VOLUME 39 MARCH 22, 1974 NUMBER 6 JOCEAH

THE JOURNAL OF Organic Chemistry

Editorial, page 4A

PUBLISHED BIWEEKLY BY THE AMERICAN CHEMICAL SOCIETY

THE JOURNAL OF Organic Chemistry

Published by the
AMERICAN CHEMICAL SOCIETY
1155 16th Street, N.W.
Washington, D. C. 20036

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Published biweekly by the American Chemical Society at 20th and Northampton Sts., Easton, Pa. 18042. Second-class postage paid at Washington, D. C., and at additional mailing offices.

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JOCEAH 39 (6) 739-862 (1974)
ISSN 0022-3263

THE JOURNAL OF Organic Chemistry®

VOLUME 39, NUMBER 6 MARCH 22, 1974

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AUTHOR INDEX

EDITORIAL

Readers of the *Journal of Organic Chemistry* (JOC) are probably aware that *Chemical Abstracts* (CA) index names for specific chemical substances have been extensively revised beginning with the CA Volume 76 (January–June, 1972) indexes. This date corresponds to the first volume of the ten-volume, five-year Ninth Collective Index (9CI) period (1972–1976). In the past such nomenclature changes have been detailed in papers in JOC. Because of the magnitude of these changes and their accompanying explanations, such a publication is not possible in today's JOC. The purpose of this editorial is to alert readers to the existence of the index name changes, to supply some of the reasons for the changes, and to point out where detailed descriptions of the changes may be found.

The most numerous and most obvious CA index name changes are the conversions of previously used trivial, author, and commercial substance names into more systematic names. While remaining generally within the framework of IUPAC and other existing nomenclature rules. the most systematic recommended names have been chosen for use in future CA Chemical Substance Indexes. These names are more easily derived from molecular structural diagrams and, therefore, are more quickly found by index users. Computer editing of index names and translation of these names into structural representations in the Chemical Abstracts Service computer-based information system are also aided substantially by the revisions. Thus, the former index names Anisole, Gentisic acid, and *p*-Toluidine are replaced by Benzene, methoxy-, Benzoic acid, 2,4-dihydroxy-, and Benzenamine, 4-methyl-, respectively. When a nonsystematic name conveys stereochemical information, it has often been retained; examples are Pregnane, D-Glucose, and Lanostane.

The 9CI changes include simplification of general name-selection rules and elimination of special treatment for small classes of substances. Specific identifiable alloys, elemental particles, enzymes, and mixtures of known substances are now indexed the same as conventional substances. All of the changes help provide a more consistent Chemical Substance Index.

The CA revised rules for naming chemical substances are described with examples in Section IV (120 pages) of the introduction to the CA Volume 76 Index Guide. This section, which includes a revised list of substituent prefixes (radicals) and a selective bibliography of chemical nomenclature rules, is also available separately under the title "Naming and Indexing of Chemical Substances for CHEMICAL ABSTRACTS during the Ninth Collective Period (1972–1976)" from the Marketing Department, Chemical Abstracts Service, The Ohio State University, Columbus, Ohio 43210, for $5.00. The complete Index Guide itself, comprising cross-references for both substances and general subjects (including those no longer used by CA), synonyms, and notes on where to find related subjects, has been thoroughly revised for Volume 76. Users of CA indexes will find it helpful to consult the Index Guide and its latest supplement (issued with Volume 77 and each odd-numbered Volume thereafter) before employing the individual indexes.

A publication version of the index name changes, together with comparisons of old and new names, appears in the February, 1974, issue of the *Journal of Chemical Documentation.*

Russell J. Rowlett, Jr.
Editor, Chemical Abstracts Service

THE JOURNAL OF Organic Chemistry®

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MARCH 22, 1974

Skipped Diynes. V. Secondary Diethynylcarbinols, a Base-Catalyzed Ynol to Enol Rearrangement, and Ultraviolet Spectra and Conjugation[1]

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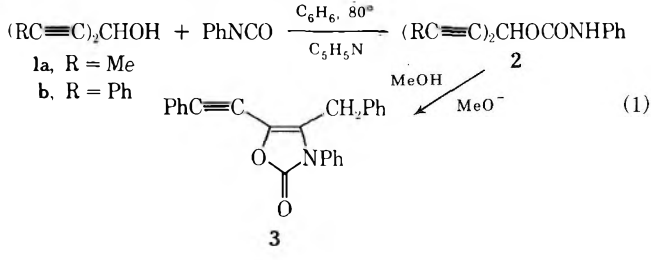
Received June 5, 1973

Bis(1-propynyl)methanol (**1a**), bis(phenylethynyl)methanol (**1b**), and tetrakis(1-propynyl)ethane-1,2-diol (**10**) are highly activated propargyl alcohols. Because of their sensitivity to acid, conversions of **1** to carbamate, ester, ether, and halide best proceed under neutral or basic conditions. Even so, disruptions of the diyne system are common, *e.g.*, the formation of 4-bromo-2,5-heptadiyne and 2-bromo-2,3-heptadien-5-yne from **1a**, thermal cleavage of **10**, and a base-catalyzed ynol to enone rearrangement of **1b** to 1,5-diphenylpent-1-en-4-yn-3-one (**14**). It is shown that the conversion of 1,3-diphenylpropynol (**15**) to 1,3-diphenylpropenone (**16**) in the presence of base is another example of this rearrangement and that reactions which appear to be characteristic of the ynol (**1b, 15**) are probably those of the enone (**14, 16**). The question of conjugation in skipped 1,4-diynes is discussed in the context of the uv spectra of several series and it is concluded that, in the diethynylmethanes, -carbinols, and ketones, the central function at the 3 carbon does transmit conjugation. The trialkylethynylcarbinols are anomalous in that their uv absorption bands are decidedly hypsochromic relative to all members of the diethynyl families.

In a skipped diyne, a methylene or other functionality is interposed between the two triple bonds. Such compounds could conceivably display properties that result from reciprocal effects of the alkyne and the middle group. Elsewhere we have reported on diethynylmethanes,[2] diethynyl ketones,[3] triethynylcarbinols, and related allenes.[4] Here we examine the chemistry of the diethynylcarbinols (**1**).

Relatively few (*ca.* 12) skipped diynols are known.[5,6] In their reactions, *e.g.*, hydration or hydrogenation of the triple bond and oxidation or functional exchange of the hydroxy group, these compounds appear to be unexceptional propargyl alcohols.[5,6] However, because the "propargylic" effect has been enhanced and vulnerable sites abound, we also find that competing processes are easily initiated. After describing a few "standard" processes we shall describe an unusual rearrangement of certain ethynylcarbinols.

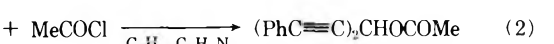
Carbinol Reactions. Reaction of **1** with phenyl isocyanate yielded the expected urethanes (**2**).[7]



(1)

Efforts to cyclize bis(1-propynyl)methyl *N*-phenylcarbamate either thermally (*ca.* 130°) or under basic conditions (*ca.* 60°) led only to intractable tars or recovery of unreacted carbamate. Likewise, bis(phenylethynyl)methyl *N*-phenylcarbamate did not cyclize in refluxing xylene but formed 4-benzyl-3-phenyl-5-phenylethynyl-4-oxazolin-2-one (**3**) in refluxing methanolic sodium methoxide.[7a] This product presumably arises from the base-catalyzed isomerization of the initially formed adduct, 4-benzylidene-3-phenyl-5-phenylethynyl-2-oxazolidinone (eq 1).

We have also prepared esters of **1** under basic or neutral conditions, which preclude possible acid-catalyzed Meyer–Schuster rearrangements of ethynylcarbinols to α,β-unsaturated ketones.[8] It was possible to esterify **1b** with acetyl chloride by refluxing them in benzene containing sufficient pyridine to neutralize the hydrochloric acid formed (eq 2), although **1a** was only partially esterified by benzoyl chloride under these conditions. However, the alkylation of preformed dipropynylmethyl alkoxide with a suitable acid chloride was successful and we were able to prepare bis(1-propynyl)methyl *m*-bromobenzoate (**5**) in fair yield (eq 3).



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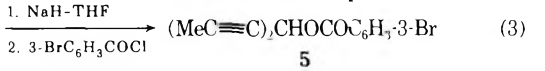
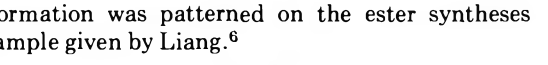


(3)

Ether formation was patterned on the ester syntheses and an example given by Liang.[6]



(4)

The diethynylhalomethanes could possibly lead to polyethynylated methanes, ethanes, or ethylenes. A recent report, for example, describing the conversion of bis(phenylethynyl)methyl bromide into tetrakis(phenylethynyl)ethylene in the presence of potassium *tert*-butoxide was encouraging.[9] We were able to prepare bis(phenylethynyl)-methyl bromide (**7b**) by treating **1b** with phosphorus tribromide in absolute ether at 0° (eq 5). This bromide was a yellow solid which decomposed to a red tar upon standing for several hours at 25°. It was, however, found to be stable indefinitely at −78°. Compound **1a** and phosphorus

tribromide in absolute ether at 0° yielded an unstable oil which decomposed to a black tar within several hours at 25°. Spectral analysis indicated that the oil was a mixture of 4-bromo-2,5-heptadiyne (**7a**, 98%) and 2-bromo-2,3-heptadien-5-yne (**8a**, 2%). If the bromination was carried out in the presence of pyridine, the ratio of the two products changed to 1:1. Similar acetylene–allene rearrangements are known.[10]

$$\mathbf{1} + PBr_3 \xrightarrow[0°]{Et_2O} \underset{\mathbf{7}}{(RC{\equiv}C)_2CHBr} + \underset{\mathbf{8}}{RBrC{=}C{=}CHC{\equiv}CR} \quad (5)$$

a, R = Me
b, R = Ph

Attempts to separate the bromides (*e.g.*, distillation or column chromatography) resulted only in their decomposition and partial hydrolysis to **1a**, although they could be stored at −78° for several weeks without detectable decomposition.

We record observations on two of several reactions attempted with **7**. The bromides from **1a** reacted only slowly with magnesium metal in ether at 25°. An aqueous quench of the reaction mixture after 24 hr gave starting bromides and small amounts of 2,5-heptadiyne (**9**) and **8a**. When the reaction was repeated with **7b**, a yellow solid containing at least three compounds (one major product and two minor products) precipitated from the reaction mixture after 1 hr. Since mass spectral analysis showed that the heaviest fragment had *m/e* 430 and the base peak had *m/e* 215, it is probable that the major product in the mixture was a species of molecular weight 430, perhaps 1,1,2,2-tetrakis(phenylethynyl)ethane, which cleaves into two identical fragments of *m/e* 215 upon electron impact. The coupling process would then be

$$Mg + \mathbf{7b} \longrightarrow \underset{m/e\ 430}{(PhC{\equiv}C)_2CHCH(C{\equiv}CPh)_2} + \text{other products} \quad (6)$$

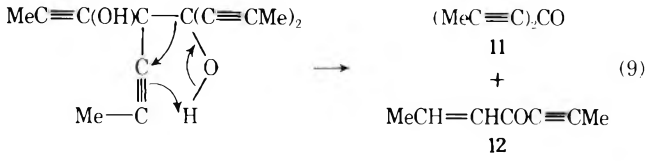
With another reductant, namely Cr(II),[11] **7a** gave 2,5-heptadiyne, and **7b** gave a yellow solid, identical in all respects with that of eq 6.

$$\mathbf{7a} + CrSO_4 \longrightarrow \underset{\mathbf{9}}{(MeC{\equiv}C)_2CH_2} \quad (7)$$

Tetraethynylglycols are analogs of **1** which were of interest to us as possible precursors of tetraethynylethylene. The sensitivity of **10**, one of the two known glycols[12] in this class (eq 8), precluded certain conversions.

$$MeC{\equiv}CMgX + (COOEt)_2 \longrightarrow \underset{\mathbf{10}}{[(MeC{\equiv}C)_2COH]_2} \quad (8)$$

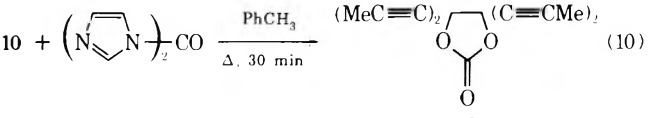
In dilute aqueous acid the glycol was destroyed. Reaction of **10** with phosphorus tribromide gave only a complex mixture of vinyl allenes, glycols, etc. Attempted esterification with pyridine and benzyol chloride did not yield the expected diester but rather mixtures of the glycol and half-esters; alternatively, treatment of **10** with butyllithium at −40° followed by addition of acetyl chloride at 0° gave only small amounts of the desired diacetate along with large quantities of tarry materials. In an attempt to condense **10** with benzaldehyde, their solution in toluene was heated at 110° over molecular sieves for several hours. From this mixture only dipropynyl ketone was isolable. This product may have formed by an oxy-Cope rearrangement, for which there is precedent among the diacetylenic glycols.[13]



(9)

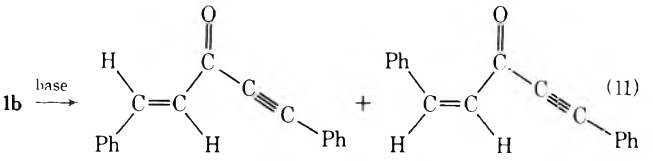
The presence of the second predicted product from this reaction, hept-2-en-5-yn-4-one (**12**), in the reaction mixture was inferred from the ir and nmr spectra of the product solution.

