–112 (8)	30
62448-87-7	17	$CH_3CH_2CH_2$	p-$CH_3OC_6H_4$	H[a]	(113)	80
62448-88-8	18	$CH_3CH_2CH_2$	p-$C_2H_5OC_6H_4$	H[a]	(84)	87
62460-39-8	19	$CH_3CH_2CH_2$	p-BrC_6H_4	H[a]	(109)	78
62448-89-9	20	$CH_3(CH_2)_3$	p-BrC_6H_4	H[a]	(104)	92
62448-90-2	21	$CH_3(CH_2)_3$	p-$C_2H_5OC_6H_4$	H[a]	(87)	78
62448-91-3	22	$CH_3(CH_2)_3$	$(CH_3)_2CH(CH_2)_2$	H[a]	150 (8)	65
62448-92-4	23	$CH_2(CH_2)_3$	CH_3CH_2	CH_3CH_2[a]	132 (8)	60
62448-93-5	24	$(CH_3)_2CH(CH_2)_2$	p-BrC_6H_4	H[a]	(112)	70
62448-94-6	25	$(CH_3)_2CH(CH_2)_2$	p-$CH_3OC_6H_4$	H[a]	(86)	86

[a] New compounds.

corresponding selenonesters and in refrigeration there is no change after 6 months.

Experimental Section

General. Proton magnetic resonance spectra were determined with a Varian T-60 spectrometer using tetramethylsilane as an internal standard. A Beckman IR-20A spectrophotometer was used for IR spectra. Microanalyses were performed by CNRS (Service Central de Microanalyse, 94 Thiais, France) and Dornis U. Kolbe, Hohenweg 17, West Germany.

Aliphatic and Aromatic Imido Esters. The above-mentioned compounds were obtained by the method of Reynaud and Moreau.[5]

General Procedure for Synthesis of Aliphatic and Aromatic Selenonesters. The following description for the conversion of imido esters to selenonesters (Table I, **1**) may be considered general. A solution of 8.7 g (0.1 mol) of ethyl acetimidate, 30 mL of dry pyridine, and 10 mL of triethylamine in a 100-mL round bottom flask is cooled to −30 °C. About 25 g (0.3 mol) of anhydrous hydrogen selenide (hydrogen selenide is generated from aluminum selenide by addition of water and passed through the calcium chloride tube) is passed through the solution in 30 min at −30 to −20 °C. The flask temperature is allowed to come to 0 °C and immediately poured into 200 mL of ice water. The mixture is extracted with three 50-mL portions of ether. The extracts are combined and treated with diluted hydrochloric acid and washed with water. The ether solution is dried over anhydrous sodium sulfate, concentrated, and distilled to afford 4 g of *O*-ethyl selenoacetate (26%), bp 129 °C.

General Method for Synthesis of N-Monoalkyl or Aryl Aliphatic Selenoamides. The following preparation of *N*-*p*-bromophenylselenoacetamide (Table II, **10**) will serve as general procedure for the preparation of the above-mentioned selenoamides. To 0.96 g (0.04 mol) of magnesium turnings covered with 20 mL of anhydrous diethyl ether in the usual Grignard apparatus, a solution of 4.36 g (0.04 mol) of ethyl bromide in diethyl ether was added dropwise. A solution of 6.88 g (0.04 mol) of *p*-bromoaniline in anhydrous diethyl ether was added dropwise during 30 min, at such a rate that the mixture refluxed. To the resulting suspension, a solution of 3.02 g (0.02 mol) of *O*-ethyl selenoacetate in diethyl ether was added at once. After the addition was completed, the mixture was refluxed 1 h, cooled, and poured into 400 mL of ice water. The reaction mixture was treated with dilute hydrochloric acid. The mixture was extracted with three 50-mL portions of ether. The combined ether phases were washed with water and dried over anhydrous sodium sulfate. Evaporation of the solvent leaves a solid which after recrystallization from benzene–petroleum ether gave 4.54 g (82%) of **10**, mp 156 °C. The solid-substituted selenoamides listed in Table II were recrystallized from benzene–petroleum ether to afford analytically pure products.

The N-monoalkyl-substituted aliphatic selenoamides were prepared in dipropyl ether.

General Procedure for Synthesis of *N,N*-Dialkyl Aliphatic Selenoamides. The following description for the preparation of *N,N*-diethylselenopropionamide (Table II, **13**) may be considered general. To 3.30 g (0.02 mol) of *O*-ethyl selenopropionate, a solution of 2.19 g (0.03 mol) of diethylamine in 5 mL of anhydrous ethanol was added. After 15 days, the alcohol solution was fractionated to give 2.69 g (70%) of **13**, bp 122 °C (7 mmHg).

Registry No.—Ethanimidic acid ethyl ester, 1000-84-6; propanimidic acid ethyl ester, 1070-17-3; butanimidic acid ethyl ester, 998-97-0; isopropylimidic acid ethyl ester, 1069-52-9; pentanimidic acid ethyl ester, 999-09-7; hexanimidic acid ethyl ester, 1001-25-8; benzenethanimidic acid ethyl ester, 4971-77-1; benzenecarboximidic acid ethyl ester, 825-60-5; benzenecarboximidic acid 4-methyl ethyl ester, 827-71-4; H_2Se, 7783-07-5; *O*-ethyl selenoisohexanoic ester, 62448-97-9; magnesium, bromo(4-bromobenzenaminato), 58655-99-5; magnesium, bromo(4-methylbenzenaminato), 58655-94-0; magnesium, bromo(4-ethoxybenzenaminato), 62448-95-7; diethylamine, 109-89-7; magnesium, bromo(4-methoxybenzenaminato), 58655-97-3; magnesium, bromo(isopentanaminato), 62448-96-8.

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Reaction of Methylmagnesium Iodide with Methyl Propiolate. A Correction

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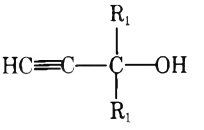
Rhinesmith[1] has recently reported the reaction of methylmagnesium iodide or ethylmagnesium bromide with methyl or ethyl propiolate. Beside the expected acetylenic carbinol **1** (R_1 = CH_3 or C_2H_5) resulting from the addition of 2 mol of Grignard reagent to the ester function, a higher boiling, labile compound was found to which the structure of a doubly unsaturated epoxy ester **2** (R_1 = CH_3 or C_2H_5; R_2 = CH_3 or C_2H_5)



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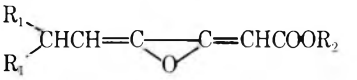
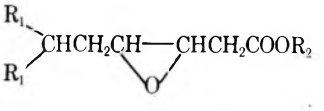


2

was assigned based on a combustion analysis, the uptake of 2 mol of hydrogen on catalytic hydrogenation, the IR spectrum, and negative tests for the functional groups –HC=O, >C=O, and –C≡CH. In each case these compounds presumed to have structure **2** were reduced to the alleged saturated β,γ-epoxy esters **3**, which on treatment with methanolic



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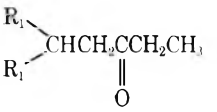

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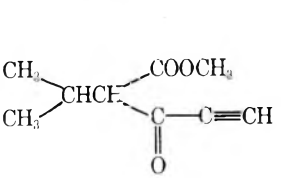
potassium hydroxide gave the corresponding ethyl ketones **4** (R_1 = CH_3 or C_2H_5) identified with authentic material. The isolation of a monoepoxide of a 1,2,3-triene such as **2** from a Grignard reaction is unexpected in view of the known instability of epoxides of simple allenes.[2] We therefore repeated the reaction of excess methylmagnesium iodide with methyl propiolate under the conditions described by Rhinesmith[1] while slightly modifying the workup to minimize secondary reactions. VPC analysis of the crude product showed the presence of 3-methyl-1-butyn-3-ol (**1**, R_1 = CH_3, 20–50% of the volatile material), two further major components (20–30% each), and several minor components (less than 5% each) which were not investigated. Distillation, column chromatography, and preparative VPC led to the isolation of methyl 2-isopropyl-3-oxo-4-pentynoate (**5**) and methyl (*Z*)-2-ethyl-



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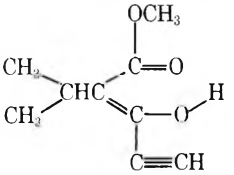


6

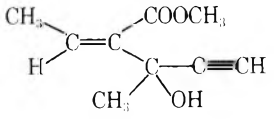
idene-3-hydroxy-3-methyl-4-pentynoate (**7**) besides the known[3] alcohol **1**.

The structure of **5** follows from spectroscopic evidence. The IR spectrum shows the presence of an acetylenic proton at 3305 cm^{-1}, a peak of medium intensity for a conjugated triple bond at 2095 cm^{-1}, and two carbonyl absorptions at 1745 and 1685 cm^{-1}. The ^1H NMR spectrum confirms the presence of an ester methyl group, of an acetylenic proton, and of an iso-

propyl group adjacent to a proton at δ 3.35 ppm which is slowly exchanged by added D_2O (H at C-2). In addition the spectrum displays peaks ascribed to the enol **6** which is present to the extent of ca. 8% in $CDCl_3$ or Me_2SO-d_6. The ^{13}C NMR spectrum and the UV spectrum are fully consistent with the proposed structure (see Experimental Section). The mass spectrum displays the molecular ion at *m/e* 168 and a base peak at *m/e* 126 due to a McLafferty rearrangement. Additional support for the β-keto ester function comes from a positive ferric chloride test. With the structure of β-keto ester **5** proven, it is now also clear why 2-methyl-4-hexanone (**4**, $R_1 = CH_3$) was found by Rhinesmith[1] on catalytic hydrogenation of the reaction product followed by decarboxylation of the resulting saturated β-keto ester with methanolic potassium hydroxide.

The IR spectrum of **7** shows a hydroxy group (3450 cm^{-1}, broad), a proton bonded to a triple bond (3310 cm^{-1}), and an unsaturated ester at 1720 cm^{-1}. The ^1H NMR spectrum confirms the presence of an ester methyl group, of a hydroxy and an acetylenic proton, of a methyl group at a quaternary carbon, and a methyl group coupled (J = 7 Hz) with a vinylic proton at δ 6.55 ppm. Additional evidence for the structure of **7** comes from the broad band and off-resonance decoupled ^{13}C NMR spectra which display the ester carbonyl carbon, two vinylic and two acetylenic carbon atoms, a fully substituted carbon bearing an oxygen function, and three methyl carbon atoms. The UV spectrum is consistent with the structure of an α-substituted crotonic ester. The mass spectrum shows a very weak molecular ion (*m/e* 168, 0.5%) and a prominent peak for loss of CH_3 which is also found with the acetylenic alcohol **1**. The *Z* configuration of the double bond follows from the ^1H NMR spectrum in the presence of $Eu(fod)_3$.[4] The europium complexes at the hydroxy group alone, and the large shift induced at the vinyl proton indicates a cis relationship between this proton and the carbinol function.