Even if diesters or dihalides are excluded, several attractive routes from a 1,2-glycol to an alkene are known. In one of these, our attempts to prepare the intermediate thionocarbonate from the glycol and 1,1′-thiocarbonyldiimidazole[14] did not succeed. On the other hand, the carbonate formed readily but could not be converted to the alkene by the usual techniques.[15]



(10)

Base-Catalyzed Rearrangements. Although base-catalyzed rearrangements of propargylic compounds are familiar in acetylene chemistry,[2,10,16] we were rather surprised to find the following.



trans-**14** (J_{HH} = 16.1 Hz) *cis*-**14** (J_{HH} = 12.3 Hz)

(11)

One must credit Nineham and Raphael and Lappin with the discovery of this rearrangement (eq 12, 13), even though Lappin was unable to isolate the phenyl aroyl ketone (eq 13).[17] We have since located one other example (eq 14).[18]

$$PhCHOHC{\equiv}CCO_2CH_3 \xrightarrow{base} PhCOCH{=}CHCO_2CH_3 \quad (12)$$

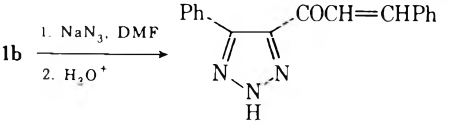
$$PhC{\equiv}CCHOHAr \xrightarrow{base} \underset{\mathbf{15},\ Ar = Ph}{(PhCH{=}CHCOAr)} \longrightarrow \underset{\mathbf{16},\ Ar = Ph}{} PhCHO + CH_3COAr \quad (13)$$

$$HC{\equiv}CC{\equiv}CCHOHCH_3 \xrightarrow{base} [HC{\equiv}CCH{=}{=}CHCOCH_3] \quad (14)$$

Earlier, Liang had reported that, in the presence of alcoholic potassium hydroxide, **1b** is converted into bis(phenylacetyl)methanol, $(C_6H_5CH_2CO)_2CHOH$,[6] an altogether implausible transformation. Moreover, these reactions are clearly different from the known acid-catalyzed Meyer–Shuster rearrangement.[8b]

$$\mathbf{1b} \xrightarrow{H_3O^+} \underset{\mathbf{17}}{PhCOCH{=}CHC{\equiv}CPh} \quad (15)$$

The first indication that **1b** might undergo a base-catalyzed rearrangement arose during the triazole synthesis of eq 16.[19] It was established that phenylethynyl β-styryl



(16)

ketone (**14**) yields the same triazole under similar conditions and that various bases, *e.g.*, hydroxide, acetate, azide, and triethylamine, catalyzed the isomerization of **1b** to **14**. In order to be sure that isomerization of **1b** actually preceded triazole formation, we monitored reactions 11 and 16 by ir or nmr. The $\nu_{C\equiv C}$ bands are diagnostic in that $\nu_{C\equiv C}$ (2205 cm^{-1}) of **1b** is lost early in the reaction while $\nu_{C\equiv C}$ (2255 cm^{-1}) of **14** appears, then disappears. Thus it is probable that isomerization of **1b** to **14** is faster

than triazole formation. Heated at reflux in triethylamine or in toluene in the presence of triethylamine for 24 hr, **1b** yields *trans*-**14** (>90%); heated at 50° in an aprotic solvent in the presence of base, **1b** yields *cis*- and *trans*-**14**. The cis and trans structural assignments of eq 11 are based on the observed nmr data.[20]

Finally, *cis*-**14** is formed under kinetic control and is gradually converted to *trans*-**14** (Table I). Moreover, the overall conversion of **1b** to **14** increases as the aprotic solvents become more polar, in the order benzene ~ dioxane < THF < DMF < DMSO. At this stage it becomes necessary to examine possible mechanisms in order to provide a rationale for our observations and the kinds of experiments to be described later.

Three possible pathways were considered, that is, *via* a carbene, a monocarbanion, and a dicarbanion (eq 17). A trapping experiment in which **1b** was treated with sodium hydride in the presence of an excess of olefin (cyclohexene, ethyl cinnamate, *trans*-stilbene) gave only starting material, **14**, phenylacetylene, and unreacted olefin. These results indicated that the carbene mechanism probably did not apply, although carbene mechanisms are known to operate under similar conditions in related propargylic systems.[21]

Table I
Rearrangement of Diphenylethynylcarbinol (1b) in the Presence of Triethylamine at 60° to Give β-Styryl Phenylethynyl Ketone (14)

Solvent[a]	$[(C_2H_5)_3N]$, vol. %	Reaction time, hr	PhCH=CHCOC≡CPh % trans[b]	% cis[b]
Benzene	4.8	10	*c*	2.5
Ethanol	4.8	10	1	3.5
Dioxane	4.8	10	~0	~0
THF	4.8	10	5	5
THF	8.5	10	29	19
DMF	4.8	5	21	54
DMF	4.8	10	34	57
DMSO	4.8	10	79	16
TEA	100	3.5	15	18
TEA	100	15	80	14
TEA	100	72	96	0

[a] THF, tetrahydrofuran; DMF, dimethylformamide; DMSO, dimethyl sulfoxide; TEA, triethylamine. [b] The values obtained by comparing the intensities of nmr for ethylenic hydrogens and the alcohol hydrogen. [c] The solvent peaks partially overlap the trans peak.

We also attempted to detect intermediates by nmr. Under typical rearrangement conditions, we added small amounts of sodium hydride to a solution of **1b** in benzene and recorded the chemical shift of the α proton (R_2CHOH + R_2CHO^- + R_2COH^-) after each portion reacted. The results were as follows (ν_{CH} in hertz, equivalents of NaH): 327.5, 0; 344, <0.5; 358, ~0.5; 368, >0.5; ν disappears, ~1.

Since the resonance of the α proton moves downfield as the alkoxide concentration increases, the resonance of the alkoxide proton (**3**) may simply be overlapped by the aromatic protons. When **1b** was treated with *n*-butyllithium in ether–hexane at −80°, the nmr spectrum of the reaction mixture showed a sharp resonance at 434 Hz superimposed on a broad, unresolved, presumably aromatic resonance. When **1b** was treated with dimsyl sodium in dimethyl sulfoxide at 25°, the resonance occurred at 424 Hz superimposed on a broad resonance. Thus, although we could not define the chemical shift of the α proton of **19** precisely, its direction was downfield relative to the α-proton resonance of the starting carbinol.

In passing, we note this relative downfield shift. The relative upfield shift of a proton at a carbanionic site (>CH) is well known.[24a] The relative downfield shift of a proton β to the carbonionic center (>CHC<⁻) is documented but less familiar.[24b] The analogy between the alkoxide series (>CHO⁻) and this second carbanion is clear.

The preceding experiments indicated that the species which was present in highest concentration in the reaction mixture, or which was the most reactive, was **19**. Apparently no carbanionic or dianionic species **20**–**22** were detectable, although conditions appeared to be favorable for their formation and subsequent reaction.[25] Alternatively, one may speculate that, if **19**–**22** were intermediates, either

Incidentally, the phenylacetylene observed in eq 17 arises from the decomposition of **1b** under strongly basic conditions. This type of decomposition is simply the microscopic reverse of ethynylation, and hence the usual products are the parent alkynyl and carbonyl compounds.[22] In the case of **1b**, the related phenylpropiolaldehyde decomposes primarily to phenylacetylene under basic conditions.[23] Phenylacetylene did not interfere with the product analysis, since its concentration was usually less than 5% of the total residual product mixture.

Treatment of **1b** with sodium hydride in benzene followed by the addition of various substrates such as benzaldehyde, acetone, methyl iodide, benzyl chloride, tetramethylammonium iodide, ethyl cinnamate, ethyl bromoacetate, and acetyl chloride, gave, in every case except that of acetyl chloride, only **1b**, **14**, and small amounts of phenylacetylene. The reaction with acetyl chloride, however, gave bis(phenylethynyl)methyl acetate (*ca.* 98%) along with small amounts of starting material, **14**, and phenylacetylene.

Reaction of **1b** with a threefold excess of sodium hydride liberated only 1 equiv of hydrogen gas. Quenching this reaction mixture with deuterium oxide led to *O*-deuterio-**1b**, which was identified by nmr. A quench with chlorotrimethylsilane gave **23** (97%) along with small amounts of phenylacetylene and another silylated product which was not identified.

$$(PhC{\equiv}C)_2CHOH \xrightarrow[\text{excess}]{NaH} \underset{\mathbf{19}}{(PhC{\equiv}C)_2CHO^-} \xrightarrow{Me_3SiCl} (PhC{\equiv}C)_2CHOSiMe_3 \quad (18)$$

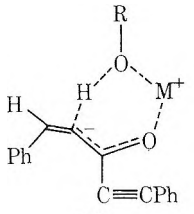
23

Table II
Reactions of 1,3-Diphenyl-2-propyn-1-ol (15) or Chalcone (16)

15 or 16 (g)	p-C_7H_7SH, (g)	Base (ml or g)	Solvent (ml)	Temp, °C	Time, hr	Product (yield, %)
15 (2.17)	1.29	$(C_2H_5)_3N$ (0.50)	DMF (20)	140	3	Oil[a]
15 (2.08)	1.24		DMSO (20)	140	20	**10** (3.5)
16 (3.01)	1.97		DMSO (20)	130	20	(p-C_7H_7S)$_2$ (16)[b]
15 (1.0)		$(C_2H_5)_3N$ (0.25)	DMSO (4)	140	10	**9**[c]
15 (3.0)		NaOH (0.50)	DMF (25)	25	3	Oligomer (17)[d]
15 (3.0)		NaN_3 (0.94)	DMF (30)	130	3	Oligomer (~10)[e]

[a] Mass spectrum shows a "parent" m/e 332 (no 330) consistent with **10**. [b] p-Tolyl disulfide, mp 46–48°. [c] Identified by mass spectral comparison. [d] Mp 254–255°. [e] Mp 188–189°.

the conversion rates exceeded the trapping rates by a factor of *ca.* 10^2 or proton transfers between them occurred within ionic aggregates. Certainly, there is evidence to support intramolecular proton transfer, at least in the product-forming step,[26] since the kinetically controlled product in DMF is *cis*-**14**. Secondly, 1,3-diphenylallyl anions possess significant rotational barriers.[27] Accordingly, species **24** depict proton transfers within bulky ionic clusters involving metallic alkoxide (RO^-M^+) and triethylamine. If in fact these selective proton transfers depict what happens, they are examples of Cram's conducted tour processes.[26] As for the slower cis to trans isomerization of **14**, this may or may not be base catalyzed; we did not investigate this point.



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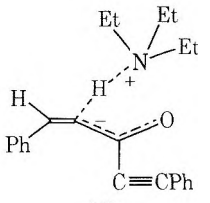
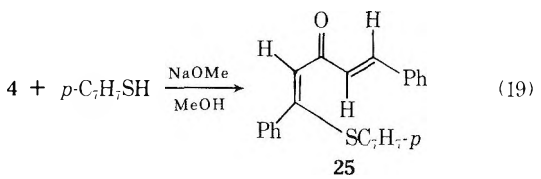


24b

We did look into the scope of this rearrangement with other ethynyl alcohols. Although bis(*tert*-butylethynyl)-methanol in triethylamine at 70° in 20 hr and **1a** in DMF at 135° in 18 hr do not isomerize, 1,3-diphenylpropynol (**15**) does isomerize in the presence of triethylamine at 140° in DMF (eq 13). Strong bases such as azide and sodium hydroxide and possibly protic solvents[17b] convert **15** into different oligomers, according to the reaction conditions. (As pointed out earlier, Lappin obtained cleavage products in eq 13 for several analogs of **15**.)[17b] Thus far, at least, the structural requirement for the ynol → enone rearrangement seems to be that the substituents on the ethynyl carbinol be electron-withdrawing groups, *e.g.*, Ph.

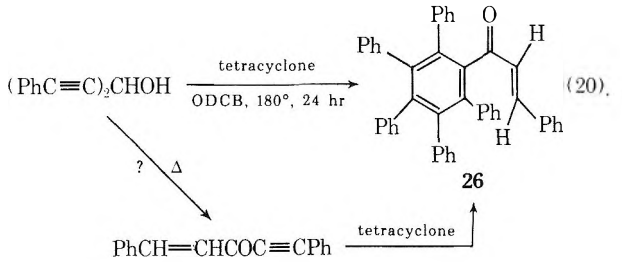
A number of other interesting conversions appear to depend on the rearrangement process. For example, **4** and p-toluenethiol in the presence of methanolic sodium methoxide at reflux yielded the single product, 1,5-diphenyl-2-(p-tolylthio)-1,4-pentadien-3-one (**25**). It was readily



(19)
25

found that **4** was essentially saponified in 2–5 min in methanolic sodium methoxide. The nmr spectrum of the reaction mixture indicated the presence of **1b** and **14** but no ester. We were also able to make **25** from both **1b** and **14** under the same reaction conditions. Hence the sequence hydrolysis, isomerization, and addition is quite reasonable.

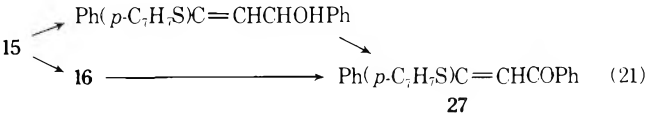
We have observed that at 180° in *o*-dichlorobenzene, both **1b** and **14** give the same Diels–Alder adduct with tetracyclone in the absence of added base.



(20)

Here we are inclined to believe that **1b** is first isomerized to **14**, presumably in a polar process, and **14** leads to the adduct.

In a reaction of p-toluenethiol with **15** in a solution of DMSO and triethylamine, we obtained 1,3-diphenyl-1-(p-tolythio)-prop-1-en-3-one (**27**) (eq 21). It appears that



(21)
27

amine is not essential in this curious synthesis but DMSO is. Replacement of DMSO by DMF as solvent in the reaction of **15** with p-toluenethiol in the presence of triethylamine does not give **27**. Clearly, overall rearrangement *and* oxidation–reduction has occurred; alternative routes to the product are given in eq 21. Now, DMSO can function as an oxidant, for we find that p-toluenethiol in an excess of DMSO yields di(p-tolyl) disulfide. It is thus possible that DMSO promotes oxidation on either or both branches of eq 21. Somewhat related examples in which thiyl radicals may be involved in oxidations have been reported, although redox processes involving interconversions of secondary alcohols and ketones seem most pertinent.[28] The results of several rearrangement conditions related to processes 13 and 21 are given in Table II.

To summarize this section, we note that the base-catalyzed ynol → enone rearrangement (eq 11–14) does not occur with alkyl ynols but appears to require at least a phenyl or extra ethynyl group to facilitate the formation of the anionic intermediates, *e.g.*, **19**. A number of strange-looking processes, eq 18–21, turn out to be straightforward once the basic rearrangement (eq 11, 13) is accepted.