When the addition product of methylmagnesium iodide with methyl propiolate is hydrolyzed with ammonium chloride instead of ammonium sulfate, the product mixture is even more complex. Besides **1**, **5**, and **7**, (*E*)-1-chloro-3-methyl-



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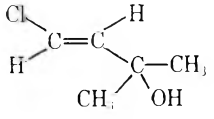
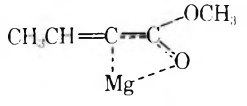


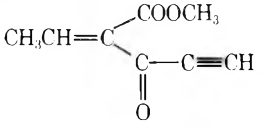
8

1-buten-3-ol (**8**, ca. 5% of the volatile products) was isolated and identified by spectroscopic methods and comparison with material obtained by reduction of 1-chloro-3-methyl-1-butyn-3-ol with lithium aluminum hydride.[5]

The formation of both compounds **5** and **7** can be explained by 1,4-addition of methylmagnesium iodide to methyl propiolate to yield the vinyl Grignard compound **9**, which then



9



10

adds to the ester function of another molecule of methyl propiolate. The resulting unsaturated keto ester **10** reacts with excess methylmagnesium iodide either by a 1,2-addition to the keto carbonyl function to give alcohol **7**, or by a 1,4-addition to the ethylenic carbonyl function leading to β-keto ester **5**.[6]

Experimental Section

General. IR spectra were measured on a Perkin-Elmer 177 spectrometer. NMR spectra were obtained on a Bruker WH-90 FT spectrometer at 90 (^1H NMR) or 22.63 MHz (^{13}C NMR) using tetramethylsilane as an internal standard. UV spectra were recorded on a Beckman DK 2 spectrometer, and mass spectra on a AEI-MS 30 at 70 eV. VPC analyses and separations were carried out on a Perkin-Elmer 3920 chromatograph using glass columns packed with SE-52 or Carbowax 20M on Chromosorb DMCS. Combustion microanalyses were carried out by Mr. E. Thommen.

Grignard Reaction. A solution of 14.2 g (100 mmol) of freshly distilled methyl iodide in ethyl ether (40 mL) was added dropwise with stirring to 2.43 g (100 mmol) of magnesium under nitrogen. After refluxing for 30 min, the reaction mixture still contained some unreacted magnesium. It was cooled to −5 °C in an ice/salt mixture, and a solution of 1.68 g (20 mmol) of methyl propiolate (Fluka, freshly distilled) in ethyl ether (15 mL) added at such a rate that the temperature remained between −5 and 0 °C. The reaction mixture was stirred at 0 °C for an additional 15 min, then poured into a large excess of cooled, saturated aqueous ammonium sulfate. The mixture was extracted twice with ethyl ether, and the extractions were washed with aqueous sodium chloride, stabilized by the addition of a trace of hydroquinone, and dried over magnesium sulfate. The solution was analyzed by VPC, then concentrated on a vacuum rotary evaporator and distilled in a Kugelrohr at 120 °C (12 mm) to give 0.49 g (29%) of a yellowish oil. Redistillation led to the separation of **1** and low-boiling impurities. The remaining oil was chromatographed on silica gel with petroleum ether/ethyl ether. Fractions rich either in **5** or in **7** were obtained and purified by preparative VPC.

3-Methyl-1-butyn-3-ol (1)[3] was a colorless oil: bp 130 °C (Kugelrohr); IR (CCl_4) 3620 (OH), 3315 (≡CH), 2120 w (C≡C), 953, 882 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.54 (s, 6 H, CH_3), 1.9 (s, 1 H, OH), 2.42 (s, 1 H, ≡CH); MS *m/e* 83 ($M^- - 1$, 6.5%), 69 ($M^+ - CH_3$, 100).

Methyl 2-isopropyl-3-oxo-4-pentynoate (5) was a slightly yellow oil: bp 120 °C (12 mm) (Kugelrohr); IR (CCl_4) 3305 (≡CH), 2095 m (C≡C), 1745, 1685 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.01 (d, J = 7 Hz, 6 H, CH_3), 1.6 (m, 1 H, CH), 3.34 (s, 1 H, ≡CH), 3.35 (d, J = 8 Hz, 1 H, slowly exchangeable with D_2O in Me_2SO-d_6, H at C-2), 3.75 (s, 3 H, OCH_3), and peaks for the enol **6** (8 ± 2%) at δ 1.17 (d), 3.46 (s), 3.82 (s), 11.7 (in Me_2SO-d_6, OH); ^{13}C NMR ($CDCl_3$) δ 20.2 (q, CH_3), 20.4 (q, CH_3), 28.7 (d, CH), 52.4 (q, CH_3O), 67.8 (d, CH-2), 80.9 (d, ≡CH), 81.8 (s, ≡C–), 168.4 (s, COO), 181.9 (s, CO); MS *m/e* 168 (M^+, 4), 153 (11), 137 (33), 126 (100); UV (cyclohexane) 210 nm (log ε 3.58), 276 (3.06).

Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.11; H, 7.36.

Methyl (*Z*)-2-ethylidene-3-hydroxy-3-methyl-4-pentynoate (7) was a colorless oil: bp 120 °C (12 mm) (Kugelrohr); IR (CCl_4) 3610, 3450 b (OH), 3310 (≡CH), 1720 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.71 (s, 3 H, CH_3), 1.94 (d, J = 7 Hz, 3 H, CH_3), 2.55 (s, 1 H, ≡CH), 3.85 (s, 3 H, OCH_3), 3.91 (s, 1 H, OH), 6.55 (q, 1 H, =CH). Induced shift by $Eu(fod)_3$[4] calculated from eight measurements in the range of 0.05–0.6 molar ratio, substrate 0.15 M in $CDCl_3$, gradient G (ppm) OH (29), CH_3CO (7.8), =CH (5.1), ≡CH (2.6), $=CCH_3$ (2.0), OCH_3 (1.5). ^{13}C NMR ($CDCl_3$) δ 15.4 (q, CH_3), 29.4 (q, CH_3), 51.6 (q, CH_3O), 68.8 (s, CO), 72.6 (d, ≡CH), 86.2 (s, ≡C). 133.5 (d, =CH), 136.6 (s, =C), 168.4 (s, COO); MS *m/e* 168 (M^+, 0.5), 153 (48), 121 (100); UV (cyclohexane) 214 nm (log ε 3.68).

Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.33; H, 7.32.

When the Grignard reaction mixture was hydrolyzed with aqueous ammonium chloride, **(*E*)-1-chloro-3-methyl-1-buten-3-ol (8)** was isolated by distillation and preparative VPC: colorless oil; bp 60 °C (12 mm) (Kugelrohr); IR (CCl_4) 3615, 3400 b (OH), 3085 (=CH), 1624 (C=C), 932 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (s, 6 H, CH_3), 1.50 (s, 1 H, OH), 6.05 and 6.27 (AB, J = 13.5 Hz, 1 H each, =CH); MS *m/e* 107 ($M^+ - CH_3$, 31), 105 ($M^+ - CH_3$, 100), 85 ($M^+ - Cl$, 65).

Independent Synthesis of 8. A suspension of 0.21 g (5.5 mmol) of lithium aluminum hydride in ethyl ether (20 mL) was added dropwise with stirring to 0.62 g (5.2 mmol) of 1-chloro-3-methyl-1-butyn-3-ol[5] in ethyl ether (20 mL) at 0 °C under nitrogen. After 3 h at 0 °C, 1 mL of 1 N NaOH was added drop by drop, the resulting crystalline precipitate filtered off, and the filtrate distilled to give 0.53 g (84%) of a colorless oil, bp 92–96 °C (100 mm), identical (IR, NMR, MS, VPC) with the material obtained above.

Anal. Calcd for C_5H_9OCl: C, 49.80; H, 7.52; Cl, 29.40. Found: C, 49.89; H, 7.72; Cl, 29.06.

Acknowledgment is made to Professor P. W. Schiess, who suggested the problem, and Dr. U. Séquin for helpful advice. We thank also the CIBA-GEIGY AG for financial support.

Registry No.—**1** ($R_1 = CH_3$), 115-19-5; **5**, 62493-29-2; **6**, 62493-28-1; **7**, 62493-30-5; **8**, 62493-31-6; methyl propiolate, 922-67-8; 1-

chloro-3-methyl-1-butyn-3-ol, 29552-15-6; methylmagnesium iodide, 917-64-6.

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(4) Eu(fod)$_3$ = tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octadionato)-europium(III). For a general account on lanthanide shift reagents see A. F. Cockerill, G. L. O. Davies, R. C. Harden, and D. M. Rackham, *Chem. Rev.*, **73**, 553 (1973).
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(6) The mode of formation of **8** is not clear at the moment. A blank reaction of alcohol **1** with excess methylmagnesium iodide gave no trace (<0.1%) of **8** upon workup with ammonium chloride.

Lithiation of 4,4-Dimethyl-2-(2-thienyl)-2-oxazoline

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Numerous aromatic substituents with ortho-directing metalation abilities have been reported and their synthetic potential has been discussed.[1] The knowledge of the relative directing effect of these groups has become increasingly important for synthetic planning. For the benzene ring, a relative order of ortho-directing strength for some of these substituents has been recently established.[2] In heteroaromatic compounds, the ortho-directing group competes with the heteroatom in the aromatic ring for the site of metalation. Slocum and co-workers have recently reported[3] that the lithiation of thiophene substituted at the 2 position with strong ortho directors, such as carboxamides, sulfonamides, and dimethylaminomethyl groups, leads to metalation at the 5 position (α-lithiation) rather than the 3 position (ortho lithiation) of the thiophene nucleous. Kauffman and co-workers, on the other hand, observed[4] that the lithiation of 2-(2-pyridyl)-thiophene leads to mixtures of 3- and 5-lithiothiophene derivatives and that the product ratio is greatly affected by the solvent of the lithiation reaction. We wish now to report that the metalation of 2-(2-thienyl)-2-oxazoline **1** in ether proceeds predominantly ortho to the oxazoline group.

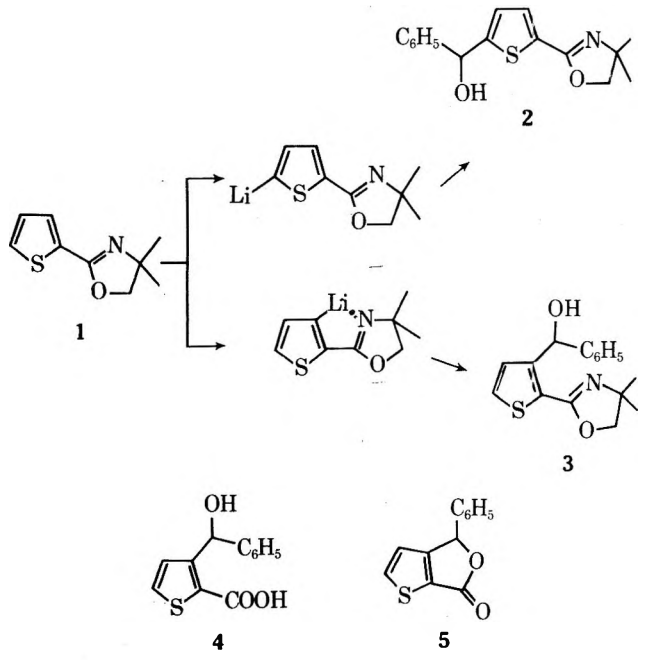

Table I

Lithiating reagent	Solvent	Temp, °C	Metalation time, h	Yield, %[b] Isomer 2	Isomer 3
n-BuLi	THF	−70	1	55	36
sec-BuLi	Ether	−70	1	2.3	81.3
n-BuLi	Ether	−70–0	0.75[a]	4.1	91

[a] 0.25 h at −70 °C and 0.5 h at 0 °C. [b] Based on the starting oxazoline **1**. Recovered oxazoline **1** constitutes the balance of the material.

This investigation of the metalation of **1** was prompted by our need for an efficient synthesis of 3-substituted thiophene-2-carboxylic acids and was based on the well-known ortho-directing ability of the oxazoline[5] group and the easy accessibility of **1**.[6] Lithiation of **1** with *n*-BuLi in ether or THF followed by condensation with benzaldehyde gave mixtures of products **2** and **3**, with the desired isomer **3** being clearly favored in ether. The metalation results are summarized in Table I. The structural assignments of the two isomers were based on their NMR spectra and were also verified by hydrolysis[6] of **3** to the acid **4** and conversion to the lactone **5**.