Ultraviolet Spectra. The availability of a number of skipped diynes as well as adducts derived from **1** made a uv spectral study possible (Table III).[2-4] Here it was of special interest to see whether evidence for skipped conjugation could be found, that is, whether the central group was "chromolatory."[29]

Normally, λ_{max} for an alkyne is higher than λ_{max} for the corresponding alkene.[30] Thus, the data which are

Table III
Ultraviolet Spectra of Acetylenes and Their Polyarylated Derivatives, λ_{max} (Log ϵ_{max})[a]

R	$(RC{\equiv}C)_2CHOH$[c]	$(RC{\equiv}C)_3COH$[d]	$(RC{\equiv}C)_2C{=}O$[e]	2-$RPh_4C_6COC{\equiv}CR$[f]	$(2\text{-}RPh_4C_6)_2CO$[g]
CH_3	236 (1.95) 247 (1.95)	EA	236 (4.0) 247 (4.0)	233 sh (4.72) 280 sh (3.86)	
n-C_4H_9		EA	239 (4.08) 250 (4.08)	233 sh (4.66) 278 sh (3.94)	238 (4.84) 295 (4.08)
t-C_4H_9	239.5 (2.4) 251 (2.4)	EA	239 (4.15) 250 (4.15)	230 (4.63) 270 sh (3.87) 278 sh (3.77)	
C_6H_5	244 (4.53) 253 (4.56) 271 sh (3.33) 278 sh (3.03)	246 (4.73) 256 (4.73) 271 sh (3.79) 278 sh (3.48)	230 (4.3) 308 (4.36) 321 (4.36)	240 sh (4.72) 280 sh (4.32)	242 sh (4.85) 278 sh (4.32)

n-$BuC{\equiv}CCH_2C{\equiv}CCH_3$[b,h]	$(PhC{\equiv}C)_2CH_2$[b,i]	$PhCH{=}CHCOC{\equiv}CPh$[j]	$PhCH{=}CHCOC_6Ph_5$[k]
225 (2.71) 232.5 (2.66) 237 (2.68) 252 (2.48)	239 (4.95) 251 (5.05) 264 (3.23) 271.5 (3.12) 278.5 (2.96) 282 sh (2.55)	229.5 (4.22) 290 sh (4.24) 320 (4.40)	242 sh (4.51) 279 sh (4.17) 303 (4.21)

[a] EA = end absorption; sh = shoulder. The solvent was ethanol, unless otherwise noted. [b] Reference 2b. [c] Registry no.: R = t-C_4H_9, 50428-39-2. [d] Registry no.: R = C_6H_5, 50428-40-5. [e] Registry no.: R = n-C_4H_9, 18621-56-2; R = t-C_4H_9, 35845-67-1; R = C_6H_5, 15814-30-9. [f] Registry no.: R = CH_3, 50278-27-8; R = n-C_4H_9, 18627-92-4; R = t-C_4H_9, 50428-46-1; R = C_6H_5, 50278-28-9. [g] Registry no.: R = n-C_4H_9, 18627-95-7; R = C_6H_5, 18627-94-6. [h] Registry no., 50428-50-7. [i] Registry no., 6089-08-3. [j] Registry no., 16121-39-4. [k] Registry no., 50428-53-0.

given in Table III show that the 1,4-diynes are in our accessible range. On the other hand, 1,4-dienes, which include 1,3-dimethylenecyclobutane, two allene trimers,[31a] 1,4-cyclohexadiene [λ 270 nm (sh, log ε −0.5), 224 (sh, 1.5)],[31b] and 1,4-pentadiene [λ_{max} 181 nm (log ε 4.0)],[32] showed only end absorption, while the strained bicycloheptadiene showed several peaks of low intensity at λ_{max} 205 nm (log ε 3.32), 214 (3.17), 220 (2.94).[33] We shall return to this comparison shortly.

On the basis of negligible spectral changes between arylacetylenes and bis(arylethynyl)methanes and the large bathochromic shifts observed in the corresponding 1,3-diynes, we concluded previously that conjugation effects in the diethynylmethanes were small.[2b] Since 2,5-decadiyne[2b] (Table III) does indeed show a bathochromic shift relative to 1-butyne [λ_{max} 172 nm (log ε 3.65)] or 1-octyne [λ_{max} 1.85 nm (log ε 3.6), 225.5 (3.7)],[32,34] it appears that there is substantial conjugation in a 1,4-diyne, which is effectively overwhelmed in the aryl alkynes. The introduction of a hydroxyl group does not in general cause significant changes (Table III); the spectra of the bis(alkynyl)carbinols are much like those of the 1,4-alkadiynes, and the spectra of the bis- and tris(phenylethynyl)carbinols are still very similar to that of phenylacetylene.

By contrast, the trialkylethynylcarbinols appear to be anomalous in that their spectra show only the end absorption of simple alkynes (Table III).[30,32] This is all the more striking, since bicyclooctatriene has λ_{max} 208 nm (log ε 3.05) and 239 (2.48);[35] a bathochromic shift between divinyl- and diethynylmethane becomes hypsochromic between trivinyl- and triethynylmethane. It is the triethynylmethane, of course, which poses the problem in that the expected trend from mono- through diethynylmethane is broken.

Facile rationalizations may be hazardous here, since refined Pariser–Parr calculations have proved to be inadequate to reproduce observed spectral properties of bicycloheptadiene and bicyclooctatriene.[33]

The spectra of the diethynyl ketones have several interesting features (Table III). Despite the presence of cross-conjugation, λ_{max} of the triple bond chromophore is hardly affected relative to that in the bis(alkylethynyl)methanes or methanols, although the corresponding ε values are substantially increased. On the other hand, the low-intensity n → π* transition usually observed in the spectra of ketones, enones [MeCH=CHCHO, λ_{max} 321 nm (log ε 2.3)] and dienones [$(MeCH{=}CH)_2CO$, λ_{max} 336 nm (log ε 2.7)] was not in evidence.[30,36a] This may be rationalized as follows: the presence of a triple bond in a conjugated system does not appreciably alter λ_{max} but often decreases ϵ_{max} considerably;[30] the n → π* transition is symmetry forbidden and usually of low intensity (ϵ_{max} ~100); the cross-conjugation of the carbonyl chromophore between two double bonds can result in the total disappearance of the n → π* transition (possibly because the π system enforces planarity and inhibits the twisting needed to achieve a finite n → π* transition moment).[30,36a] The presence of an aryl group in **1b** restores normalcy in that more allowed transitions become available. Thus, the n → π* absorption, which is typical of aryl-substituted α,β-unsaturated carbonyl compounds, *e.g.*, *trans*-1,3-diphenyl-3-oxopentenyne (Table III) or bis(β-styryl) ketone [λ_{max} 330 nm (log ε 4.53)],[37] is now intense.

The absorption spectra of the Diels–Alder mono- and diadducts (Table III) may be regarded in part as those of polysubstituted benzenes and in part as ketones more or less related to acetophenone or benzophenone.[36b,38] Now, the single band (λ_{max} 251 nm) of biphenyl is comprised of the weak $^1B_{2u} \leftarrow {}^1A_{1g}$ (λ_{max} 262 nm) and the intense $^1B_{1u} \leftarrow {}^1A_{1g}$ (λ_{max} 208 nm) bands. The spectrum of hexaphenylbenzene, in which the outer phenyl groups are close (±10–25°) to perpendicular to the central ring, as in a paddlewheel,[39] clearly shows two intense peaks [λ_{max} 266 nm (log ε 4.54) and 247 (4.75)].[40] Evidently all of our adducts with the structural unit 2-RPh_4C_6- possess an analogous λ_{max} at *ca.* 278 and 235 nm. In somewhat simpler systems, *e.g.*, the triphenylbenzenes, spectral data indicate that steric interference may reduce conjugation and give rise to hypsochromic shifts: 1,3,5-, 1,2,4-, and 1,2,3-triphenylbenzenes have λ_{max} 252 nm (ε 58,000), 249 (33,000), and 239 (33,600), respectively.[41] However, the benzenoid bands of the series 2-$RPh_4C_6COC{\equiv}CR$ appear to be relatively insensitive to changes in substituents (Table III); presumably the dominant effect is that of the four phenyl groups essentially locked almost perpendicular to the central ring.

Benzophenone has a weak n → π* band [λ_{max} 333 nm (log ε 2.2)], a strong π → π* band [λ_{max} 253 nm (log ε

Table IV
Infrared Carbonyl ν(CO) Bands of the Dialkynyl Ketones and Their Diels–Alder Adducts[a]

Ketone	ν, cm⁻¹	Ketone	ν, cm⁻¹
$(MeC{\equiv}C)_2CO$	1630[b]	$(t\text{-}BuC{\equiv}C)_2CO$	1605
2-$MePh_4C_6COC{\equiv}CMe$	1655	2-t-$BuPh_4C_6COC{\equiv}CBu$-t	1655
$(PhC{\equiv}C)_2CO$	1605	$(n\text{-}BuC{\equiv}C)_2CO$	1625[c]
$Ph_5C_6COC{\equiv}CPh$	1645	2-n-$BuPh_4C_6COC{\equiv}CBu$-n	1655
$(Ph_5C_6)_2CO$	1670	(2-n-$BuPh_1)_2CO$	1660

[a] In KBr pellets, unless otherwise noted. [b] In CCl_4. [c] Neat.

4.20)], and end absorption.[42] If anything, the n → π* transition is slightly intensified with alkyl substitution in the benzophenones, as in 2,4,6,2′,4′,6′-hexakis(isopropyl)-benzophenone [λ_{max} 336 nm (log ε 2.47)], although a minor reversal may be found in other series, *e.g.*, acetophenones or benzaldehydes.[36b] In general, however, strong deviation from coplanarity in the benzoyl moiety is reflected in a diminished intensity, *e.g.*, 2,2′-di-*tert*-butylbenzophenone [λ 330 nm (log ε 1.9)].[42] If, as we suppose, the carbonyl group is close to perpendicular to the ring in our adducts, the intensity should approach zero, which is observed (Table III). In these adducts, the phenylethynyl group does not elicit ("bring out") the n → π* transition, although the β-styryl group in $Ph_5C_6COCH{=}CHPh$ does bring it in with high intensity (log ε 4.21), albeit at lower wavelength (λ 303 nm). This again indicates that the triple bond conjugates less efficiently than the double bond.[30]

There is independent evidence that supports our picture of a balance between steric hindrance and conjugation in the Diels–Alder adducts. Briefly, conjugation lowers the normal ir stretching frequency of a carbonyl band. Several series of molecules in Table IV illustrate the trend from "maximum" conjugation in the dialkynyl ketones through partial to "no" conjugation in the mono- and diadducts. For this group of compounds, the maximum $-\Delta\nu$ is 40 and 65 cm^{-1}, respectively, as one or both triple bonds flanking the carbonyl are converted to perphenylated rings (Table IV).

Experimental Section

Infrared spectra were recorded on a Beckman IR-8 spectrophotometer. Solution spectra were measured in a matched set of 0.1-mm sodium chloride or calcium fluoride cells. Ultraviolet and visible spectra were recorded on either a Beckman DK-2 or DBG spectrophotometer. Proton magnetic resonance spectra were obtained on a Varian A-60 spectrometer and are reported in δ units (parts per million) relative to internal tetramethylsilane. The reported line frequencies are estimated to be accurate within 0.5 Hz; s, d, t, q, and m are used to designate singlet, doublet, triplet, quartet, and multiplet, respectively. Mass spectra were obtained on a Varian MAT CH-7 instrument at approximately 50 eV. All reported compounds were purified by standard techniques before the spectra were taken. All melting points were taken in glass capillary tubes on a Mel-Temp heated block instrument and are uncorrected. Microanalyses were performed by M-H-W Laboratories, Garden City, Mich.

Materials. Bis(1-propynyl)methanol (**1a**) was prepared from 1-propynylmagnesium bromide and ethyl formate[5c] with the modification that the course of the exchange reaction between ethylmagnesium bromide and propyne was monitored by nmr. The reaction was assumed to be complete when the ethylmagnesium bromide resonance [$\delta(CH_2) = -0.60$] became negligible and the propynylmagnesium bromide resonance [$\delta(CH_3) = 1.86$] reached maximum amplitude. **1a** had mp 102–103° (lit.[5c] mp 107°); ir (KBr) 3270, 2290, 2260, 2230 cm^{-1}; nmr ($CDCl_3$) δ 1.86 (d, 6 H, J = 2.2 Hz), 2.66 (d, 1 H, J = 6.8 Hz), 5.1 (m, 1 H, J = 6.8 Hz).

Bis(phenylethynyl)methanol (**1b**) was prepared from phenylethynylmagnesium bromide and ethyl formate.[3a] It had mp 84–86° (lit.[3a] mp 84–86°); ir (CCl_4) 3585, 2250, 1040, 1020, 1005 cm^{-1}; nmr ($CDCl_3$) δ 3.0 (s, 1 H), 5.5 (s, 1 H), 7.3 (m, 10 H).

1,3-Diphenylpropynol (15) was obtained from phenylethynylmagnesium bromide and benzaldehyde as a yellow oil (51%):[17b] bp 165° (3.0 mm) [lit.[17b] bp 168° (5 mm)]; nmr (CCl_4) δ 3.99 (s, 1 H), 5.52 (s, 1 H), 7.7 (m, 10 H); ir (CCl_4) 3360, 2210, 2180, 1600, 1592 cm^{-1}.

Bis(phenylethynyl)methyl *N*-Phenylcarbamate (2b). Phenyl isocyanate (4 ml, 0.037 mol), **1b** (4 g, 0.017 mol), and pyridine (1 ml) were dissolved in dry benzene (60 ml) and stirred for 18 hr at ~25°. This solution was then poured into cold, dilute acetic acid and extracted twice with ether. The extracts were washed with saturated sodium bicarbonate solution and then dried over sodium sulfate. Work-up gave 3.4 g of a white solid, mp 125–127°, from carbon tetrachloride. The analytical sample had mp 129–130°, from carbon tetrachloride or ligroin: ir (KBr) 3410 (NH), 2235 (C≡C), 1705 cm^{-1} (C=O); nmr ($CDCl_3$) δ 6.6 (s, 1 H), 6.9 (broad, 1 H), 7.3 (m, 15 H).

Anal. Calcd for $C_{24}H_{17}NO_2$: C, 82.08; H, 4.87. Found: C, 82.34; H, 5.11.

4-Benzyl-3-phenyl-5-phenylethynyl-4-oxazolin-2-one (3). A mixture of **2a** (1.0 g, 2.9 mmol) and sodium methoxide (0.76 g, 15 mmol) in absolute methanol (50 ml) was refluxed for 3 hr and then poured into ice water. The solution was extracted with ether (30-ml portions), and the extract was washed with saturated salt solution and dried with sodium sulfate. Removal of the ether left a red oil which was chromatographed on alumina. With ether–hexane (4:1, v/v) as the eluting solvent, the first fractions yielded a yellow oil which was rechromatographed on alumina with the same solvent. From one of the fractions we obtained white needles: mp 134–136°; ir (KBr) 2260 (C≡C), 1775 (C=O), 1620 cm^{-1} (C=C); nmr ($CDCl_3$) δ 4.58 (s, 2H), 7.1–7.6 (m, 15 H); mass spectrum m/e (rel abundance) 351 (P^+, 100), 322 (10), 274 (20), 215 (40), 91 (10).