In synopsis, the lithiation of 2-(2-thienyl)-2-oxazoline **1** provides an efficient route to 2,3-disubstituted thiophenes. Our results, together with those of Kauffman[4] and Slocum,[3] seem to establish a relative order of ortho-directing substituents in thiophene as follows: oxazoline > pyridyl > sulfonimides, carboxamides, and dimethylaminomethyl.

Experimental Section

4,4-Dimethyl-2-(2-thienyl)-2-oxazoline (1). To a solution of 2-thiophenecarboxyl chloride (100 g, 0.68 mol) in methylene chloride (200 mL) a solution of 2-amino-2-methyl-1-propanol (121.6 g, 1.36 mol) in methylene chloride (500 mL) was added dropwise while maintaining the temperature below 20 °C. The mixture was stirred at room temperature for 2 h and washed with water, and the organic layer was dried over $MgSO_4$ and evaporated. The residue was suspended in benzene (600 mL) and thionyl chloride (270.7 g, 2.28 mol) was added dropwise with stirring while maintaining the temperature below 30 °C. The stirring continued overnight, the benzene was evaporated at aspirator pressure, the residue was dissolved in water, and then the solution was basified with 1 N aqueous NaOH and extracted twice with ether. The ether extracts were dried over $MgSO_4$ and evaporated, and the residue was distilled to give 90 g of oxazoline **1**: bp 71–73 °C (0.1 mm Hg); NMR ($CDCl_3$) δ 7.63 (d of d, 1 H, J = 5 and 2 Hz, 5-thienyl-H), 7.44 (d of d, 1 H, J = 6 and 3 Hz, 3-thienyl-H), 7.05 (d of d, 1 H, J = 5 and 6 Hz, 4-thienyl-H), 4.06 (s, 2 H, $-OCH_2$), 1.35 (s, 6 H, 2× CH_3). Anal. Calcd for $C_9H_{11}NOS$: C, 59.64; H, 6.12; N, 7.73. Found: C, 59.35; H, 6.29; N, 7.92.

Lithiation Procedure. To a solution of 4,4-dimethyl-2-(2-thienyl)-2-oxazoline (**1**) in ether or THF (5 mmol of oxazoline in 20 mL of solvent) the lithiating reagent was added dropwise at −70 °C with stirring under nitrogen. The reaction mixture was stirred at the designated temperature for the designated time, the benzaldehyde (5 mmol) was added, and the mixture was allowed to warm up to room temperature. It was poured into water and extracted with ether. The ether extracts were washed with water, dried over $MgSO_4$, and evaporated. The residue was subjected to preparative thin-layer chromatography (SiO_2, on CH_2Cl_2:EtOAc, 9:1) to give the less polar 2-(3-hydroxyphenylmethyl-2-thienyl)-4,4-dimethyl-2-oxazoline **3** [oil; R_f 0.68; NMR ($CDCl_3$) δ 6.72 (d, 1 H, J = 5.3 Hz, 4-thienyl-H), 6.07 (s, 1 H, PhCH–), 4.01 (s, 2 H, OCH_2), 1.33 (s, 3 H, CH_3), 1.2 (s, 3 H, CH_3). Anal. Calcd for $C_{16}H_{17}NO_2S$: C, 66.87; H, 5.96; N, 4.87. Found: C, 66.51; H, 6.2; N, 5.06] and the polar isomer **2** [mp 121–124 °C; R_f 0.11; NMR ($CDCl_3$) δ 6.84 (d, 1 H, J = 3.5 Hz, 4-thienyl-H), 6 (s, 1 H, PhCH). 4.02 (s, 2 H, OCH_2), 1.27 (s, 6 H, 2× CH_3). Anal. Found: C, 66.05; H, 6.01; N, 5.03].

4-Phenylthieno[2,3-*c*]furan-6(*4H*)-one (5). A mixture of the oxazoline **3** (344 mg, 0.0012 mol) and 3 N aqueous hydrochloric acid was refluxed for 10 min and evaporated under aspirator pressure. The residue was stirred with 40% aqueous NaOH (3.6 mL) at room temperature for 10 min, methanol (3.6 mL) was added, and the mixture was refluxed for 30 min. It was poured into water, acidified with 6 N

aqueous HCl, and extracted with ether; the extract was dried over $MgSO_4$ and evaporated to give crude 3-hydroxyphenylmethylthienyl-2-carboxylic acid (**4**), which was characterized as its methyl ester prepared from **4** by treatment with diazomethane: NMR ($CDCl_3$) δ 7.02 (d, 1 H, J = 5 Hz, 4-thienyl-H), 6.42 (s, 1 H, PhCH), 3.7 (s, 3 H, OCH_3). The crude acid (200 mg) was dissolved in 20 mL of benzene, *N,N*-dicyclohexylcarbodiimide (170 mg) was added, and the mixture was refluxed for 30 min and evaporated. The residue was subjected to preparative thin-layer chromatography (SiO_2, CH_2Cl_2:EtOAc, 9:1) to give 160 mg of the lactone **5** as an oil: IR ($CHCl_3$) 1760 cm^{-1}; NMR ($CDCl_3$) δ 7.86 (d, 1 H, J = 5 Hz, 5-thienyl-H), 7.35 (s, 5 H, Ph), 6.95 (d, 1 H, J = 5 Hz, 4-thienyl-H), 6.31 (s, 1 H, PhCH). Anal. Calcd for $C_{12}H_8O_2S$: C, 66.63; H, 3.73. Found: C, 66.45; H, 4.11.

Acknowledgment. The authors acknowledge the support and advice of Dr. H. Gschwend and thank G. Robertson for analyses, and N. Cahoon, R. Behnke, and B. Warren for spectra.

Registry No.—**1**, 62521-42-0; **2**, 62521-43-1; **3**, 62521-44-2; **4**, 62521-45-3; **4** methyl ester, 62521-46-4; **5**, 62521-47-5; 2-thiophenecarboxyl chloride, 5271-67-0; 2-amino-2-methyl-1-propanol, 124-68-5; benzaldehyde, 100-52-7.

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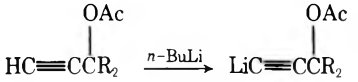
Communications

Preparation of Allenes and Acetylenes from Ethynylalkanol Acetates via Organoboranes

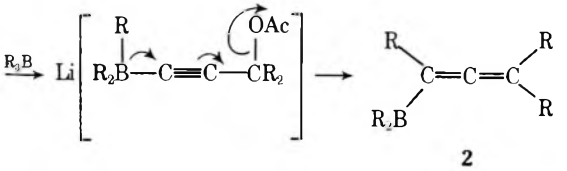
Summary: Sequential treatment of an ethynylalkanol acetate with *n*-butyllithium and a trialkylborane produces an allenic borane, $R_2BRC{=}C{=}CR_2$, which may be protonated to form either an allene, $RHC{=}C{=}CR_2$, or an acetylene, $RC{\equiv}CCHR_2$.

Sir: Allenes have conventionally been prepared from ethynylalkanol acetates through organocopper reagents.[1] However, these organocopper reagents are generally prepared from reactive organometallics which preclude the presence of many functional groups. Allenes may also be prepared from organoboranes by treatment with the lithium salt of propargyl chloride.[2] While the organoboranes can accommodate a wide variety of functional groups,[3] it is not clear that the reaction could be accomplished in the presence of these functional groups. Furthermore, this process is limited by the availability of propargyl chlorides.

We have now found that the use of the more readily available ethynylalkanol acetates[4] provides a general method for making allenic boranes (**2**) and, thus, allenes and acetylenes.



1

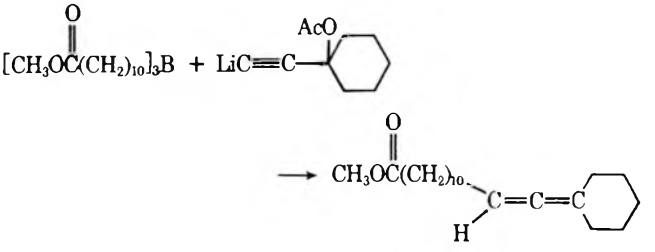


2

Formation of the desired lithium salt (**1**) was accomplished without interference by the acetate group by reaction of the ethynylalkanol acetate with *n*-butyllithium at low temperature (−78 or −120 °C). Addition of a trialkylborane followed by warming to room temperature and then protonation with acetic acid results in the formation of an allene.[2,5,6] The overall sequence results in the transformation of a ketone or aldehyde to an allene.

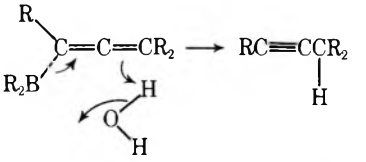
$$R_3B + HC{\equiv}CH + O{=}CR'_2 \rightarrow RHC{=}C{=}CR'_2$$

The reaction is quite general both with respect to the organoborane and the ethynylalkanol acetate (Table I). Slightly better results were usually obtained when the reaction was run at −120 rather than −78 °C. Finally, the reaction is able to accommodate an ester functionality in the organoborane with no difficulty.



3

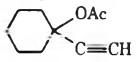
Allenic boranes have the potential of reacting as allylic boranes, which are known to undergo a number of reactions that are unusual for vinyl- or alkylboranes, such as addition to carbonyl compounds or protonation with water.[7] Addition of water to **2** results in the exclusive formation of an acetylene. As with allylic boranes, the product presumably results from protonation with rearrangement via a cyclic process.



The overall transformation results in the reductive alkynylation of a ketone.

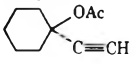
$$R_3B + HC{\equiv}CH + O{=}CR'_2 \rightarrow RC{\equiv}CCR'_2 \quad (H)$$

Table I. The Conversion of Ethynylalkanol Acetates to Allenes

$R_2'C(OAc)C{\equiv}CH$	% yield, $RHC{=}C{=}CR_2'$[a]		
	n-Bu_3B[b]	i-Bu_3B[b]	sec-Bu_3B[b]
$(CH_3)_2C(OAc)C{\equiv}CH$	80	90	76
n-$C_5H_{11}CH(OAc)C{\equiv}CH$	87 (78), 90[c]	76, 92[c]	80, 92[c]
$C_6H_5CH(OAc)C{\equiv}CH$	77, 94[c]	70, 91[c]	82, 90[c]
$C_6H_5CH{=}CHCH(OAc)C{\equiv}CH$	(64)[c]		
$CH_3CH{=}CHCH(OAc)C{\equiv}CH$	87 (72)[c]		
	82	78 (75)	81 (73)

[a] % yield based on acetate by VPC (isolated yields are in parentheses). [b] R_3B. [c] −120 °C, other reactions at −78 °C.

Table II. The Conversion of Ethynylalkynol Acetates to Acetylenes

$R_2'C(OAc)C{\equiv}CH$	R_3B	% yield,[a] $RC{\equiv}CCHR_2'$
n-$C_5H_{11}CH(OAc)C{\equiv}CH$	n-Bu_3B	87 (78)
$C_6H_5CH(OAc)C{\equiv}CH$	n-Bu_3B	91
$C_6H_5CH(OAc)C{\equiv}CH$	sec-Bu_3B	91
$CH_3CH{=}CHCH(OAc)C{\equiv}CH$	n-Bu_3B	(60)
	n-Bu_3B	84 (70)

[a] % yield based on acetate by VPC (isolated yields are in parentheses). All reactions were run at −78 °C.

The reaction is quite general and gives high yields of the acetylene (Table II).

The following procedure for the preparation of methyl cyclohexylidenetetradeca-12,13-dienoate (3) is representative. The trialkylborane was prepared[3a] in a 50-ml flask under nitrogen from 15.5 mmol of borane–methyl sulfide and 50 mmol of methyl 10-undecenoate using 20 mL of tetrahydrofuran, 5 mL of diethyl ether, and 5 mL of pentane as a solvent.[8] A separate, dry 100-mL flask was flushed with nitrogen and charged with 20 mL of THF, 5 mL of ether, 5 mL of pentane, and 15 mmol of 1-ethynylcyclohexanol acetate. The solution was cooled to −120 °C[8] [petroleum ether (30–60 °C)–isopropyl alcohol–acetone (4:1:1)/1N_2]. n-Butyllithium, 15 mmol (9.6 mL of a 1.56 M solution in hexane) was added dropwise followed by the dropwise addition of the organoborane solution. The solution was then warmed from −120 °C to room temperature. The solution became slightly cloudy. After 15 min at room temperature, 3 mL of dry acetic acid was added. The mixture was stirred for 15 min and then neutralized (phenolphthalein) with 3 M sodium hydroxide. The aqueous layer was separated, and the THF dried (K_2CO_3) and removed under vacuum. Pentane (60 mL) was added, followed by 15 mmol of ethanolamine. The solution was warmed briefly and a heavy solid ethanolamine adduct of R_2BOH was removed by filtration. After removal of the pentane, the residue was distilled to give 3.35 g of product (73%): bp 140–145 °C (0.02 mm); IR (neat) 1950 (allene), 1740 cm^{-1} (carbonyl); ^1H NMR (CCl_4, TMS) δ 1.2–2.3 (br m, 30 H), 3.62 (s, 3 H), 4.9 (br m, 1 H). The product contained ~5% isomer resulting from hydroboration at the internal position of methyl 10-undecenoate. No acetylene was detected. Repetition of the reaction at −78 °C resulted in a 61% isolated yield.

The hydrocarbon allenes were conveniently isolated by column chromatography on silica gel or alumina following oxidation of the organoborane by-product. The acetylenes were prepared by substituting water for acetic acid.

This procedure offers a general method for preparing allenic boranes which can be converted to either allenes or acetylenes. Furthermore, the allenic boranes may be extremely versatile intermediates, similar to allylic boranes in their reactions. For example, preliminary experiments have shown that they will add readily to ketones and aldehydes to give homopropargylic alcohols, $RC{\equiv}CCR_2CR'_2OH$.[9] We are continuing to explore these versatile reagents.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

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(4) The ethynylalkanol acetates are readily prepared by the addition of monolithium acetylide to a ketone or aldehyde [M. M. Midland, *J. Org. Chem.*, **40**, 2250 (1975)] followed by acetylation of the propargyl alcohol [H. Rupe, W. Messner, and E. Kambli, *Helv. Chim. Acta*, **11**, 449 (1928)].
(5) We have previously prepared the allenic boranes, **1** (R = n-Bu; R' = C_6H_5, H) [IR 1950 cm^{-1}; NMR δ 6.15 (t, J = 3.0 Hz)] by addition of dilithium trialkylboraacetylides, $(R_3BC{\equiv}CLi)Li$, to aldehydes followed by acetylation (M. M. Midland, the 172nd National Meeting of the American Chemical Society, San Francisco, Aug 29–Sept 3, 1976).
(6) In a few cases up to 10% acetylene was formed.
(7) B. M. Mikhailov, *Organomet. Chem. Rev. A*, 1 (1972).
(8) G. Köbrich and H. Trapp, *Chem. Ber.*, **99**, 680 (1966).
(9) In contrast to our results, Zweifel has found that allenic boranes react with aldehydes to give allenic alcohols.[2]

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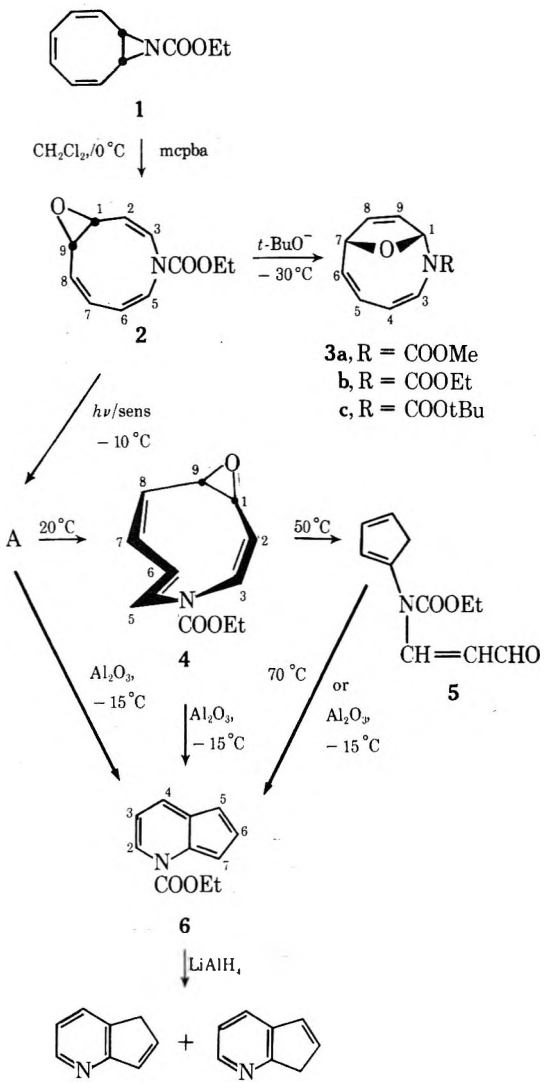
1,2- and 1,4-Oxides of Azonine. A Unique Synthetic Entry into N-Substituted 1-Pyrindines

Summary: The preparation and characterization of three isomeric oxides of azonine, a hitherto unknown C_8H_8XY family of heterobicyclics, and the development of a convenient synthetic scheme for the construction of the interesting, yet rare, N-substituted 1-pyrindine system are described.

Sir: We wish to offer brief description of work which led to (i) the synthesis of three isomeric oxides of azonine, a hitherto unknown C_8H_8XY family of diheterobicyclics and (ii) the development of a general synthetic scheme for the construction of the interesting, but rare,[1] N-substituted 1-pyrindine system depicted as **6**.

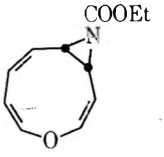
We discovered that reaction between urethane **1** and m-chloroperbenzoic acid (mcpba) leads, in ~55% yield, predominantly[2] to the 1,2-azonine oxide shown as **2**[3] [colorless liquid; ^1H NMR (100 MHz, $CDCl_3$) τ 3.53 (1 H, d, H^3, $J_{3,2}$ = 6.5 Hz), 3.75 (1 H, d, H^5, $J_{5,6}$ = 11.0 Hz), 3.9–4.3 (4 H, m), 5.73 (2 H, q), 6.62 (1 H, m, H^1 or H^9), 6.78 (1 H, m, H^9 or H^1), 8.72 (3 H, t); ^{13}C NMR (25 MHz, $CDCl_3$) 57.64 (C^9 or C^1), 55.76 ppm (C^9 or C^1); λ_{max} (C_6H_{14}) 260 nm (ϵ 2000); m/e 207 (P^+,

28%)]. On contact with strong base, **2** readily isomerizes to the *1,4* counterpart, **3**. Specifically, exposure of **2** to an excess of potassium *tert*-butoxide in THF at −30 °C followed by electrophilic quench with methyl chloroformate at −78 °C yields three structurally related carbamates,[4] **3a**[3] (26%) [colorless



liquid; ^{1}H NMR (100 MHz, benzene-d_6) τ 2.96 (1 H, s, H^1), 3.48 (1 H, d, H^3, $J_{3,4}$ = 11.5 Hz), 4.30 (1 H, dd, H^5, $J_{4,5}$ = 8.0 Hz, $J_{5,6}$ = 11.5 Hz), 4.60 (1 H, dd, H^6, $J_{5,6}$ = 11.5 Hz, $J_{6,7}$ = 6.0 Hz), 4.68 (2 H, s, H^8 + H^9), 4.82 (1 H, dd, H^4, $J_{3,4}$ = 11.5 Hz, $J_{4,5}$ = 8.0 Hz), 4.84 (1 H, d, H^7, $J_{7,6}$ = 6.0 Hz), 6.68 (3 H, s); ^{13}C NMR (20 MHz, $CDCl_3$) 81.79 (C^7), 86.81 ppm (C^1); λ_{max} (C_6H_{14}) 273 (ϵ 7530); *m/e* 193 (P$^+$, 21.8%)], **3b**[5] (18%) (physically and spectroscopically analogous to **3a**), and **3c**[5] (21%) (white crystals; mp 63.5–64.5 °C; spectroscopically analogous to **3a** and **3b**). Exposure to sensitized irradiation (acetone at ca. −10 °C), on the other hand, transforms **2** to an extremely labile substance (A)[6] which, in turn, rearranges to a thermally labile white solid tentatively formulated as **4** [^{1}H NMR (100 MHz, $CDCl_3$, 0 °C) τ 3.24 (1 H, br d, H^3, $J_{3,2}$ = 9.0 Hz), 3.48 (1 H, d, H^7 or H^8, $J_{7,8}$ = 10.0 Hz), 3.66 (1 H, d, H^7 or H^8, $J_{7,8}$ = 10.0 Hz), 3.82 (1 H, br d, H^5 or H^6, $J_{5,6}$ = 14.0 Hz), 4.04 (1 H, d, H^5 or H^6, $J_{5,6}$ = 14.0 Hz), 4.78 (1 H, dd, H^2, $J_{2,3}$ = 9.0 Hz, $J_{2,1}$ = 2.0 Hz), 5.72 (2 H, q), 6.74 (1 H, br s, $W_{1/2}$ ~ 7 Hz, H^9), 7.04 (1 H, dt, H^1, $J_{1,9}$ ~ 3 Hz, $J_{1,2}$ ~ 2 Hz), 8.68 (3 H, t); ^{13}C NMR (20 MHz, $CDCl_3$, −11 °C) 59.13 (C^1 or C^9), 61.94 (C^1 or C^9); λ_{max} (C_6H_{14}) 270 nm (ϵ 2440); *m/e* 207 (P$^+$, 4%)] on warming to 0 °C. The presence in **4** of basically the same [7.1.0] frame as **2** was securely established by catalytic hydrogenation (Rh/C) whereby **2** and **4** were independently converted to the same three-component mixture consisting of an epoxide (IR, mass spectrum, ^{1}H NMR, ^{13}C NMR) (~50% of the mixture), the saturated counterpart of **2** and **4**, and two isomeric alcohols (IR, ^{13}C NMR, mass spectrum). It follows that **2** and **4** must be geometrical isomers, the observation of a large vicinal coupling constant (J = 14 Hz) in the olefinic region of the ^{1}H NMR spectrum of **4** attesting to the presence of a trans double bond in this molecule. Further, the specified location of this key function, i.e., α to nitrogen and not directly linked to the oxirane unit, draws its support primarily from the ready thermal rearrangement of **4** [k (acetone-d_6, 56.2 °C) = 2.38 ± 0.47 × 10^{-4} s^{-1}; $\Delta G^{\ddagger}$ = 24.8 kcal/mol] to **5**.[5,7,8] Besides its key role in the structural elucidation of **4**, **5** is a synthetically useful intermediate cleanly undergoing thermal or alumina-catalyzed cyclodehydration to the hitherto unknown *N*-carbethoxy-1-pyrindine **6**[3,9] [deep purple liquid; ^{1}H NMR (80 MHz, $CDCl_3$) τ 1.80 (1 H, d, H^2, $J_{2,3}$ = 7.0 Hz), 2.25 (1 H, dd, H^4, $J_{4,3}$ = 7.0 Hz, $J_{4,6}$ = 1.5 Hz), 2.75 (1 H, dd, H^6, $J_{5,6}$ = 3.0 Hz, $J_{6,7}$ = 5.0 Hz), 3.20 (1 H, ddd, H^5, $J_{5,6}$ = 3.0 Hz, $J_{5,7}$ = 2.0 Hz, $J_{4,6}$ = 1.5 Hz), 3.46 (1 H, dd, H^7, $J_{6,7}$ = 5.0 Hz, $J_{5,7}$ = 2.0 Hz), 3.50 (1 H, t, H^3, $J_{3,2}$ = $J_{3,4}$ = 7.0 Hz), 5.40 (2 H, q), 8.45 (3 H, t); λ_{max} (C_6H_{14}) 249 nm (ϵ 9900), 326 (6600), 332 (6200), 340 (6900), 357 (3900), 502 sh (1300), 512 sh (1330), 524 (1250, 546 sh (1100), 573 sh (790), 602 (520), 626 sh (260), 662 (110); *m/e* 189 (P$^+$, 5.5%)], a very stable[10] and extensively delocalized (UV) substance.