Anal. Calcd for $C_{24}H_{17}NO_2$: C, 82.08; H, 4.87. Found: C, 82.28; H, 4.91.

Bis(1-propynyl)methyl *N*-Phenylcarbamate (2a). Phenyl isocyanate (2.2 ml, 0.06 mol), **1a** (1 g, 0.01 mol), and pyridine (1 ml) were dissolved in dry benzene and refluxed for 20 hr. The resulting solution was poured into 3% acetic acid at 0°, stirred, and extracted with ether. Work-up yielded 1.9 g of solid, which on recrystallization (ligroin or carbon tetrachloride) or sublimation at 80° (2 mm) gave a white solid: mp 84–86°; ir (KBr) 3410 (NH), 2260, 2290, 2320 (C≡C), 1705 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.8 (d, 6 H), 6.1 (m, 1 H), 7.02 (broad, 1 H), 7.35 (m, 5 H); mass spectrum m/e (rel abundance) 227 (P^+, 85), 182 (10), 91 (100).

Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.76. Found: C, 74.34; H, 5.65.

Methoxybis(1-propynyl)methane (6). Dipropynylcarbinol (0.5 g) in dry benzene was refluxed over an excess of freshly cut sodium metal for 2 hr. The unreacted sodium was then removed and an excess of methyl iodide was added. After standing at 25° for 5 days, the reaction mixture was filtered and the solvent was evaporated. The resulting yellow oil was chromatographed on silica gel with benzene–chloroform (1:1, v/v) as eluent. Three distinct bands appeared, of which the first eluted contained the desired methoxy compound as a yellow oil: nmr ($CDCl_3$) δ 1.85 (d, 6 H), 3.35 (s, 3 H), 4.81 (m, 1 H); mass spectrum m/e (rel abundance) 122 (P^+, 5), 91 (100), 65 (60), 47 (30), 39 (20).

Bis(phenylethynyl)methyl Acetate (4). Acetyl chloride (2 ml, 2.2 g, 28 mmol) was added dropwise to a solution of **1b** (2 g, 8.16 mmol) in dry benzene (40 ml) and dry pyridine (1 ml). This solution was refluxed for 12 hr and then poured onto crushed ice. Work-up, identical with that of the bromo ester (see below), yielded 2.1 g of cream-colored solid: mp 65–66°; ir (thin film) 2901 (CH_3), 2230 (C≡C), 1750 (C=O), 1220 cm^{-1} (CO); nmr ($CDCl_3$) δ 2.15 (s, 3 H), 6.66 (s, 1 H), 7.5 (m, 10 H).

Anal. Calcd for $C_{19}H_{14}O_2$: C, 83.19; H, 5.14. Found: C, 83.10; H, 5.18.

When **4** (0.27 g) and 3,4-xylidine (0.24 g) were refluxed in methanol, removal of the methanol gave a red oil which consisted of unreacted **4**, **1b**, and **14**. Prolonged reflux in methanol eventually yielded a small amount (~15%) of an adduct of 3,4-xylidine and **14**. This appeared to be a typical amine-alkyne adduct,[3] namely, *trans,trans*-3,4-$(Me)_2C_6H_3NHC(Ph){=}CHCOCH{=}CHPh$: ir ($CHCl_3$) 3400 (NH), 1610 (C=O), 1590, 1550 cm^{-1} (C=C); nmr ($CDCl_3$) δ 2.2 (s, 3 H), 2.1 (s, 3 H), 5.5 (s, 1 H).

Bis(1-propynyl)methyl *m*-Bromobenzoate (5). To 0.3 g of sodium hydride dispersion (50% in oil, washed with pentane prior to use) under dry benzene (5 ml) in a nitrogen atmosphere was

added **1a** (0.5 g, 5 mmol). After all the sodium hydride had reacted, the reaction mixture was cooled to 0° and a solution of *m*-bromobenzoyl chloride (1.1 g, 5 mmol) in dry benzene (2 ml) was added dropwise. The resulting suspension was stirred for 30 min at 25° and then poured into ice water. Work-up gave a yellow oil which was then chromatographed on silica gel with ligroin–benzene (2:1, v/v) as the eluent. This yielded white crystals: mp 88–90° from ligroin; ir (CCl_4) 2265 (C≡C), 1735 (C=O), 1250 cm^{-1} (CO); nmr ($CDCl_3$) δ 1.85 (d, 6 H), 6.25 (m, 1 H), 7.1–8.3 (m, 4 H).

Anal. Calcd for $C_{14}H_{11}BrO_2$: C, 57.91; H, 3.78. Found: C, 57.78; H, 3.43.

4-Bromo-2,5-heptadiyne (7a) and 2-Bromo-2,3-heptadien-5-yne (8a). A mixture of **1a** (2 g, 20 mmol) and phosphorus tribromide (2 g, 7.5 mmol) in absolute ether (20 ml) was stirred at 0° for 2 hr and then treated with saturated aqueous sodium bicarbonate (100 ml) at 0° for 15 min. The ether layer was separated and the bicarbonate solution was extracted with ether (2 × 20 ml). The combined extract was dried over magnesium sulfate and evaporated to yield a bright yellow semisolid which was unstable at 25° but stable at −78°. This material consisted of *ca.* 98% **7a** and *ca.* 2% **8a** based on ir and nmr analyses. In a second synthesis, a mixture of **1a**, phosphorus tribromide, and dry pyridine (1 equiv) in absolute ether was refluxed for 18 hr and then poured onto ice. Work-up yielded a yellow semisolid which was shown by combined ir and nmr analyses to contain a 1:1 ratio of **7a** and **8a**. **7a** had ir (CCl_4) 2320, 2270, 2255 (C≡C), 630 cm^{-1} (CBr) and no OH absorption; nmr ($CDCl_3$) δ 1.88 (d, 6 H, J = 2.0 Hz), 5.17 (m, 1 H, J = 2.0 Hz); mass spectrum *m/e* (rel abundance) 172 (P^+, 20), 170 (2), 92 (40), 91 (100), 90 (35), 89 (50), 65 (80), 39 (50). **8a** had ir (CCl_4) 2320, 2270, 2255 (C≡C), 1945 (C=C=C), 630 cm^{-1} (CBr); nmr ($CDCl_3$) δ 1.8, 5.5 (m).

2,5-Heptadiyne (9). To 1 equiv of aqueous chromium(II) sulfate[43] in a flask sealed under nitrogen with a serum stopper was injected 1 g of **7a** in 10 ml of peroxide-free tetrahydrofuran. The blue color of chromium(II) was immediately discharged and the reaction mixture warmed up. The reaction mixture was stirred for 5 min, saturated with ammonium chloride, and extracted with ether. This extract was washed with water, dried over sodium sulfate, and distilled under nitrogen. The residue (*ca.* 0.5 ml) was cooled to −78° and left at 0.6 mm for 15 min. The remaining oil, which appeared to be mainly the desired heptadiyne (*ca.* 95%), discolored on standing at 25°, although it appeared to be stable indefinitely at −78°. It had ir (CCl_4) 2240 (C≡C), 1318 cm^{-1} (C≡CCH_2C≡C); nmr ($CDCl_3$) δ 1.75 (t, 6 H, J = 2.6 Hz), 3.06 (m, 2 H, J = 2.6 Hz); mass spectrum *m/e* (rel abundance) 92 (P^+, 40), 91 (100), 65 (72), 47 (35), 39 (20).

The ethynyl–allenic (9:1) bromide mixture (**7a** + **8a**) was treated with an excess of magnesium metal in absolute ether. This reaction mixture was stirred at 25° for 24 hr and then poured into cold, saturated ammonium chloride solution. Standard work-up yielded an oil which consisted of unreacted bromides, **9**, and 2,3-heptadien-5-yne, as determined by ir and nmr.

3-Bromo-1,5-diphenyl-1,4-pentadiyne (7b). A solution of **1b** (6 g, 26 mmol) and phosphorus tribromide (3 g, 11 mmol) in absolute ether (100 ml) was stirred at 0° for 6 hr, and then treated with saturated aqueous sodium bicarbonate solution at 0° for 15 min. The ether layer was separated and the bicarbonate solution was extracted with ether (2 × 20 ml). The combined extract was dried over magnesium sulfate, evaporated under reduced pressure to *ca.* 30 ml, and treated with ligroin (100 ml), and the resulting solution was heated gently to drive off the remaining ether. When the resulting solution was cooled rapidly to −78° and the vessel was scratched vigorously, a solid precipitated. Two recrystallizations from hexane yielded a lemon-yellow solid, mp 48–49°, which could be stored for several weeks at −78°, but which was unstable at 25°, turning into a red tar in *ca.* 8–12 hr. The solid had ir (CCl_4) 2300, 2260, 2240 (C≡C), 630 cm^{-1} (CBr), and no OH bands; nmr ($CDCl_3$) δ 5.8 (s, 1 H), 7.3 (m, 10 H); mass spectrum *m/e* (rel abundance) 296 (10), 294 (P^+, 10), 216 (80), 215 (100), 213 (75), 189 (20).

When **7b** in THF was treated with an excess of chromium(II) sulfate in THF–water under nitrogen, the blue color of chromium(II) was immediately discharged. Extraction of the mixture with ether followed by removal of the ether gave a red oil which crystallized upon addition of methanol to give a yellow solid, mp 90–115°. Tlc on silica (chloroform) showed one major and two minor components. Column chromatography on silica gel or on a column of silver nitrate on silica gel also failed to separate the components. The ir spectrum of this solid showed only typical aromatic absorptions. The nmr spectrum showed an aromatic multiplet at δ 7.2 along with a doublet at δ 6.1 and a singlet at δ 4.3. Mass spectral data indicated a molecular weight of 430, with a base peak at *m/e* 215; 1,1,2,2-tetrakis(phenylethynyl)ethane would have P^+ 430.

When **7b** (1.5 g) was treated with magnesium metal (0.12 g) in absolute ether under nitrogen and stirred at 25° for 1 hr, a yellow precipitate appeared. Stirring was continued for 1 hr and the mixture was quenched with saturated ammonium chloride solution. Work-up yielded a yellow solid identical in all respects with that obtained from chromium(II) reduction.

Tetrakis(1-propynyl)ethylene Glycol (10). To a cooled solution of propynylmagnesium bromide in ether (1 *M*, prepared from ethylmagnesium bromide and propyne) was added an ethereal solution of freshly distilled diethyl oxalate (36.5 g, 0.25 mol). After the addition was completed, the reaction mixture was warmed to 25°, stirred overnight, refluxed for 2 hr, and finally poured into cold, saturated ammonium chloride solution. Extraction with ether followed by work-up gave a yellow-white solid (25 g, 50%), mp 153–154° dec (lit.[12a] mp 150–154° dec), from ligroin–benzene: ir ($CHCl_3$) 3540 (OH), 2240 (C≡C), 1135 cm^{-1} (CO); nmr ($CDCl_3$) δ 1.92 (s, 12 H), 3.07 (s, 2 H). A solution of this glycol in toluene was refluxed for 18 hr. Removal of the solvent left a red oil, whose ir spectrum had bands at 2240, 1650, 1640, 1605, and 970 cm^{-1}. This oil was worked up to yield dipropynyl ketone, mp 75–77° (lit.[5c] mp 78–80°), on sublimation. The ir bands at 1650, 1605, and 970 cm^{-1} indicate the presence of hept-2-en-5-yn-4-one (**12**) [lit.[44] ir (neat) 1650, 1600, and 960 cm^{-1}] in the crude product.

4,4,5,5-Tetrakis(1-propynyl)-1,3-dioxolan-2-one (13). A solution of **10** (1.06 g) and 1,1′-carbonyldiimidazole (0.66 g) in toluene (50 ml) was refluxed for 30 min. The reaction mixture was cooled to 25° and washed several times with water. After the toluene layer was dried with sodium sulfate, the solvent was removed to give a brown-tan solid. Two recrystallizations from benzene–ligroin (Norit) gave white crystals, mp 166–168°, in 80% yield: ir ($CHCl_3$) 2260 (C≡C), 1815 (C=O), 1160, 1000 cm^{-1} (CO); nmr ($CDCl_3$) δ 1.93 (s, 12 H).

Anal. Calcd for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03. Found: C, 75.29; H, 4.94.

Isomerization of Bis(phenylethynyl)methanol (1b) to 1,5-Diphenylpent-1-en-4-yn-3-one (14). A solution of **1b** (1.92 g, 8.27 mmol) and sodium acetate (0.75 g) in DMF (20 ml) was warmed to 50° for 3.5 hr and then worked up to give *trans*-**14** (0.35 g, 18%) as a white solid, mp 69° (lit.[37] mp 69–70°), from petroleum ether: nmr ($CDCl_3$) δ 6.8 (d, 1 H, J = 16.1 Hz), 7.5 (m, 10 H) 7.9 (d, 1 H, J = 16.1 Hz); ir (CCl_4) 2225 (C≡C), 1660, 1650, (C=O), 1580 (C=C), 980 cm^{-1} (trans C=C). Alternatively, a solution of **1b** (1 g, 4.25 mmol) in anhydrous triethylamine (40 ml) was refluxed for 24 hr. The solvent was then removed (Rotovap) and the oil was taken up in hot ligroin. Upon cooling, this solution deposited a yellow solid (0.8 g, 85%) of *trans*-**14**, mp 67–68°.

The stereochemical preference of the rearrangement was checked as follows. A solution of **1b** (1.00 g, 4.31 mmol) and triethylamine (0.20 ml) in DMF (10 ml) was charged into an ampoule and sealed. The ampoule was heated at 50° for 5 hr, opened, and analyzed by nmr. The products, *ca.* 29% *cis*-**14**, *ca.* 12% *trans*-**14**, and unchanged **1b** could be estimated from the peak areas of ethylenic and tertiary carbon hydrogens. The accuracy of these and similar analyses (Table I) was reduced at lower concentrations of the solution when the solvent peak (DMF) interfered. The solution was evaporated under vacuum at 50° to leave a yellow oil, which was chromatographed on silica gel. Carbon tetrachloride, as the first developing solvent, gave *cis*-**14** (0.24 g, 24%); dichloromethane–carbon tetrachloride (3:7) as the next solvent gave *trans*-**14** (0.045 g, 4.5%); finally, dichloromethane as the solvent gave the unchanged reactant (0.36 g, 36%). *cis*-**14** had nmr (acetone) δ 6.40 (d, J = 12.3 Hz, 1 H), 6.28 (d, J = 12.3 Hz, 1 H), 7.80–7.35 (m, 10 H); ir (neat) 2220 (C≡C), 1650, 1630 (C=O), 1570 (C=C), 693 cm^{-1} (cis C=C); mass spectrum *m/e* 232 (P^+), 231, 203,202, 169, 168, 104, 76.