To conclude it is worth noting that, while the high thermal and chemical instability of photoisomer A precludes the type of direct observation necessary for a firm structural assignment, the close pericyclic association of this substance with isomers **2** and **4** does provide a basis for tentative assignment. Specifically, we propose structure **7** as a mechanistically viable



7

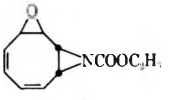
structural possibility for A, i.e., one whose [$_\sigma 2_s$ + $_\pi 2_s$ + $_\pi 4_s$] photogeneration from **2** and [$_\sigma 2_a$ + $_\pi 2_s$ + $_\pi 4_s$] thermal conversion to **4** are fully "allowed" by orbital symmetry. Moreover, the thermal instability of **7** relative to **2** and **4** may reasonably be traced to the well-documented decrease in thermal stability one observes on passing from *cis*-1,2-divinyloxirane (a function present in **2** and **4**) to the aziridine counterpart (a group present in **7**).[11]

Acknowledgment. We thank the National Science Foundation (CHE 76-06462) and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this work. We also express our appreciation to Mr. L. McCandless for the determination of the 100-MHz spectra. The NMR spectrometer employed in the determination of the ^{13}C spectra was purchased with funds provided under NSF instrument grant MPS75-06106.

References and Notes

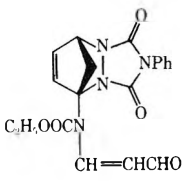
(1) *N*-Methyl-1-pyrindine constitutes the only previously known member of this family: C. B. Reese, *J. Am. Chem. Soc.*, **84**, 3979 (1962). See also A. G. Anderson, Jr., and H. L. Ammon, *Tetrahedron*, **23**, 3601 (1967).

(2) Careful purification of the mixture by column chromatography led to the isolation of small quantities (~2%) of unrearranged product shown (IR, ^{1}H NMR, ^{13}C NMR, mass spectrum) to possess the structure and stereochemistry shown in i.



i

(3) The elemental composition of this substance was established by C. H, and N combustion analysis.
(4) Separation of the mixture into its individual components was accomplished by column chromatography at −15 °C.
(5) This substance was characterized by fully consistent spectroscopic (^{1}H NMR, ^{13}C NMR, IR, UV, mass spectrum) data.
(6) All efforts to purify this substance by column chromatography at −15 °C were frustrated by its tendency to undergo overall dehydration to **6**.
(7) The structure of **5** was further confirmed through low-temperature (−78 °C) cycloadditive coupling with *N*-phenyltriazolinedione to produce a single cycloadduct (mp 70–72 °C dec) whose spectroscopic characteristics (IR, ^{1}H NMR, ^{13}C NMR, mass spectrum) are fully consistent with the structure shown as ii.



ii

(8) For obvious reasons, the primary product generated in the thermolytic ring contraction of **4** must be the symmetrically substituted counterpart of **5** and one which is related to the observed product, **5**, by a simple (1,5) hydrogen shift.
(9) Chemically, the structure of **6** receives unequivocal support from its reductive ($LiAlH_4$) conversion to the previously described [A. G. Anderson, Jr., and H. I. Ammon, *Tetrahedron Lett.*, 2579 (1966)] mixture of 5*H*- and 7*H*-1-pyrindines (^{1}H NMR, UV, IR).
(10) It is significant to note in this connection that compounds **4**, **5**, and A cleanly dehydrate to **6** on passage through alumina at ca. −15 °C.
(11) For pertinent information in this connection see W. Grimme and K. Seel, *Angew. Chem.*, **85**, 514 (1973).
(12) C. Weizmann postdoctoral fellow.

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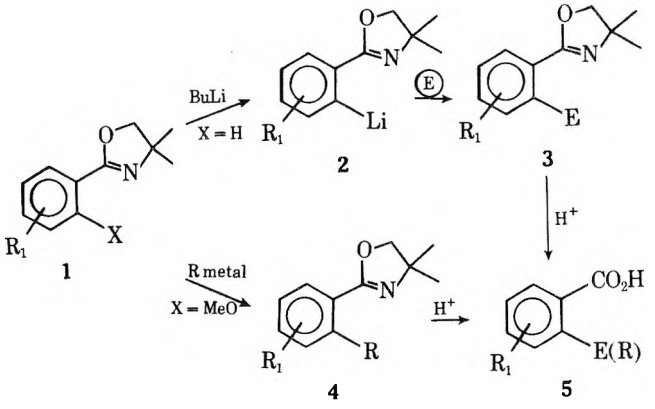
The Displacement of Methoxy by Amino Groups in Aryloxazolines. A Novel Approach to *o*-Amino-, *o*-Alkylamino-, and o-Dialkylaminobenzoic Acids

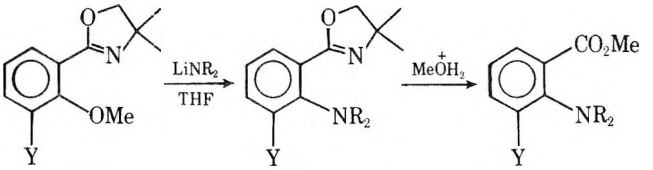
Summary: Treatment of o-(methoxyaryl)oxazolines with lithio amides at room temperature results in a facile methoxy displacement furnishing the o-(aminoaryl)oxazolines.

Sir: The synthetic utility of aryloxazolines as precursors to various substituted benzoic acids has been demonstrated in this and other laboratories.[1,2] Thus, 2-aryloxazolines **1** (X = H) may be readily metalated using *n*-butyllithium furnishing exclusively the *o*-lithio derivative **2** which, when treated with various electrophiles (E), affords the ortho-substituted aryloxazolines **3**. In contrast to the above, 2-(o-methoxyphenyl)oxazolines **1** (X = MeO) were found to react with organometallics (RLi, RMgX) not by metalation, but by direct



substitution of the methoxyl group furnishing the *o*-alkyl or o-aryl derivative **4**. This latter process occurs under unexpectedly mild conditions (−45–25 °C, THF) in high yields. Both electrophilic (**1** → **3**) and nucleophilic (**1** → **4**) routes lead ultimately to elaborated benzoic acids **5**.

We now wish to describe a significant extension to the methoxy-displacement reaction using various lithio salts of primary and secondary amines as well as lithium amide.[3] When lithio amides are treated with either **6a** or **6b** at room temperature (THF, 1–6 h), the *o*-amino substituent is directly introduced in place of the *o*-methoxyl group in fair-to-excellent yields. The only other major product observed is the starting methoxy derivative which was readily separated and recovered by column or preparative layer chromatography. The aminated oxazolines were transformed into their corresponding methyl benzoates **8** by acidic hydrolysis (3 N HCl,



6a, Y = H
b, Y = MeO

7a, Y = H
b, Y = MeO

8a, Y = H
b, Y = MeO

12–24 h, reflux) followed by esterification using methanolic hydrogen chloride.[4] The versatility of this substitution process can be seen by the examples listed in Table I. Most striking are those examples using so called "nonnucleophilic" bases such as LDA and *tert*-butylamine, indicating that there are virtually no steric effects to inhibit methoxy displacement.[5] In fact, the methoxy group displaced in **6b** is one which is flanked by two ortho substituents and seemingly sterically encumbered. The process may be envisioned as a nucleophilic addition followed by elimination of lithium methoxide en-

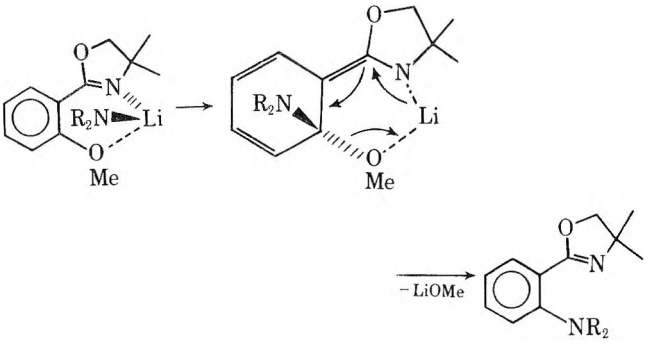


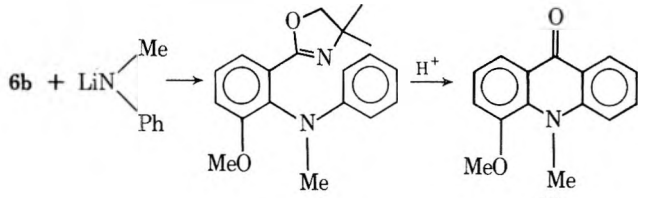
Table I. Amination of 2-(*o*-Methoxyphenyl)oxazolines 6 Leading to *o*-Aminated Benzoic Esters

Oxazoline	$LiNR_2$	% 7[a]	% 8[b]
6a	$LiNH_2$	58	45
6a	$LiNEt_2$	98	*c*
6a	$LiN(i\text{-}Pr)_2$	78	*c*
6a	$LiNH(t\text{-}Bu)$	41	*c*
6b	$LiNH_2$	59	72
6b	$LiNEt_2$	93	40
6b	$LiN(i\text{-}Pr)_2$	78	*c*
6b	$LiNH(t\text{-}Bu)$	63	75[d-f]

[a] Yields are those for pure, isolated material. [b] Obtained by heating **7** in 3 N HCl (15–20 h) followed by treatment with methanolic hydrogen chloride. These conditions have not as yet been optimized. [c] Not attempted. [d] Hydrolysis proceeds with dealkylation producing methyl 2-amino-3-methoxy benzoate. [e] All new compounds gave correct analytical data. [f] The alternative basic hydrolysis to remove the oxazoline should allow the *tert*-butyl group to remain intact (see ref 2).

hanced by strong chelation of the lithium cation. This mode of entry would be relatively free of nonbonded interactions thus allowing bulky amino substituents easy access to the sp^2 carbon at the ortho position. There exists the remote possibility that these displacements as well as those previously reported[2] using alkyl metallics are proceeding via an electron-transfer process and this aspect is currently under investigation.

An interesting example which may have considerable potential in heterocyclic syntheses is given by the reaction of **6b** with the lithio salt of *N*-methylaniline. The adduct **9** was



9 10

formed in 50% yield (+50% recovery of **6b**) which gave, after acidic hydrolysis, the acridone **10** (mp 91 °C, 40%)[6] and the expected uncyclized benzoic acid (25%).

These preliminary results indicate that the amination of o-(methoxyaryl)oxazolines may provide additional methodology to aromatic substitution and further studies in this respect are in progress.

Acknowledgment. The authors wish to express their gratitude to the Army Research Office (Durham) for financial support of this work.

References and Notes

(1) A. I. Meyers and E. D. Mihelich, *J. Org. Chem.*, **40**, 3158 (1975); H. W. Geschwend and A. Hamdam, *ibid.*, **40**, 2008 (1975).
(2) A. I. Meyers and E. D. Mihelich, *J. Am. Chem. Soc.*, **97**, 7383 (1975).
(3) A number of nucleophilic reagents have been surveyed in addition to alkyl and aryl metallics and the results to date indicate that enamines, thiolates, enolates, and other "soft" anions fail to substitute the methoxyl group. The reactions observed with these nucleophiles are those which cleave the methyl–oxygen bond. Details of these reactions will be reported in the full account of this work.
(4) The oxazolines **6a** and **6b** were prepared from the corresponding o-methoxybenzoic acids, thionyl chloride, and 2-amino-2-methylpropanol as described previously [A. I. Meyers et al., *J. Org. Chem.*, **39**, 2787 (1974)].
(5) At this time, the only lithio amine which failed to displace the methoxy group is 2,2,6,6-tetramethylpiperidine.
(6) G. K. Hughes, N. K. Matheson, A. T. Norman, and E. Ritchie [*Aust. J. Sci. Res., Ser. B*, 5, 206 (1952)] report mp 89–91 °C.

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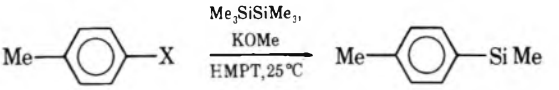
Trimethylsilyl Anions. Direct Synthesis of Trimethylsilylbenzenes

Summary: The reaction of aryl halides with hexamethyldisilane and potassium methoxide (or sodium methoxide or methyllithium) in hexamethylphosphoric triamide (HMPT) affords the corresponding trimethylsilyl-substituted benzene and some reduction product.

Sir: Silyl anions are highly reactive nucleophiles and one-electron-transfer reagents.[1,2] The synthetic utility of trimethylsilylpotassium,[2g,h] -sodium,[2d] and -lithium,[2j] (TMSK, TMSNa, TMSLi, respectively) has increased owing to recently reported convenient methods of in situ generation from the reaction of hexamethyldisilane and potassium methoxide, sodium methoxide, and methyllithium, respectively. The reaction of silyl anions and aromatic halides has been known in the literature for over 20 years but the chemistry reported to date has not been very clean.[2a,d] We report a mild one-step procedure at 25 °C for the conversion of aryl halides to trimethylsilylbenzenes, formally a trimethylsilyldehalogenation on an aromatic compound.[3] Trimethylsilyl-substituted benzenes are very useful intermediates for directing specific mild electrophilic substitution on carbon as shown in the work of Eaborn and coworkers.[4]

Reaction of aryl halides, ArX (X = Cl, Br, I), with hexamethyldisilane and KOMe (or NaOMe or MeLi) in anhydrous

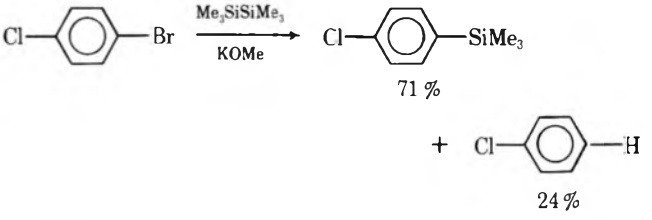


ArX, X = Cl, Br, I ArTMS

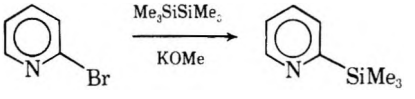
HMPT at 25 °C under argon for 3 h affords the corresponding substitution product $ArSiMe_3$ (92–63%) and some reduction product ArH (4–26%) depending mostly on the choice of aryl halide. Typical yields are shown in Table I.

In general we find that (1) the ratio of substitution/reduction increases in the direction I < Br < Cl; (2) this ratio is relatively insensitive to the choice of metal cation; (3) the rates of reaction appear to decrease in the direction I, Br > Cl; (4) substitution occurs exclusively on the carbon bearing the halogen substituent; (5) the ratio of substitution/reduction increases as substituent position on the aromatic ring changes from ortho > meta > para;[5] (6) yields and substitution/reduction ratios are sensitive to temperature.[6]

Differences in reactivity of the halogen substituent could be distinguished on the same molecule. 1-Bromo-4-chlorobenzene reacts with hexamethyldisilane and KOMe to afford



reaction mostly (>95%) at the carbon bearing bromine.[7] Substitution also occurs in heteroaromatic molecules, for example, 2-bromopyridine. No reduction product was found in this case.



80 %

The mechanisms of these reactions are not yet known. In a formal sense, the silylated product is derived from a nucleophilic aromatic substitution reaction. At least four mechanisms can be considered: (1) the aryne mechanism, (2) direct nucleophilic substitution (S_NAr), (3) halogen–metal interchange to afford an ArM (M = K, Na, Li) intermediate, (4) radical-anion chain reaction ($S_{RN}1$).[8] The aryne pathway can be excluded based on the stereochemical results. Concerted nucleophilic displacement at aromatic carbon is more difficult to eliminate,[8b] especially in view of the strong nucleophilicity of silyl anions. However, this S_NAr mechanism is seldom encountered with unactivated aryl halides and requires a second competing pathway for reduction product. Quenching the reaction mixture of iodobenzene and TMSK with D_2O after 5 min affords reduction product (benzene) with 30% d_1 incorporation.[9] This is permissive evidence that at least

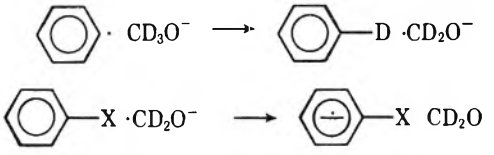
Table I. Reactions of Trimethylsilyl Anions with Aryl Halides

Reagent	ArX	ArTMS	ArH	Total[a] yield, %	ArTMS/ ArH
Me_3SiK[b]	Cl	86	5	91	17
	Br	92	7	99	13
	I	68	26	94	2.6
Me_3SiNa[c]	Cl	87	5	92	17
	Br	91	8	99	11
	I	70	27	97	2.6
Me_3SiLi[d]	Cl	69	4	73	17
	Br	84	7	91	12
	I	63	26	89	2.4

[a] Percent yield based on aryl halide determined by VPC analysis after workup (20 ft × ⅛ in. 10% SE-30; internal standard, decane). [b] Generated by the reaction of hexamethyldisilane and potassium methoxide in HMPT at 25 °C. [c] Generated by the reaction of hexamethyldisilane and sodium methoxide in HMPT at 25 °C. [d] Generated by the reaction of hexamethyldisilane and methyllithium in HMPT/Et_2O at 0 °C, then allowed to warm to 25 °C.[2j]

part of the reaction may be proceeding via a phenylpotassium intermediate.[2a] Whether this phenyl anion comes from nucleophilic attack of silyl anion on halogen or from the reduction of phenyl radical by silyl anion cannot be distinguished at this time.

The relative rates with regard to halogen substitution and the observation of reduction product are reminiscent of other aromatic nucleophilic substitution reactions proposed to proceed by radical-chain mechanisms.[8] Sakurai has shown that trimethylsilyl anion is a convenient one-electron donor.[2e] Replacement of CH_3OK with CD_3OK[10] in the reaction of iodobenzene and hexamethyldisilane affords reduction product with 64% d_1 incorporation,[9] consistent with the chain-carrying properties ascribed to methoxide found in the growing list of aromatic free radical-chain mechanisms.[8,11] The observation



that some but not all of the hydrogen-atom source in the reduction product is methoxide is compatible with the finding that, for the cases using TMSLi, which contains no methoxide owing to the method of generation, reduction product is still observed. Further investigations will be necessary before these reactions are fully understood.[12] However, it appears from the present deuterium incorporation data that the iodobenzene reaction with TMSK may involve *at least* two aromatic intermediates, phenyl radical and phenyl anion.

A typical procedure is as follows. To 1.91 g (0.027 mol) of potassium methoxide[13] in 50 mL of anhydrous HMPT[14] under argon at 25 °C was added 3.12 g (0.018 mol) of *p*-bromotoluene followed by 4.38 g (0.029 mol) of hexamethyldisilane.[15] The yellow reaction mixture was allowed to stir for 6 h. Aqueous NH_4Cl (5%) was added to the reaction mixture and this was extracted twice with pentane. The pentane layers were combined and dried (Na_2SO_4). Distillation under reduced pressure afforded 2.46 g (82% isolated yield) of *p*-tolyltrimethylsilane, 99.6% pure by vapor phase chromatography (VPC).[17]

Acknowledgment. The authors are grateful to the National Science Foundation (MPS 75-06776) for their generous support of this work. We appreciate stimulating discussions with Professor David A. Evans.

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(3) For recent direct syntheses of arylsilanes, see (a) H. Matsumoto, S. Nagashima, K. Yoshikiro, and Y. Nagai, *J. Organomet. Chem.* **85**, C1 (1975); (b) G. L. Larson, *Syn. React. Inorg. Metal. Org. Chem.*, **6**, 21 (1976).
(4) For a review of this field, see C. Eaborn, *J. Organomet. Chem.*, **100**, 43 (1975).
(5) For example, the reaction of *o*-, *m*-, and *p*-bromotoluene with TMSK afforded substitution/reduction ratios of 3, 10, and 13, respectively.
(6) As the temperature is raised above 25 °C the yields and ratio of substitution/reduction decreases. If the reaction is run at 0 °C in HMPT/Et_2O (10:1 ratio), the substitution/reduction ratio apparently increases although the mass balance (yield) of the substitution product does not increase significantly.
(7) Benzene, 1-bromo-4-trimethylsilylbenzene, and bromobenzene were not observed in the reaction mixture (<1%) under analytical conditions (VPC) independently shown to separate authentic mixtures. Trimethylsilylbenzene and 1,4-bis(trimethylsilyl)benzene were observed in 1 and 2% yields, respectively.
(8) (a) J. K. Kim and J. F. Bunnett, *J. Am. Chem. Soc.*, **92**, 7463, 7464 (1970); (b) J. F. Bunnett, *J. Chem. Educ.*, **51**, 312 (1974); (c) J. A. Zoltewicz and T. M. Oestreich, *J. Am. Chem. Soc.*, **95**, 6863 (1973); (d) J. A. Zoltewicz, T. M. Oestreich, and A. A. Sale, *ibid.*, **97**, 5889 (1975). For radical-chain mechanisms formulated for certain nucleophilic substitutions at saturated carbon, see N. Kornblum, R. E. Michel, and R. C. Kerber, *ibid.*, **88**, 5662 (1966); G. A. Russell and W. C. Danen, *ibid.*, **88**, 5663 (1966), and **90**, 347 (1968).
(9) Determined by the Caltech Analytical Facility on a Du Pont 21-492B mass spectrometer.
(10) Made from CD_3OD (Aldrich) and potassium hydride.
(11) In the cases using potassium and sodium methoxide, *p*-methoxytoluene was never observed in the products under VPC conditions capable of detecting <1% of this compound.
(12) For recent work on the reactions of trialkylstannyllithium, and -sodium with aryl halides, see J. P. Quintard, S. Hawrette, and M. Pereyre, *J. Organomet. Chem.*, **112**, C11 (1976), and H. G. Kuivila and K. R. Wursthorn, *J. Organomet. Chem.*, **105**, C6 (1976), respectively.
(13) Obtained from Alfa.
(14) Distilled from lithium wire under reduced pressure and redistilled from CaH_2. HMPT was handled with the precautions appropriate to a potential carcinogen.
(15) Hexamethyldisilane was prepared by the method of Gilman.[16]
(16) H. Gilman, K. Shiina, D. Aoki, B. Gaj, D. Wittenberg, and T. Brennan, *J. Organometal. Chem.*, **13**, 323 (1968).
(17) 20 ft × ⅛ in. SE-30, flame ionization detector, electronic integration.
(18) National Science Foundation Predoctoral Fellow, 1973–1976.
(19) Alfred P. Sloan Research Fellow, 1977–1979.