1-(2,4-Dinitrophenyl)-3-(β-styryl)-5-phenylpyrazole. To a boiling solution of 2,4-dinitrophenylhydrazine (0.25 g) in acidified ethanol (20 ml) was added a solution of **14** (0.3 g) in ethanol (10 ml). The solid (0.89 g), which formed immediately, was recrystallized from acetic acid to yield orange-red needles: mp 232–234°; ir ($CHCl_3$) 1620 (C=C, C=N), 980 cm^{-1} (trans C=C).

Anal. Calcd for $C_{23}H_{16}N_4O_4$: C, 66.98; H, 3.91. Found: C, 67.32; H, 3.88.

Trapping Experiments during the Conversion 1b → 14. Compound **1b** (0.5 g, 2 equiv) in dry benzene was added to sodium hydride (0.3 g, 50% dispersion in oil, prewashed with pentane)

under benzene in a nitrogen atmosphere. After being stirred at 25° for 10 min or until gas evolution ceased, the reaction mixture was treated in different ways.

1. When excess absolute ethanol was added and the mixture was worked up, the resulting oil consisted of **1b** and **14** (2:1) plus a trace of phenylacetylene, according to an nmr analysis.

2. When the reaction mixture was quenched with D_2O and filtered through sodium sulfate, evaporation of the solvent gave an oily solid consisting of **1b** (90%) and **14** (10%). Subsequent experiments showed that deuterated **1b** exchanges upon contact with the sodium sulfate used here.

3. When the reaction mixture was quenched with excess chlorotrimethylsilane at 0° and the reaction mixture was stirred for 30 min at 25°, evaporation of the solvent gave an oil consisting of 95% **23**, 1% unreacted **1b**, and 4% **14** by ir and nmr analysis. Attempts to purify **23** were unsuccessful; $(PhC{\equiv}C)_2CHOSi(CH_3)_3$ had nmr ($CDCl_3$) δ 7.3 (m, 10 H), 5.72 (s, 1 H), 0.3 (s, 9 H); ir (CCl_4) 2230 (C≡C), 1250, 950 ($SiCH_3$), 1085 cm^{-1} ($OSiCH_3$).

4. When the reaction mixture was quenched with acetyl chloride, a red solution and a white precipitate formed. The solid was filtered off and the solvent was removed to give a red oil, which consisted of bis(phenylethynyl)methyl acetate (98%), **14** (1%), and a trace of phenylacetylene.

5. When the reaction mixture was quenched with other substrates such as benzaldehyde, acetone, iodomethane, benzyl chloride, tetramethylammonium iodide, ethyl cinnamate, and ethyl bromoacetate and stirred for 30 min at 25°, work-up generally yielded unreacted **1b** and **14** in varying proportions as well as 1–5% phenylacetylene.

In experiments in which possible carbene intermediates were sought, we modified the standard procedure slightly: sodium hydride (1 equiv) was suspended either in dry cyclohexene (10 ml) or in a solution of *trans*-stilbene in ether or in ethyl cinnamate in benzene, and **1b** (0.5 g) was added at 0°. After work-up, only **1b**, **14** and unreacted alkene could be detected and isolated.

Other Observations Relevant to 1b → 14. When **1b** was treated with 1 equiv of *n*-butyllithium in ether–hexane at −78°, the nmr spectrum of this solution showed that the α-CH resonance of **1a** (δ 5.5) had disappeared. Here OH resonance (δ 3.0) was obscured by the solvent and could not be traced. When **1b** was treated with sodium hydride (1 or 2 equiv) in dry benzene, only 1 equiv of hydrogen gas was evolved, within experimental error. The nmr spectrum of the resulting deep-red solution showed that both the α-CH (328 Hz, δ 5.5) and the OH resonances (129 Hz, δ 2.19) of **1b** had disappeared and a new resonance at 416 Hz (δ 6.93) had appeared. This resonance is attributed to the α-CH of $(PhC{\equiv}C)_2CHO^-$ (**19**).

1-(Pentaphenylphenyl)-3-phenylprop-2-en-1-one (26). Tetracyclone (11 g, 0.03 mol) and **1b** (7 g, 0.03 mol) were refluxed in *o*-dichlorobenzene under nitrogen for 24 hr. The resulting solution was cooled at −78° for 1 hr and filtered. The retained brown solid was washed with acetone until the washings became colorless. Recrystallization from methylene chloride–acetone gave 4 g of cream-colored solid, mp 335–336°. Alternatively, **14** and tetracyclone (1:1) were refluxed in xylene for 3 days. At 25°, a white solid crystallized out. One recrystallization from methylene chloride–acetone gave a white solid: mp 335–336° (sealed tube); ir (KBr) 1640 (C=O), 1620 cm^{-1} (C=C); nmr ($CDCl_3$) δ 6.33 (d, 1 H, J = 16 Hz), 6.8–7.25 (m, 31 H); mass spectrum *m/e* (rel abundance) 588 (P^+, 100), 487 (20).

Anal. Calcd for $C_{45}H_{32}O$: C, 91.8; H, 5.48. Found: C, 92.08; H, 5.67.

1,5-Diphenyl-2-(*p*-tolylthio)-1,4-pentadien-3-one (25). To a solution of bis(phenylethynyl)methyl acetate (02.7 g, 1 mmol) and *p*-toluenethiol (0.12 g, 1 mmol) in absolute methanol (20 ml) was added a saturated solution of sodium methoxide in methanol (5 ml). After 10 min at *ca.* 65° and cooling to 25°, the reaction mixture deposited a yellow precipitate. In a second approach, a solution of **1b** (0.23 g, 1 mmol) and *p*-toluenethiol (0.12 g, 1 mmol) in absolute methanol was treated and worked up essentially as above to give the same solid. In a third approach, the same solid dropped out on mixing a saturated solution of methanolic sodium methoxide, a solution of **14** (0.23 g, 1 mmol), and *p*-toluenethiol (0.12 g, 1 mmol) in methanol. All of the solid products were recrystallized from methanol to give yellow needles: mp 169–171°; ir ($CHCl_3$) 1665, 1650 (C=O, cis and trans), 1590 cm^{-1} (C=C); nmr ($CDCl_3$) δ 2.17 (s, 3 H), 6.9 (d, 1 H, J = 16 Hz), 6.92 (s, 1 H), 7.75 (d, 1 H, J = 16 Hz), 7.0–7.6 (m, 14 H); mass spectrum *m/e* (rel abundance) 356 (P^+, 30), 279 (20), 249 (30), 225 (35), 181 (100), 131 (50), 103 (10), 91 (5).

Anal. Calcd for $C_{24}H_{20}OS$: C, 80.86; H, 5.65. Found: C, 81.13; H, 5.32.

Isomerization of 1,3-Diphenyl-2-propyn-1-ol (15) to Phenyl β-Styryl Ketone (16). An ampoule (25 ml) containing **15** (2 g, 9.18 mmol), triethylamine (0.4 ml), and DMSO (10 ml) was flushed with nitrogen, sealed, and heated at 140° for 10 hr. Work-up gave a brown oil which contained essentially **15** and **16** (*ca.* 10%), according to mass spectral analysis. To separate **16** the oil was dissolved in DMF (10 ml) and treated with phenyl isocyanate (1.19 g, 10 mmol) and stannous chloride (0.050 g). This mixture was heated at 100° for 2 hr, treated with methanol (2 ml), heated at 100° for another 1 hr, cooled, and poured into water (10 ml). Work-up afforded **16** (0.044 g, 2.2%): mp 54–56° (lit.[45] mp 57–58°); nmr ($CDCl_3$) δ 8.10–7.75 (m); ir (CCl_4) 1668, 1647, 1450 cm^{-1}.

The results of a number of other similar experiments are given in Table II. We describe the last two entries in some detail. The product solution from the sodium hydroxide reaction was poured into cold water (40 ml) and extracted three times with ether (*ca.* 100 ml). The ether extract was washed with water. Removal of half the ether (50 ml) gave a white solid, which was filtered off. The solid was reprecipitated from ether (yield 0.51 g, 17%). The structure of this material is unknown: mp 254–255°; nmr ($CDCl_3$) δ 6.7–7.7 (m, *ca.* 35 H), 5.44 (d, J = 2.4 Hz, 1 H, -OH), 4.0–4.74 (m, 4 H), 2.25–2.6 (m, 2 H); ir (Nujol) 3480 (OH), 1670 (C=O), *1640 (C=O or C=C)*, 1259, *1222*, 1070, *1005*, *977*, 702 cm^{-1}; mass spectrum P^+ *ca.* 670.

The product solution from the azide reaction was extracted with ether and dried to yield a white solid. This was purified by several reprecipitations with cyclohexane or ether (0.3 g, 10%). The molecular weight of the product corresponds to that of a dimer but the structure is unknown: mp 188–191°; nmr ($CDCl_3$) δ 7.90–7.25 (m, 22 H), 5.32 (d, J = 2.6 Hz, 1 H), 4.83 (d, J = 2.6 Hz, 1 H); ir ($CHCl_3$) 3030, 1680, 1658, 1597, 1495, 1450 cm^{-1}.

1,3-Diphenyl-1-(*p*-tolylthio)-prop-1-en-3-one (27). A solution of *p*-toluenethiol (1.24 g, 10 mmol), **15** (2.07 g, 10 mmol), and triethylamine (0.5 ml) in DMSO (20 ml) was heated at 140° for 20 hr, cooled, poured into cold water (20 ml), and extracted three times with ether. The ether extract was then washed with water to remove DMSO and triethylamine. Removal of ether left **27**, a yellow solid from CCl_4–$CHCl_3$ (1:1) (0.680 g, 21%): mp 179–181°; nmr ($CDCl_3$) δ 8.25–7.95 (m, 2 H), 7.60–6.75 (m, 13 H), 2.18 (s, 3 H); ir ($CHCl_3$) 1635, 1600, 1580, 1530 cm^{-1}.

Anal. Calcd for $C_{22}H_{18}OS$: C, 79.97; H, 5.49; S, 9.70. Found: C, 80.06; H, 5.36; S, 9.60.

Registry No.—**1a**, 50428-54-1; **1b**, 15814-32-1; **2a**, 50428-56-3; **2b**, 50428-88-1; **3**, 50428-89-2; **4**, 50428-57-4; **5**, 50428-58-5; **6**, 50428-59-6; **7a**, 50428-60-9; **7b**, 27871-98-3; **8a**, 50428-62-1; **9**, 50428-63-2; **10**, 50428-64-3; **13**, 50428-65-4; *trans*-**14**, 37845-36-6; *cis*-**14**, 50428-67-6; **14** adduct, 50428-68-7; **15**, 1817-49-8; **16**, 94-41-7; **25**, 50428-71-2; **26**, 50428-53-0; **27**, 50428-73-4; 1-(2,4-dinitrophenyl)-3-(β-styryl)-5-phenylpyrazole, 50428-74-5.

References and Notes

(1) Abstracted from the Ph.D. Theses of K. G. M., May 1973, and Y. T., May 1972, Illinois Institute of Technology.

(2) I. M. Mathai, H. Taniguchi, and S. I. Miller, *J. Amer. Chem. Soc.*, **89**, 115 (1967); H. Taniguchi, I. M. Mathai, and S. I. Miller, *Tetrahedron*, **22**, 867 (1966).

(3) (a) T. Metler, A. Uchida, and S. I. Miller, *Tetrahedron*, **24**, 4285 (1968); (b) K. G. Migliorese and S. I. Miller, *J. Org. Chem.*, **39**, 843 (1974).

(4) C. K. Tseng, K. G. Migliorese, and S. I. Miller, *Tetrahedron*, in press.

(5) (a) A. W. Johnson, "The Chemistry of Acetylenic Compounds," Vol. I, Edward Arnold Co., London, 1946, p 135 ff; (b) E. R. H. Jones, L. Skattebøl, and M. C. Whiting, *J. Chem. Soc.*, 4795 (1956); (c) J. Chauvelier, *Ann. Chim. (Paris)*, **3** (12), 393 (1948).

(6) C. K. Liang, *Bull. Soc. Chim. Fr.*, 33 (1933); (b) *ibid.*, 41 (1933).

(7) (a) R. D. Dillard, D. R. Cassady, and N. R. Easton, *J. Med. Chem.*, **10**, 1180 (1967); (b) R. D. Dillard, G. Poore, D. R. Cassady, and N. R. Easton, *ibid.*, **10**, 40 (1967); (c) N. R. Easton, D. R. Cassady, and R. D. Dillard, *J. Org. Chem.*, **27**, 2927 (1962); (d) K. Sisido, K. Hukuoka, M. Tuda, and H. Nozaki, *ibid.*, **27**, 2663 (1962); (e) S. L. Shapiro, V. Bandurco, and L. Freedman, *ibid.*, **26**, 3710 (1961).

(8) (a) S. Swaminathan and K. V. Narayanan, *Chem. Rev.*, **71**, 429 (1971). (b) I. Iwai and Y. Okajima, *Yakugaku Zasshi*, **79**, 1284 (1959); *Chem. Abstr.*, **54**, 4474 (1960).

(9) Y. Hori, K. Noda, S. Kobayashi, and H. Taniguichi, *Tetrahedron Lett.*, 3563 (1969).

(10) J. H. Wotiz in, "Chemistry of Acetylenes," H. G. Viehe, Ed., Marcel Dekker, New York, N. Y., 1969, pp 365–424.

(11) J. R. Hanson and E. Premuzic, *Angew. Chem., Int. Ed. Engl.*, **7**, 247 (1968).