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Synthesis of Cycloalkenes by Intramolecular Titanium-Induced Dicarbonyl Coupling

Summary: Cycloalkenes of ring size 4–16 are prepared in good yield by treatment of dicarbonyl compounds with a reagent prepared from $TiCl_3$/Zn–Cu.

Sir: We have reported recently that ketones and aldehydes can be reductively coupled to olefins by treatment with low valent titanium.[1-3] The intermolecular version of this reaction works best when identical carbonyl species are coupled to give symmetrical olefins,[2] but we have also demonstrated that, in

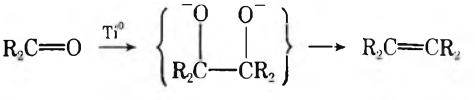
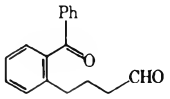
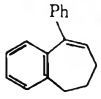
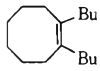
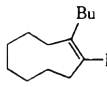
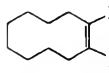


Table I. Cycloalkene Formation by Dicarbonyl Coupling

Dicarbonyl substrate	Cycloalkene	Yield, %[a]
$PhCO(CH_2)_2COPh$		87
$CH_3CO(CH_2)_3COPh$		70
$CH_3CO(CH_2)_4COBu$		79
$PhCO(CH_2)_4COPh$		95
$CH_3CO(CH_2)_4COCH_2CH_2Ph$		50
		80
$BuCO(CH_2)_6COBu$		67
$BuCO(CH_2)_7COBu$		68
$BuCO(CH_2)_8COBu$		75
$BuCO(CH_2)_9COBu$		76
$CHO(CH_2)_{10}CHO$		76
$CHO(CH_2)_{11}CHO$		52
$CHO(CH_2)_{12}CHO$		71
$CHO(CH_2)_{13}COPh$		80
$CHO(CH_2)_{14}CHO$		85

[a] The figures given represent isolated yields.

certain cases, unsymmetrical olefins can be prepared in good yield.[3] Mechanistically, we have shown that the coupling reaction proceeds by an initial pinacol dimerization, followed by titanium-induced deoxygenation.

The pinacol coupling of ketones and aldehydes is, of course, mechanistically similar to the acyloin coupling of esters[4] in that one-electron donation to the carbonyl group produces an intermediate ketyl which then dimerizes. Since the acyloin reaction of diesters is of great value in synthesis owing to its effectiveness in the construction of medium and large rings, we began a study of the titanium-induced *intra*molecular coupling of dicarbonyl compounds with a view toward developing a general synthesis of medium- and large-ring olefins. We now wish to report that we have successfully coupled dicarbonyl compounds to construct cycloalkenes of ring size 4–16, and that good yields were obtained in all cases. Our results are presented in Table I.

Several points should be emphasized. The first is that the cyclization reaction appears general for both aldehydes and ketones. The examples we report are structurally simple, however, and clearly one would not expect other, readily reducible functional groups (ester, nitro, nitrile, sulfoxide, etc.) to be compatible with the reaction conditions. The second point is that the yields of medium-ring olefins (ring size 7–11) are remarkably high compared with those of other known methods of ring synthesis.[5] The Thorpe–Ziegler[6] dinitrile cyclization, for example, fails utterly to produce ring sizes 9–13. The acyloin cyclization, a much better method,[4] also shows a dip in yields for ring sizes 9–11. The titanium-induced dicarbonyl coupling, by contrast, appears equally effective for all ring sizes. A final point involves the titanium reagent itself. For our *inter*molecular coupling experiments, we employed active titanium powder prepared from $TiCl_3$ by reduction with either metallic potassium[2] or lithium.[3] Although both of these reagents systems effect intramolecular coupling as well, we have found[7] that a safer and even more effective coupling reagent can be prepared by reducing anhydrous $TiCl_3$ with Zn–Cu couple under inert atmosphere in dimethoxyethane (DME) solution.

In a representative procedure, $TiCl_3$ (1.031 g, 6.68 mmol) and Zn–Cu couple[8] (1.011 g, 15.4 mmol) were placed in a flask via a Schlenk tube under argon. Anhydrous dimethoxyethane (20 ml) was added and the mixture was refluxed for 1 h. Nonadecane-5,15-dione (182 mg, 0.61 mmol) in 40 ml of DME was added to the refluxing slurry via a motor-driven syringe pump over a 30-h period. After an additional 14-h reflux period, the reaction mixture was cooled to room temperature, passed through a small Florisil pad, and concentrated at the rotary evaporator. After a short chromatography on alumina, 1,2-di-*n*-butylcycloundecene (122 mg, 0.46 mmol, 76%) was isolated: mp 80.5–82.5 °C (acetone); NMR (CCl_4) 1.8–2.3 (m, 8 H), 1.4–1.25 (br, 22 H), 0.93 (t, 6 H); *m/e* 264 (M^+). The other examples reported in Table I were carried out in a similar manner.

In conclusion, the titanium-induced intramolecular coupling of dicarbonyl compounds to form cycloalkenes appears to be a most promising procedure. Because of its generality with respect to ring size, and the high product yields obtained, we feel that this method may well prove to be a significant advance in medium- and large-ring carbocyclic synthesis.

Acknowledgment. We thank the National Science Foundation for their support of this work through Grant CHE 76-06161.

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(1) J. E. McMurry and M. P. Fleming, *J. Am. Chem. Soc.*, **96**, 4708 (1974).
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(3) J. E. McMurry and L. R. Krepski, *J. Org. Chem.*, **41**, 3929 (1976).
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(5) For a comparison of the effectiveness of various large-ring syntheses, see J. Sicher in "Progress in Stereochemistry", Vol. 3, Butterworths, New York, N.Y., 1962, pp 202–263.
(6) For a review of the Thorpe–Ziegler reaction, see J. P. Schaefer and J. J. Bloomfield, *Org. React.*, **51**, 1 (1976).
(7) This discovery was made in our laboratory by Dr. Larry Krepski.
(8) The Zn–Cu couple is prepared by adding zinc dust (9.8 g, 150 mmol) to 40 ml of deoxygenated water, purging the slurry with nitrogen gas for 15 min, and then adding $CuSO_4$ (0.75 g, 4.7 mmol). The black slurry was filtered under nitrogen, washed with deoxygenated water, acetone, and ether, and then dried in vacuo. The couple can be stored indefinitely under nitrogen. This procedure is due to Dr. Larry Krepski, Ph.D. Thesis, University of Colorado, 1975.

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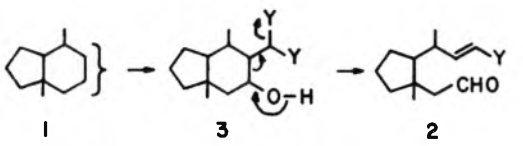
Grob-Type Fragmentation of Five- and Six-Membered Rings Promoted by Cuprous Ion

Summary: Copper(I) salts, especially the triflate and trifluoroacetate, promote efficient cleavage of 1-hydroxy-2-[bis(phenylthio)methyl]cyclohexane and cyclopentane; a cyclic intermediate is unlikely, as complete reaction requires more than 2 mol equiv of copper(I); the product contains aldehyde and latent aldehyde units.

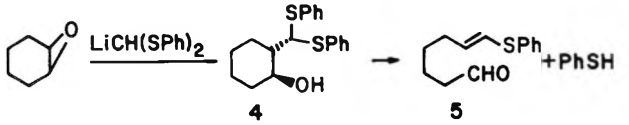
Sir: During studies directed toward the synthesis of natural sesquiterpene α-methyl-γ-lactones,[1] we required a mild technique to convert the readily accessible perhydroindan skeleton (e.g., **1**) into the open-chain homologue (e.g., **2**) with a free aldehyde and a latent aldehyde for further elaboration. An obvious sequence is nucleophilic addition of $LiCHY_2$ to some appropriate derivative of **1**, followed by Grob-type



1 3 2

fragmentation[2] of **3**. The unit Y must stabilize the reagent $LiCHY_2$ and also readily depart as Y^- during the fragmentation. We have employed the anion of bis(phenylthio)methane[3] and wish to report preliminary results which suggest a particularly mild and efficient fragmentation procedure.

The reaction of lithio bis(phenylthio)methide with 1,2-epoxycyclohexane produces the alcohol **4** in 73% yield. While



4 5

this compound is set up well for the Grob-fragmentation mechanism, the usual conditions required for parallel examples[4,5] are not mild. For example treatment of **4** with potassium *tert*-butoxide or sodium hydride (THF, 55 °C, 14 h) led to recovery of **4** (largely) accompanied by decomposition products (Table I, entries 1 and 2). None of the desired aldehyde (**5**) was obtained. Monoxidation (*m*-chloroperbenzoic acid) produced the corresponding sulfoxide (**6**), but led to no

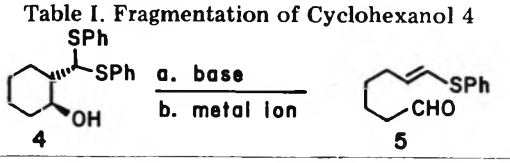
6 7

improvement in the ease and efficiency of fragmentation (**5** not detectable; NaH/THF, 65 °C, 24 h).

Metal-promoted ionization of the carbon–sulfur bond was considered, with the possibility of a cyclic intermediate (e.g., **7**) during fragmentation.[6] Treatment of **4** with *n*-butyllithium (to generate the alkoxide) followed by salts of mercury, silver, and copper produced positive results only in the case of copper (Table I). Cuprous triflate[7] and cuprous trifluoroacetate (crude reagent) were most successful; optimum conditions promoted fragmentation at 25 °C in high yields.