(12) (a) G. I. Iotsitch, G. N. Tokarski, and A. I. Chibaef, *Bull. Soc. Chim. Fr.*, 1324 (1911); *J. Russ. Phys. Chem. Soc.*, **42**, 1493

(1910); (b) F. J. Wilson and W. M. Hyslop, *J. Chem. Soc.*, 1556 (1924).
(13) A. Viola, J. H. MacMillan, R. J. Proverb, and B. L. Yates, *J. Amer. Chem. Soc.*, **93**, 6967 (1971); J. Chuche and N. Manisse, *C. R. Acad. Sci., Ser. C*, **267**, 78 (1968).
(14) E. J. Corey and R. A. E. Winter, *J. Amer. Chem. Soc.*, **85**, 2677 (1963).
(15) P. S. Wharton, G. A. Hiegel, and S. Ramaswami, *J. Org. Chem.*, **29**, 2441 (1964).
(16) R. J. Bushby, *Quart. Rev., Chem. Soc.*, **24**, 585 (1970).
(17) (a) R. Raphael and A. Nineham, *J. Chem. Soc.*, 119 (1949); (b) G. L. Lappin, *J. Org. Chem.*, **16**, 419 (1951).
(18) E. A. El'perina, B. P. Gusev, and V. F. Kucherov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2215, (1965); *Chem. Abstr.*, **64**, 11077 (1965).
(19) Y. Tanaka, S. Velen, and S. I. Miller, *Tetrahedron*, **29**, 3271 (1973).
(20) P. Laszlo and P. R. Schleyer, *Bull. Soc. Chim. Fr.*, **87** (1964); S. Castellano and J. S. Waugh, *J. Chem. Phys.*, **34**, 295 (1962).
(21) W. J. le Noble, Y. Tatsukami, and H. F. Morris, *J. Amer. Chem. Soc.*, **92**, 5681 (1970).
(22) H. Meister, *Chem. Ber.*, **98**, 2862 (1965).
(23) J. Hine and G. Koser, *J. Org. Chem.*, **36**, 1348 (1971).
(24) (a) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance in Organic Chemistry," 2nd ed, Pergamon Press, Oxford, 1969, p 262 ff; (b) K. Takahashi, M. Takaki, and R. Asami, *J. Phys. Chem.*, **75**, 1062 (1971).
(25) Y. Leroux and R. Mantione, *Tetrahedron Lett.*, 592 (1971).
(26) J. M. Figuera, J. M. Gamboa, and J. Santos, *J. Chem. Soc., Perkin Trans. 2*, 1435 (1972); D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965, pp 175–191; D. H. Hunter and D. J. Cram, *J. Amer. Chem. Soc.*, **86**, 5478 (1964).
(27) J. W. Burley and R. N. Young, *J. Chem. Soc., Perkin Trans. 2*, 1843 (1972); K. Bowden and R. S. Cook, *ibid.*, 1407 (1972).
(28) (a) T. J. Wallace, H. Pobiner, J. E. Hofmann, and A. Schriesheim, *J. Chem. Soc.*, 1271 (1965); (b) R. M. Kellog, *Methods Free Radical Chem.*, **2**, 1 (1969); (c) S. G. Cohen, S. Orman, and D. A. Laufer, *J. Amer. Chem. Soc.*, **84**, 3905 (1962).
(29) E. A. Braude, *J. Chem. Soc.*, 1902 (1949).
(30) E. S. Stern and C. J. Timmons, "Electronic Absorption Spectroscopy in Organic Chemistry," 3rd ed, Edward Arnold, London, 1970, Chapters 4 and 5.
(31) (a) B. Weinstein and A. H. Fenseleau, *J. Chem. Soc. C*, 368 (1967); (b) L. W. Pickett and E. Sheffield, *J. Amer. Chem. Soc.*, **68**, 216 (1946).
(32) L. C. Jones, Jr., and L. W. Taylor, *Anal. Chem.*, **27**, 228 (1955).
(33) C. F. Wilcox, Jr., S. Winstein, and W. G. McMillan, *J. Amer. Chem. Soc.*, **82**, 5450 (1960).
(34) J. R. Platt, H. B. Klevens, and W. C. Price, *J. Chem. Phys.*, **17**, 466 (1949).
(35) H. E. Zimmerman and R. M. Paufler, *J. Amer. Chem. Soc.*, **82**, 1514 (1960).
(36) (a) H. H. Jaffe and M. Orchin, "Theory and Applications of Ultraviolet Spectroscopy," Wiley, New York, N. Y., 1962, Chapters 5 and 10; (b) Chapter 15.
(37) J. G. Dinwoodie, H. M. White, and W. J. Day, *J. Org. Chem.*, **27**, 327 (1962).
(38) H. Suzuki, "Electronic Absorption Spectra and Geometry of Organic Molecules," Academic Press, New York, N. Y., 1967, Chapters 12 and 21.
(39) J. C. J. Bart, *Acta Crystallogr., Sect. B*, **24**, 1277 (1968).
(40) M. A. Ogliaruso and E. I. Becker, *J. Org. Chem.*, **30**, 3354 (1965).
(41) D. Buza and W. Polaczkowa, *Tetrahedron*, **21**, 3409 (1965).
(42) R. F. Rekker and W. T. Nauta, *Recl. Trav. Chim. Pays-Bas*, **80**, 765, 747 (1961).
(43) J. Lingane and R. Pecsok, *Anal. Chem.*, **20**, 425 (1948).
(44) G. N. Bondarev and A. A. Petrov., *Zh. Org. Khim.*, **2**, 782 (1966).
(45) E. P. Kohler, H. M. Chadwell, H. T. Clarke, and R. P. Leavitt, *Org. Syn.*, **2**, 1 (1922).

Reactions Involving Electron Transfer. V. Reduction of Nonconjugated Acetylenes[1a]

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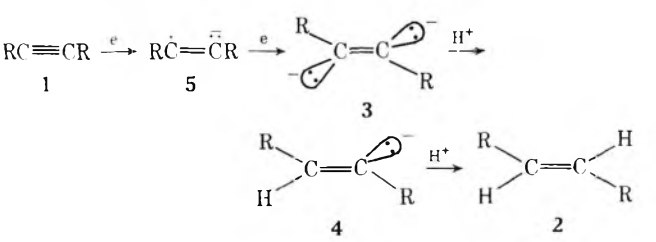
Received August 8, 1973

The reduction of 3-hexyne (**9**) and of 1-hexyne (**7**) with solutions of sodium in hexamethylphosphoramide (HMP)–tetrahydrofuran (THF) mixtures has been studied. In the absence of an added proton donor, the internal acetylene was reduced to mixtures of the 2-hexenes **28** and **29** and the 3-hexenes **24** and **25**. However, in the presence of a proton donor, *t*-BuOH, only the 3-hexenes were produced. At low temperature (−33°) in the presence of excess Na and *t*-BuOH, >95% of the olefin product was the trans isomer **24**. At higher temperatures (0 or 25°) or employing an inverse addition procedure to limit the Na concentration, mixtures containing 80–90% trans olefin **24** and 10–20% cis olefin **25** were obtained. Comparable mixtures (77–82% **24** and 18–23% **25**) were formed when 3-chloro-*cis*-3-hexene was reduced under various conditions with solutions of Na and *t*-BuOH in HMP–THF. These results are compared with reductions effected by solutions of Na in liquid NH_3 and the reaction pathways operative in these reductions are discussed.

A well-established synthetic route to trans symmetrically disubstituted olefins **2** involves the reduction of disubstituted acetylenes **1** with solutions of alkali metals (particularly sodium) in liquid ammonia[2,3] or with solutions of lithium in low molecular weight amines.[3a,b] It has been suggested[2c,d] that the stereochemistry of this reduction process is attributable to the addition of two electrons to the linear acetylene **1** to form a nonlinear dianion that adopts the trans geometry indicated in structure **3** to minimize electrostatic repulsion between the two unshared electron pairs. The successive addition of two protons at rates more rapid than the relatively slow rate of inversion of the vinyl anion **4**[4] would then account for the formation of the trans olefin **2** containing much less cis isomer than would be expected in an equilibrium mixture.

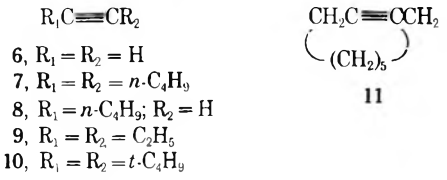
However, this process (Scheme I), involving two successive electron transfers to the acetylene **1** to form the intermediate radical anion **5** and the dianion **3**, is difficult to reconcile with polarographic studies of the electrochemical reduction of acetylenes. Although acetylenes conjugated with a carbonyl group[5] or with one or two aryl groups[6]

Scheme I



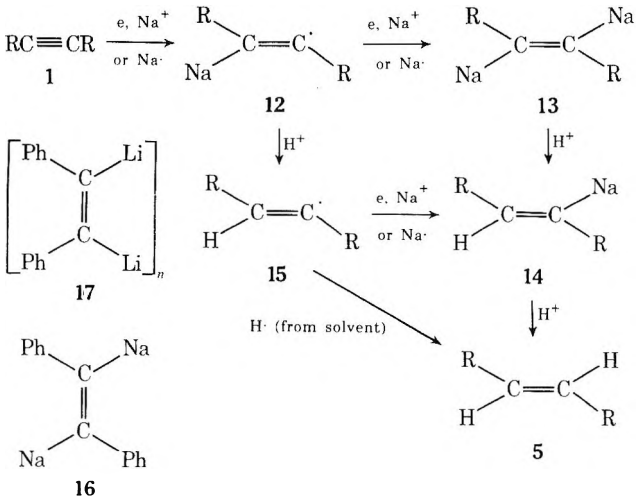
can be reduced electrochemically to the radical anion **5** in aprotic media (typically DMF or DME with *n*-$Bu_4N^+X^-$ as a supporting electrolyte) at relatively negative potentials (−2.0 to −2.9 V *vs.* sce), the formation of a free dianion **3** is uncertain[6a,b] even in these cases where delocalization of negative change is possible. This uncertainty arises both because at the very negative potentials required to reduce the anion radical **5** to the dianion **3**, competing reduction of the supporting electrolyte (*n*-$Bu_4N^+X^-$) becomes substantial (at −2.9 to −3.0 V *vs.* sce) and because the possible abstraction of either a hy-

drogen atom or a proton from the solvent by one of the intermediates **3** or **5** may form more easily reduced intermediates.[6e] Nonconjugated acetylenes (**1**, R = alkyl or H) are normally considered inert to electrochemical reduction by a process that involves electron transfer to form an anion radical.[6d,7] We have examined the polarographic behavior of several acetylenes **6**–**10** as well as the strained cyclic acetylene **11**.[8] Solutions of the acetylenes **7**–**11** and n-$Bu_4N^+BF_4^-$ in DMF exhibited no reduction waves other than reduction of the supporting electrolyte (−3.0 V *vs.* sce) when examined either by conventional polarography or by cyclic voltammetry. Solutions of acetylene (**6**), which might be expected[5] to be reduced at potentials



0.1–0.2 V less negative than the acetylenes **7**–**11** containing one or two electron-donating alkyl substituents, exhibited a "shoulder" on the edge of the wave corresponding to reduction of the supporting electrolyte. This observation suggests that the reduction potential ($E_{1/2}$) for acetylene (**6**) is *ca.* −3.0 V (*vs.* sce) and that the alkyl-substituted acetylenes **7**–**11** accept an electron (to form **5**) only at potentials more negative than −3.0 V. When these observations are considered in terms of the reduction potential[9] of a solution of sodium in hexamethylphosphoramide (−2.96 V *vs.* sce at 28°) or liquid ammonia (*ca.* −2.3 V at −33°), it is apparent that the reducing power of these sodium solutions is at best barely adequate to reduce unconjugated acetylenes **1** to the corresponding free radical anions **5** and is certainly inadequate to produce the corresponding free dianions **3**. (Typically, the potential required to form a dianion is 0.5–1.0 V more negative than the potential required to form an anion radical.) However, an alternative process that is not excluded by these reduction potential values is the simultaneous addition of an electron and a Na^+ cation (or equivalently, the addition of a Na atom) to form the organometallic intermediates such as **12**, **13**, and **14** (Scheme II). In studies of the reduction of diphenylacetylene (and other arylacetylenes)[6b,e,10] there is evidence that solutions of dimetalated intermediates such as **16** are formed by reaction of the corresponding acetylene with an alkali metal at low temperatures. Reaction of solutions of these dimetalated intermediates with a proton (or deuteron) donor produced the corresponding trans olefins.[10a] The interesting observation was made that when the solid dilithio derivative **17** was protonated only the cis olefin was formed; however if the solid cis dilithio derivative **17** was dissolved before protonation, a change in configuration occurred and the trans olefin was produced upon protonation.[10a] The most reasonable interpretation of these observations is to conclude that if a disodio intermediate **13** is formed in the reaction solution, it will preferentially adopt the indicated trans configuration (minimizing electrostatic repulsion between the C–Na dipoles) and will react with a proton donor with retention of configuration[4] to form a trans olefin. However, it is by no means clear that these studies implicating dimetalated intermediates such as **13** in the reduction of acetylenes conjugated with one or two aryl groups[6b,e,10] are also applicable to the more difficultly reducible acetylenes containing only alkyl substituents. To explore this question further we have examined the reductions of several alkyl-substituted acetylenes **7**–**10** with solutions of sodium in either hexamethylphosphoramide (HMP)[11] or liquid NH_3.

Scheme II



Previous studies of the reaction of carbon–carbon multiple bonds[12] with solutions of Na in HMP are in seeming disagreement about the utility of these solutions. Larchevêque reported that several dialkylacetylenes **1** were not reduced but rather isomerized to terminal acetylenes by treatment with solutions of Na in HMP mixed with either THF or Et_2O.[12a] However, in the presence of benzene as a cosolvent, these same reactants were reported to yield mixtures of a disubstituted olefin (stereochemistry not stated) and some terminal olefin.[12a] On the other hand, Whitesides and Ehmann found that solutions of Na in HMP containing *t*-BuOH as a cosolvent slowly reduced nonconjugated olefins to saturated hydrocarbons, and they also reported that this Na–HMP–*t*-BuOH solution reduced 3-hexyne (**9**) to a mixture of *trans*-3-hexene and hexane.[12b] We had found earlier[9] that relatively stable solutions of Na in HMP–THF mixtures (3:2 v/v) could be prepared and standardized by titration of these blue solutions to a colorless end point with pinacolone (stoichiometry 1 g-atom of Na/mol of pinacolone). Furthermore, these Na solutions reacted only very slowly with tertiary alcohols such as *t*-BuOH, so that reduction with the Na solutions could be carried out in the presence of *t*-BuOH as the proton donor. We initially examined the use of these Na solutions to reduce 5-decyne (**7**). Although this acetylene **7** was reduced to one or more olefins by reaction with solutions of Na in any of the solvent systems, liquid NH_3, HMP–THF, or HMP–THF–*t*-BuOH, our attempts to analyze mixtures of some of the possible olefinic products **18**–**21** by gas chromatography were not satisfactory. While the various cis and trans isomers were readily separable on a glpc column employing a solution of $AgNO_3$ in ethylene glycol as the liquid phase, our attempts to analyze a mixture of the structural isomers **18** and **20** or **19** and **21** (Scheme III) either by glpc analysis or spectroscopic analysis were not satisfactory.[13] Consequently, all of our subsequent studies employed either the C_{10} acetylene **10** or the C_6 acetylenes **8** and **9**. In these cases, analytical procedures (glpc) were found that permitted separation of the C_{10} hydrocarbons **22**, **23**, and **26** and of the C_6 hydrocarbons **24**, **25**, and **27**–**29**.