Cuprous triflate has been used to bring about ionization and overall elimination from bis(phenylthio) acetals[7] (e.g., **4**) and this is the primary reaction of **4** with cuprous triflate in the absence of added strong base (entry 5), but initial treatment with *n*-butyllithium followed by 4 mol equiv of cuprous triflate led to smooth fragmentation (entry 8). The cyclic intermediate is not likely, considering the fact that 1 mol equiv of cuprous triflate does not promote fragmentation at 20 °C. Presumably, the usual stereoelectronic control of the Grob fragmentation

Table I. Fragmentation of Cyclohexanol 4

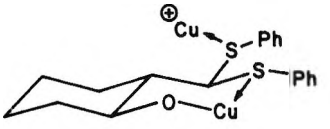


4 5

Entry	Conditions[a]	Metal ion (mol equiv)	Yield, %[b] (conversion, %)
1	NaH/THF, 55, 14	None	0 (0)
2	KOBu/DMSO, 90, 48	None	0 (90)
3	BuLi/THF, 20, 24	$HgCl_2$ (1)	0 (0)
4	BuLi/THF, 20, 3	$AgOT_f$ (4)[c,d]	0 (>80)
5	C_6H_6, 20° 3	$CuOT_f$ (2)[d,e]	0 (100)
6	BuLi/THF, 20, 3.5	$CuOT_f$ (1)[c,d]	0 (0)
7	BuLi/THF, 20, 3.5	$CuOT_f$ (2)[c,d]	30 (30)
8	BuLi/THF, 20, 3.5	$CuOT_f$ (4)[c,d]	92 (100)
9	BuLi/THF, 20, 72	CuOAc (8)	25 (50)
10	BuLi/THF, 20, 3	CuOTFA (4)[f]	90 (100)
11	BuLi/THF, 20, 3	CuOTFA (4)[g]	25 (40)

[a] Reactants, temperature (°C), time (hours). In cases where BuLi is indicated, *n*-butyllithium (1.0 mol equiv) was added to **4** in THF at −78 °C to generate the alkoxide. [b] The yield is based on isolated **5**, not corrected for recovered **4**. [c] A solution of the metal salt in benzene or toluene was added to the alkoxide in THF. [d] A small molar excess of 2,6-dimethylpyridine was present. [e] Strong base was not present. [f] Cuprous trifluoroacetate prepared in toluene solution and used without purefication. [g] The cuprous trifluoroacetate was purified by crystallization; see ref 12.

is important, with at least one cuprous ion to coordinate with the alkoxide unit and another cuprous ion to associate with the departing (anti) phenylthio unit (as depicted in **8**).[6]



8

Consistent with this picture of the intermediate is predominant formation of (*E*)-vinyl sulfide (**5**)[8] from the fragmentation reaction.

Other cuprous salts also bring about the fragmentation; the results of a number of experiments are summarized in Table I (entries 9–11). Anhydrous cuprous acetate has limited solubility in a variety of polar aprotic solvents and induces fragmentation more slowly and less efficiently that cuprous triflate. Cuprous trifluoroacetate, prepared by reaction of cuprous oxide and trifluoroacetic anhydride in toluene and used without purification as a solution in toluene, gave essentially the same results as cuprous triflate (entry 10). However, purified cuprous trifluoroacetate[10] gave slower cleavage, resulting in only 40% conversion under conditions where cuprous triflate gives complete reaction. The reason for the different reactivity of the crude and purified cuprous trifluoroacetate is not yet understood.

The five-membered-ring analogue (**9**) was prepared in the same way, and found to undergo fragmentation efficiently using the standard conditions for **4** (*n*-BuLi/THF/$CuOT_f$, 20 °C, 3 h, 93% yield). However, the mono(phenylthio) derivative **10** is inert to these conditions and does not fragment smoothly even at higher temperature.

Further questions of ring size and stereochemical requirements, versatility in the unit Y in **3** and application in more complex systems are under consideration.[11,12]

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(1) For an earlier paper in this series, see M. F. Semmelhack and E. S. C. Wu, *J. Am. Chem. Soc.*, **98**, 3384 (1976). A simple target molecule is confertin.

For a recent synthesis, see J. A. Marshall and R. H. Ellison, *ibid.*, **98,** 4312 (1976).
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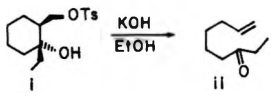
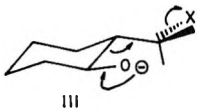
(3) E. J. Corey and D. Seebach, *J. Org. Chem.*, **31,** 4097 (1966).
(4) For example, basic solvolysis of the simple six-membered ring in i proceeded at reflux temperatures, and produced ii in only 20% yield: Y. M. Portnyagin and V. V. Sova, *J. Org. Chem. USSR*, **4,** 1515 (1968).



I II

(5) For example, an aldehyde is produced in a favorable bicyclic system after 30 min at reflux with potassium *tert*-butoxide in *tert*-butyl alcohol: J. A. Marshall and C. J. V. Scanio, *J. Org. Chem.*, **30,** 3019 (1965).
(6) The stereoelectronic factors in the general Grob fragmentation favor an anti transition state as depicted in iii.[2a]



III

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(8) A sample 7-(phenylthio)hept-6-en-1-al (**5,** mixture of *E* and *Z* isomers) was prepared by reaction of 6,6-dimethoxyhexanol with (phenylthio)(trimethylsilyl)methyllithium[9] followed by hydrolysis of the acetal unit. This material was homogeneous by TLC analysis. with R_f identical with that of **5** prepared by fragmentation. The *E* stereochemistry follows from analysis of the ^{1}H NMR chemical shifts and coupling constants.[9]
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(11) Acceptable combustion analyses and spectral data (^{1}H NMR, IR, mass spectroscopy) have been obtained for compounds **4, 5, 9,** and **10.**
(12) Acknowledgment is made to the National Institutes of Health for financial support of this work and to Professor Duilio Arigoni for helpful suggestions during his visit as Baker Lecturer at Cornell.
(13) Recipient of a Camille and Henry Dreyfus Teacher-Scholar Grant, 1973-1978.
(14) NIH Postdoctoral Fellow, 1974-1976. (Grant No. F32 CA 05353, awarded by the National Cancer Institute, DHEW.)

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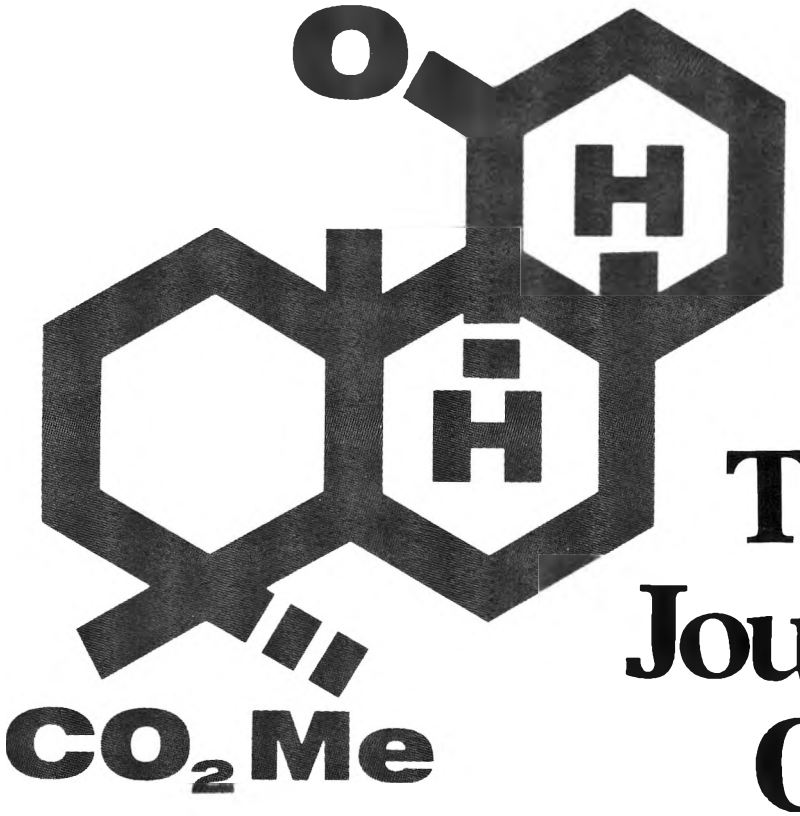

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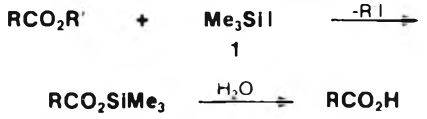
Selective Cleaving Reagents

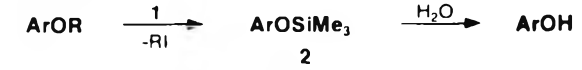
Iodotrimethylsilane

Iodotrimethylsilane (1) has recently been introduced by Jung[1] and Olah[2] as an efficient and convenient reagent for the cleavage of esters and ethers under neutral conditions. **Iodotrimethylsilane** has advantages over other dealkylating agents in that mild, homogeneous reaction conditions can be employed.[2] Hence, a mixture of **1** and a carboxylic ester, either neat[2] or in an aprotic solvent, gave the corresponding acid on heating and subsequent aqueous hydrolysis.



tert-Butyl and benzyl esters were rapidly dealkylated at 25°C, whereas methyl, ethyl, and isopropyl esters required higher reaction temperatures.

Iodotrimethylsilane has also been used to cleave alkyl and aryl ethers.[2,3] Jung and Lyster[3] have recently examined cleavage conditions for a wide variety of ethers. For example, heating an excess of **iodotrimethylsilane** with alkyl aryl ethers gave good yields of aromatic trimethylsilyl ethers (**2**). These may be converted to their respective alcohols by simple hydrolysis.



Certain alkyl ethers are selectively and quantitatively cleaved, as shown in the following equation:

R = *t*-Bu, CH_2Ph, CPh_3

The ester and ether cleavages with **iodotrimethylsilane** apparently do not affect isolated double bonds, ketones, thioethers, amines, or amides.[1]

Aldrich offers **iodotrimethylsilane** in 5- and 25-g units, stored over copper.

References:

1) M.E. Jung and M.A. Lyster, *J. Am. Chem. Soc.*, **99**, 968 (1977).
2) T.-L. Ho and G.A. Olah, *Angew. Chem., Int. Ed. Engl.*, **15**, 774 (1976).
3) M.E. Jung and M.A. Lyster, *J. Org. Chem.*, in press

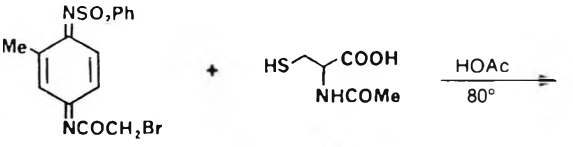
19,552-9 Iodotrimethylsilane **5g $9.60; 25g $32.00**

Cyssor I

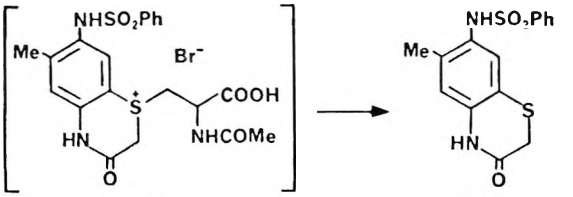
Cyssor I [2-methyl-N^1-benzenesulfonyl-N^4-(bromoacetyl)quinonediimice, **1**] is a new reagent designed by R.G. Lawton and T.J. Holmes for cysteine modification and selective cleavage of proteins.[1] The term **Cyssor I** is an acronym for "cysteine-specific scission by an organic reagent" which appropriately describes the reagent's function.

Cyssor I offers potential applications in protein modification and structure determination. It has the advantage that it can be employed under mildly acidic conditions, thereby suppressing complications arising from the use of strongly alkaline conditions.

The incubation of ovalbumin or reduced bovine pancreatic ribonuclease with **Cyssor I** resulted in fragmentation believed to occur at the sulfhydryl sites. Evidence for this selective protein cleavage is based on the reaction of **Cyssor I** with a model substrate, *N*-acetylcysteine (**2**). The reaction in-



1, Cyssor I **2**



3 **4**

volves regiospecific alkylation (easily monitored by ultraviolet spectroscopy) and subsequent cleavage to yield **4**, isolated as a solid in 75% yield. Degradation of **3** can occur *via* either of two proposed routes, both of which result in cysteine-specific cleavage.

Aldrich offers **Cyssor I** as a stable, yellow, crystalline solid.

Reference:

1) T.J. Holmes, Jr. and R.G. Lawton, *J. Am. Chem. Soc.*, **99**, 1984 (1977).

19,584-7 Cyssor I **1g $12.00; 5g $48.00**

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