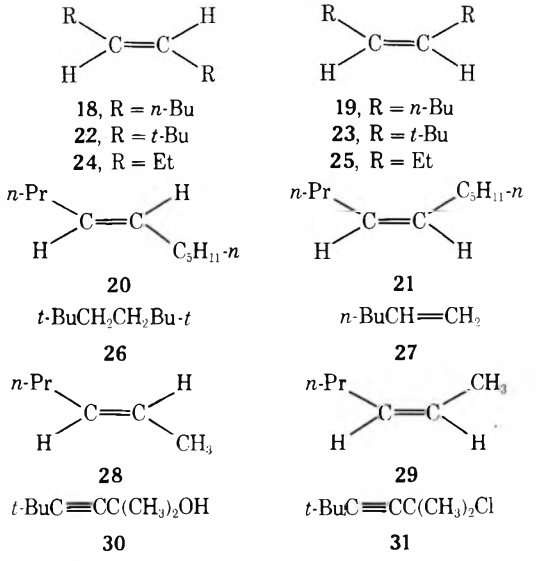
From titrations involving the addition of 3-hexyne (**9**) to solutions of Na in HMP–THF, we found that the blue color of the Na solution was discharged by the addition of 1 mol of the acetylene **9** to 2 g-atoms of Na. After hydrolysis and isolation, the major products (see Table I) were the trans olefin **24** (9–19% yield) and two rearranged ma-

Table I
Reaction of the Acetylene 9 with Na in HMP–THF

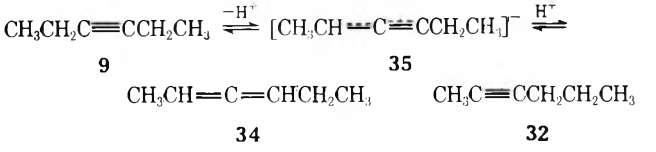
Mmol of 9	Mg-atoms of Na[a]	Mmol of *t*-BuOH	Reaction time, min	Reaction temp, °C	Product yields, % Olefin 28	Olefin 24	Olefin 29	Olefin 25	Other[b]
2.7	8		30	−33	44	13	17		
2.7	8		360	25	28	9	8	1	
1.7	20		0.5	25	30	11	12		3% *n*-hexane[c]
3.6	7.3[d]		0.5	25	63[e]	19	17		
2.9	20	13	30	25	<1	29		5	47% *n*-hexane
2.5	8	15	30	25	<1	65		11	
2.3	20	13	0.5	0	2	52		8	
2.1	8	16	0.5	0	3	74		10	
1.8	20	26	10	−33	2	77		3	
2.6	8	15	30	−33	1	76			
2.6	8	15	2	−33	2	95			
1.9	30	26[f]	10	−33	<1	75[g]			
4.6	10.9[d]	21.8[h]	0.5	−33	<1	58		2	22% recovery of acetylene 9
4.9	10.6[d]	18.7[f,h]	0.5	−33	<1	38		3	28% recovery of acetylene 9
6.0	12.5[d]	27	Inverse addition[i]	−20 to −40	2	54		5	24% recovery of acetylene 9
4.6	10.3[d]	27[f]	Inverse addition[i]	−30 to −40	<1	56[j]		6	10% recovery of acetylene 9
2.7	8.6[d]	30[f]	Inverse addition[i]	0	1	79[k]		9	

[a] Unless otherwise noted, excess Na remained after the addition of the acetylene **9** until the reaction mixture was quenched with H_2O. [b] Unless otherwise noted, the separate analyses required to determine the yields of *n*-hexane and 1-hexyne (**8**) were not performed. [c] No 1-hexyne (**8**) was detected (glpc) in the reaction product. [d] In this experiment, all the Na was consumed before the solution was quenched. [e] After the reaction mixture had been quenched with D_2O, the product contained no deuterated species. [f] *t*-BuOD was used in this experiment. [g] The olefin contained 86% d_2 species and 14% d_1 species. [h] In this experiment the *t*-BuOH (or *t*-BuOD) was added with the acetylene **9** to the Na solution. [i] In this experiment the Na solution in HMP–THF was added to the acetylene **9** and *t*-BuOH (or *t*-BuOD). [j] This olefin contained 66% d_2 species, 31% d_1 species, and 3% d_0 species. [k] This olefin contained 46% d_2 species, 39% d_1 species, and 15% d_0 species.

Scheme III



terials, the trans olefin **28** (28–63% yield) and the cis olefin **29** (8–17% yield). When one of these reaction mixtures was hydrolyzed with D_2O, no deuterium was incorporated in the major olefinic product **28**. Consequently, we concluded, contrary to the report of Larchevêque,[12a] that internal acetylenes are reduced by solutions of Na in HMP–THF, and furthermore, that all stages of the reduction (electron transfer and transfer of H^+ or H·) are complete before the reaction solutions are hydrolyzed. However, in partial agreement with Larchêveque's report, it is clear that in the absence of an added relatively acidic proton donor, extensive base-catalyzed isomerization[2a,3b,14] of the acetylene **9** to the allene **34** (and possibly to the acetylene **32**) is occurring in competition with the reduction process so that the rearranged olefins **28** and **29** are produced in greater amounts than the expected olefin **24**. Thus, in the absence of an added proton donor, the acetylene **9** must be serving as a proton donor for one of the reduction intermediates (*e.g.*, **12** or **14**, Scheme II), resulting in the formation of the anion **35**. However, several facts indicate that one or both of the reaction solvents THF or HMP must also be donating a proton to at least one of the carbanionic intermediates (*e.g.*, **12**, **14**, or **35**) in the reaction mixture. The total yields of reduction products **24**, **25**, and **28** (46–99%) and the failure to incorporate deuterium into the reduction product after quenching with D_2O are inconsistent with a reaction process in which 1 mol of acetylene is reduced by reaction with 2 g-atoms of Na and an additional 2 mol of acetylene that serve only as proton donors. The titration results (2 g-atoms of Na consumed/mol of acetylene **9** added) are also incompatible with this scheme, since further reduction of the anion **35** with Na is unlikely. Consequently, the various carbanionic intermediates (*e.g.*, **12**, **14**, or **35**) must be abstracting a proton (or a hydrogen atom) from one or both of the solvents.[6e,15]



The above results are in contrast to our observations when the more acidic terminal acetylene **8** was added to a solution of Na in HMP–THF. In this case, our titration data indicated that 2 g-atoms of Na were consumed for each 3 mol of acetylene **8** added, and the products obtained after hydrolysis were the olefin **27** (31% yield) and the acetylene **8** (63% recovery). Furthermore, when the reaction mixture was hydrolyzed with D_2O, the recovered acetylene **8** was partially deuterated. (The relatively rapid

H–D exchange of a terminal acetylene, RC≡CD, during isolation and mass spectrometric analysis clearly lowered the deuterium content of the recovered acetylene **8** in this experiment.) Thus, in this experiment two-thirds of the starting acetylene does serve as the proton donor in the reduction process, as indicated in the following equation.

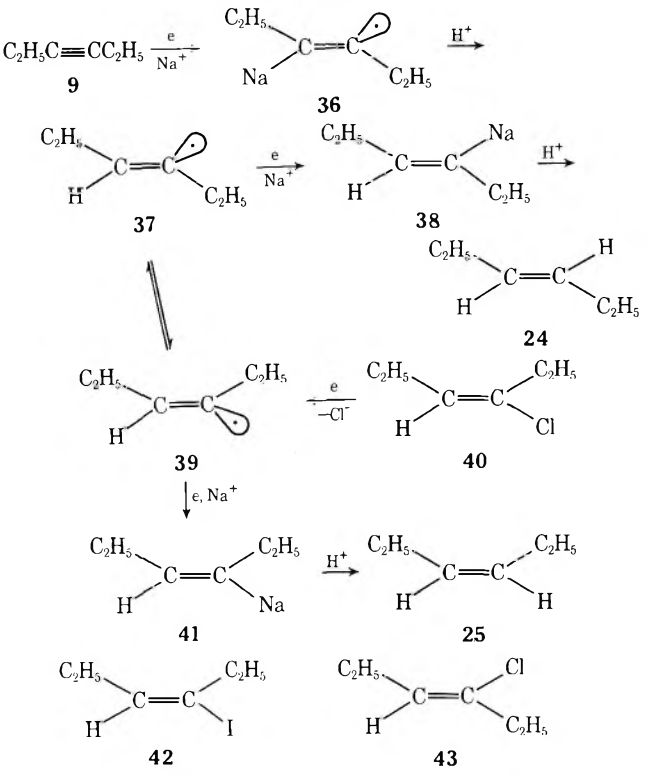
$$\underset{\mathbf{8}}{3n\text{-}C_4H_9C{\equiv}CH} + 2Na \longrightarrow \underset{\mathbf{27}}{n\text{-}C_4H_9CH{=}CH_2} + 2n\text{-}C_4H_9C{\equiv}C^-Na^+$$

The problem of isomerization of the starting acetylene **9** to the allene **34** (or the acetylene **32**) prior to reduction with Na in HMP–THF was avoided by performing the reduction in the presence of an excess of *t*-BuOH as a proton donor. Although some of the Na in these reactions was also consumed by reaction with *t*-BuOH, this process was relatively slow, especially at low temperatures (−33°), so that a total of 2.1–2.4 g-atoms of Na was consumed/mol of acetylene **9** added. The products of this reduction (see Table I) were the unrearranged olefins **24** (major product) and **25** (minor product) with at most only very minor amounts of the rearranged olefins **28** and **29**. When these reductions with Na and *t*-BuOH in HMP–THF were performed at −33° with relatively short reaction periods (2–5 min) before quenching, the yield and composition of the olefinic product (>95% trans olefin **24**) were comparable to those obtained in a reduction with Na in liquid NH_3. When this reduction with Na in HMP–THF was performed in the presence of excess *t*-BuOD, the olefinic product **24** was largely dideuterated (86% d_2 species and 14% d_1 species).

If the temperature used for reduction was raised from −33 to 0 or 25° or, particularly, if the reaction time was extended from 2 to 30 min or longer, then the further reduction[12b] of the olefins **24** and **25** to *n*-hexane became a significant side reaction. The relative rates of the further reduction of the cis olefin **25** and the trans olefin **24** to *n*-hexane were approximately equal with Na and *t*-BuOH in HMP–THF. However, the rate of reduction of the terminal olefin **27** to *n*-hexane appeared to be much more rapid. Thus, the addition of the terminal acetylene **8** to a solution of Na and *t*-BuOH in HMP–THF at 25° resulted in the formation of both *n*-hexane (53% yield) and 1-hexene (**27**, 28% yield) after a reaction period of *ca.* 1 min. Some indication that the rates of reduction of various acetylenes and olefins with Na and *t*-BuOH in HMP–THF is influenced more by the steric effects rather than by the electrical effects of alkyl substituents was provided by the fact that the rate of reduction of di-*tert*-butylacetylene (**10**) to the trans olefin **22** required 2–3 hr for completion and, even after 3 hr at 25°, only 2% of the olefin **22** had undergone further reduction to the hydrocarbon **26**.

The proportions of trans olefin **24** to cis olefin **25** formed from reduction of the acetylene **9** were examined under several sets of reaction conditions. Since the relative rates of further reduction of these two olefins **24** and **25** to *n*-hexane were approximately equal, the occurrence of this side reaction in some of our studies did not alter substantially the proportions of the olefin present. The composition of the mixture of olefins **24** and **25** obtained from reductions effected by adding the acetylene **9** to Na and *t*-BuOH in HMP–THF was clearly altered by the reaction temperature, the olefinic product containing 81–84% trans olefin **24** at 25°, 88–89% trans olefin **24** at 0°, and >98% trans olefin **24** at −33°. This latter value (>98% trans olefin **24**) was also observed for the reduction of the acetylene **9** with Na in liquid NH_3 at −33°. (Other data concerning the reduction of dialkylacetylenes with Li in liquid NH_3 at 25°[3c] or Li in $EtNH_2$ at 17°[3a] suggest that at least under some reaction conditions, the conversion of acetylenes to trans olefins can be stereoselective at temperatures above −33°).

Scheme IV



All of the reductions discussed thus far were performed using what might be called the normal mode of addition in which the acetylene **9** was added, dropwise and with good mixing, to a solution that contained excess Na. These conditions should clearly be favorable to the immediate further reduction of radical intermediates such as **12** or **15** to organosodium species such as **13** or **14**. To examine the stereochemical result under circumstances where an excess reducing agent was not present, an inverse addition procedure was followed in which a solution of Na in HMP–THF was added, dropwise and with good mixing, to a solution of the acetylene **9** and excess *t*-BuOH in THF. The Na solution was added at such a rate that after each drop of the Na solution had been added the blue color (indicating excess Na) was allowed to disappear before the next drop of Na solution was added. Thus, throughout the reaction reduction was occurring under conditions of excess proton donor and a low concentration of reducing agent, conditions that clearly would be favorable to the generation of the vinyl radical intermediate **15**. In all of these experiments (both at *ca.* −30 and 0°) the olefin product contained 86–90% of the trans olefin **24**. When *t*-BuOD was substituted for *t*-BuOH as the "proton" donor, the distribution of deuterium in the olefinic product **24** (46–66% d_2 species, 31–39% d_1 species, and 3–15% d_0 species) corresponded to significantly more monodeuterated material than had been observed in a normal addition procedure (86% d_2 and 14% d_1 species) in spite of the fact that a higher concentration of "proton" donor, *t*-BuOD, was present throughout the reaction. These results suggest that in the inverse addition procedure significant fractions of the olefins **24** and **25** are being formed by reaction of an intermediate vinyl radical **15** with the solvent to abstract a hydrogen atom.

Thus, our studies of the reduction of the acetylene **9** with Na and *t*-BuOH in HMP–THF are compatible with a reaction path (Scheme IV) in which the acetylene **9** is

Table II
Reduction of 3-Chloro-*cis*-3-hexene (40) with Sodium

Mmols of 40	Mg-atoms of Na	Mmol of *t*-BuOD	Solvent (ml)	Reaction time, min (temp, °C)	Product yields, % Trans olefin 24[e]	Cis olefin 25	Other[a]
1.4	30	17.5	HMP (30) + THF (20)	10 (−33)	47 (79)[b]	12	<1% olefin **28**
2.5	6.6	17.5	HMP (39) + THF (26)	90, inverse addition (−33)	31 (81)[c]	6	<1% olefin **28**[d]
1.4	30		HMP (30) + THF (20)	5 (−33)	33 (81)	5	10% olefin **28** and 5% olefin **29**[d]
1.1	30	17.5	HMP (30) + THF (20)	25 (0)	10 (77)	5	81% *n*-hexane
1.3 in 4 ml of THF	30		NH_3 (15)	30 (−33)	**25** (48)	28	~1% olefins **28** and **29**
1.3 in 0.33 g of methylcyclohexane	30		NH_3 (15)	30 (−33)	(26)	(74)	~3% olefin **29** in mixture

[a] Unless otherwise noted, the yield of *n*-hexane in these experiments was not determined. [b] The product contained 85% d_1 species and 15% d_0 species. [c] The product contained 81% d_1 species and 19% d_0 species. [d] No higher molecular weight products (*i.e.*, C_{12} hydrocarbons) were detected by glpc analysis. [e] % of olefin product in parentheses.

converted successively to a trans sodiovinyl radical **36** (or the equivalent nonlinear anion radical)[16] followed by protonation to give the trans vinyl radical **37**. At low temperatures (−33°) in the presence of excess Na, the conversion of this trans radical **37** to the vinylsodium intermediate **38** is apparently slightly more rapid than the conversion of the trans radical **37** to the cis radical **39** (and subsequently to the cis vinylsodium compound **41**) so that protonation yields predominantly the trans olefin **24**. However, either lowering the Na concentration (retarding the rate of the conversion **37** → **38**) or increasing the reaction temperature (increasing the rate of radical inversion **37** → **39**) would be expected to increase the proportion of the cis olefin **25** in the product.

To examine this hypothesis further, it was of interest to introduce one of the vinyl radicals **37** or **39** into our reaction solution in a different manner. Earlier stereochemical studies of alkyl-substituted vinyl radicals[17] have indicated that these intermediates are nonlinear with a relatively low energy barrier to inversion.[17a] Studies of the reduction of stereoisomeric vinyl halides[17b,c] such as **40**, **42**, and **43** have suggested that the rates of radical inversion (*e.g.*, **37** ⇄ **39**) and the rates of electron transfer to such radicals (*e.g.*, **37** → **38** or **39** → **41**) are comparable in magnitude. Thus, when a solution of sodium naphthalenide in THF was added to a THF solution of the cis chloro olefin **40** at 0°, the olefinic product contained 31% of the cis olefin **25** and 69% of the trans olefin **24**.[17b] A similar electrochemical reduction of the iodo olefin **42** produced a mixture containing 30% of the cis olefin **25** and 70% of the trans olefin **24**.[17c] In each of these studies, equilibration of the vinyl radicals was incomplete because reduction of the corresponding trans halo olefin (*e.g.*, **43**) produced olefin mixtures containing 85–94% of the trans olefin **24**.[17b,c] These results are in contrast to an earlier study in which the addition of a solution of the cis chloro olefin **40** in methylcyclohexane to a cold (−33°) solution of Na in liquid NH_3 was reported[17d] to yield only the cis olefin **25**.

We have examined the reduction of the cis chloro olefin **40** with cold (−33°) solutions of Na and *t*-BuOD in HMP–THF employing both normal and inverse addition procedures (see Table II). In all cases, the olefinic product contained 79–82% of the trans olefin **24** and this product **24** (81–85% d_1 species and 15–19% d_0 species) had been formed primarily by "protonation" of an organometallic (or anionic) intermediate. Since the cis chloro olefin **40** recovered from an incomplete reduction did not contain a significant amount of the trans isomer **43**, we conclude that the reduction itself is not stereospecific under these conditions and one of the intermediates (probably **39**) is equilibrating with its geometrical isomer (*e.g.*, **37**) at a rate competitive with the rate of electron transfer. Even when the chloro olefin **40** was reduced with solutions of Na in liquid NH_3, we did not observe the high stereospecificity previously reported.[17d] When the chloride **40** was reduced with Na and NH_3 employing THF as a cosolvent, the olefin product contained 48% of the trans olefin **24**; employing methycyclohexane as a cosolvent, the olefin product contained 26% of the trans olefin **24** accompanying the major product, the cis isomer **25**.

Thus, the results of our Na–HMP reductions indicated that even when a precursor such as the chloro olefin **40** is used to form the cis vinyl radical **39** as an initial intermediate, subsequent partial equilibration, **39** ⇄ **37**, is competitive with electron transfer and protonation so that a mixture of olefins containing *ca.* 80% of the trans isomer **24** is obtained. Our results obtained on reduction of the acetylene **9** are understandable with the assumption that, at −33° in the presence of excess Na, an initially formed trans vinyl radical **37** is reduced and protonated to form the trans olefin **24** (>95% of the olefin mixture) at a rate slightly faster than equilibration of the vinyl radicals **37** and **39**. However, either an increase in the reaction temperature or a reduction in the Na concentration permits nearly complete equilibration of the vinyl radicals **37** and **39**, leading to an olefin mixture containing 85–90% of the trans isomer **24**.

Experimental Section[18]

Di-*tert*-butylacetylene (10). Previously described procedures[19,20] yielded *tert*-butylacetylene, bp 36–38°, $n^{25}D$ 1.3738 [lit. bp 36.4–37.8° (768.3 mm),[19] 36–40°,[20] $n^{20}D$ 1.3736[21]], that was converted[20,22] successively to the carbinol **30**, $n^{25}D$ 1.4303 (lit.[22] $n^{38}D$ 1.4222), ir (CCl_4) 3620, 3380 (unassociated and associated OH), and 2230 cm^{-1} (C≡C), nmr (CCl_4) δ 3.08 (1 H s, OH), 1.42 [6 H s, $(CH_3)_2C$], and 1.20 [9 H s, $(CH_3)_3C$], the acetylenic chloride **31**, bp 63–64.5° (43 mm), $n^{25}D$ 1.4320 [lit.[22] bp 81–81.5° (100 mm), $n^{20}D$ 1.4343], ir (CCl_4) 2235 cm^{-1} (C≡C), nmr (CCl_4) δ 1.78 [6 H s, $(CH_3)_2C$] and 1.21 [9 H s, $(CH_3)_3C$], and the crude acetylene **10**, bp 113–119°, which contained (ir and nmr) small amounts of olefinic impurities. This crude product was cooled in an ice bath and Br_2 was added dropwise until the red color persisted. Then solid $Na_2S_2O_3$ was added to consume the excess Br_2 and solid K_2CO_3 was added to consume any acid present. Redistillation separated the pure acetylene **10**: bp 111–112.5° (747 mm); $n^{25}D$ 1.4027 [lit.[22] bp 111.9° (746 mm); $n^{25}D$ 1.4026]; ir (CCl_4) no absorption for C=C or C≡C; uv (95% EtOH) shoul-

ders at 232 (ε 56) and 222 mμ (ε 71) with end absorption (ε 129 at 210 mμ); nmr (CCl_4) δ 1.13 [singlet, $(CH_3)_3C$]; mass spectrum *m/e* (rel intensity), 138 ($M,^+$ 36), 123 (100), 95 (20), 81 (81), 67 (21), 43 (25), and 41 (31).

Preparation of the Di-*tert*-butylethylenes 22 and 23 and the Ethane 26.[23] A solution of the acetylene **10** in EtOH was hydrogenated over a 5% Pd/C catalyst at 25° (50 psi) to yield 58% of the ethane **26**: bp 136°; $n^{25}D$ 1.4039 [lit.[22] bp 136.2–136.4° (739 mm); $n^{20}D$ 1.4060]; nmr (CCl_4) δ 1.13 (4 H s, CH_2) and 0.88 [18 H s, $(CH_3)_3C$]; mass spectrum *m/e* (rel intensity) 142 (0.01, M^+), 71 (34), 57 (100), 56 (47), 43 (19), 41 (28), 31 (74), and 27 (73).

A solution of the acetylene **10** in EtOH was hydrogenated over Raney nickel catalyst at 25° (40 psi). After 3 hr the hydrogenation was stopped to yield a hydrocarbon product, bp 115–126°, which contained (glpc, silicone gum, SE-30, on Chromosorb P) the trans olefin **22** (*ca.* 50%), the ethane **26** (*ca.* 15%), and the cis olefin **23** (*ca.* 35%). Each of these components was collected (glpc); the ethane **26** was identified with the previously described sample by comparison of ir spectra and glpc retention times.

The trans olefin **22** was obtained as a colorless liquid: $n^{25}D$ 1.4091 (lit.[20] $n^{20}D$ 1.4116); ir (CCl_4) 975 cm^{-1} (trans CH=CH); uv (95% EtOH) end absorption (ε 18 at 210 mμ); nmr (CCl_4) δ 0.96 [18 H s, $(CH_3)_3C$] and 5.26 (2 H s, vinyl CH); mass spectrum *m/e* (rel intensity) 140 (10, M^+), 125 (54), 84 (23), 83 (81), 70 (80), 69 (100), 57 (52), 55 (43), and 41 (46).

The cis olefin **23** was isolated as a colorless liquid: $n^{25}D$ 1.4250 (lit.[20,22] $n^{20}D$ 1.4266); uv (95% EtOH) end absorption (ε 204 at 210 mμ); nmr (CCl_4) δ 5.10 (2 H s, vinyl CH) and 1.11 [18 H s, $(CH_3)_3C$]; mass spectrum *m/e* (rel intensity) 140 (2 M^+), 125 (21), 97 (2)1, 84 (30), 83 (79), 70 (100), 69 (98), 57 (61), 55 (74), 43 (24), and 39 (21).

To analyze mixtures containing the di-*tert*-butyl derivatives **10**, **22**, **23**, and **26**, *n*-nonane was added as an internal standard and the mixtures were analyzed by glpc on equipment calibrated with known mixtures of authentic samples. With the glpc column used (silicone gum, SE-30, on Chromosorb P) the retention times follow: acetylene **10**, 12.5 min; trans olefin **22**, 17.6 min; ethane **26**, 23.5 min; cis olefin **23**, 30.4 min; *n*-nonane, 38.3 min.

Preparation of 5-Decyne (7) and the 5-Decenes 18 and 19. The sodium acetylide prepared from $NaNH_2$ and 1-hexyne (**8**) in liquid NH_3 was alkylated[24] with *n*-BuBr to yield 51% of 5-decyne (**7**): bp 173–175°; $n^{25}D$ 1.4315 [lit.[24c] bp 176° (748 mm), $n^{25}D$ 1.4311]; uv (95% EtOH) shoulder at 225 mμ (ε 56) with end absorption (ε 75 at 210 mμ); nmr (CCl_4) δ 1.9–2.3 (4 H m, $C{\equiv}CCH_2$), 1.2–1.8 (8 H m, CH_2), and 0.8–1.2 (6 H m, CH_3); mass spectrum *m/e* (rel intensity) 138 (23, M^+), 96 (30), 95 (52), 81 (100), 68 (30), 67 (31), 57 (55), 55 (66), 54 (45), 53 (29), 43 (32), and 41 (21).

Reduction[24b] of 5-decyne (**7**) with Na in liquid NH_3 yielded 57% of *trans*-5-decene (**18**), bp 172–173.5°, $n^{25}D$ 1.4228 [lit.[24b] bp 170.2° (739 mm), $n^{25}D$ 1.42126], that contained (glpc) *ca.* 3% of the starting acetylene **7**: ir (neat) 965 cm^{-1} (trans CH=CH); uv (95% EtOH) end absorption (ε 137 at 210 mμ); nmr (CCl_4) δ 5.2–5.6 (2 H m, vinyl CH), 1.7–2.3 (4 H m, allylic CH_2), 0.7–1.7 (14 H m, aliphatic CH); mass spectrum *m/e* (rel intensity) 140 (M^+, 25), 69 (37), 56 (47), 5 (100), 43 (24), and 41 (41). A solution of 5-decyne (**7**) in methanol was hydrogenated at 25° (1 atm) over a 5% Pd/$BaSO_4$ catalyst in the presence of quinoline to yield 50% of *cis*-5-decene (**19**), bp 169–170°, $n^{25}D$ 1.4276 [lit.[24b] bp 169.5–169.6° (739 mm), $n^{25}D$ 1.42296], which contained (glpc) 9% of the trans isomer **18**. A pure sample of the cis isomer **19** was collected (glpc): uv (95% EtOH) end absorption (ε 50 at 210 mμ); nmr (CCl_4) δ 5.32 (2 H t, J = 5 Hz, vinyl CH), 1.8–2.4 (4 H m, allylic CH_2), and 0.8–1.8 (14 H m, aliphatic CH); mass spectrum *m/e* (rel intensity) 140 (M^+, 25), 70 (43), 69 (46), 56 (53), 55 (100), 43 (28), 42 (22), and 41 (49).

For glpc analysis of mixtures containing the 5-decyne (**7**), the 5-decenes **18** and **19**, and *n*-decane, isopropylbenzene was added as an internal standard and the glpc equipment was calibrated with known mixtures of authentic samples. For the glpc column used (20% $AgNO_3$ in ethylene glycol suspended on Chromosorb P), the retention times follow: *n*-decane, 2.3 min; trans olefin **18**, 5.6 min; cis olefin **19**, 10.6 min; isopropylbenzene, 16.7 min; and acetylene **7**, 28.6 min.

Preparation of 1-Decyne and 1-Decene. Sodium acetylide in liquid NH_3 was alkylated[24] with *n*-octyl bromide to yield 72% of 1-decyne: bp 172–174°; $n^{25}D$ 1.4268 [lit.[25] bp 174°, $n^{25}D$ 1.4242]; ir (neat) 3320 (acetylenic CH) and 2140 cm^{-1} (C≡C); uv (95% EtOH) end absorption (ε 94 at 210 mμ); nmr (CCl_4) δ 1.9–2.4 (2 H m, $C{\equiv}CCH_2$), 1.77 (1 H t, J = 2.5 Hz, C≡CH), and 0.7–1.7 (15 H m, aliphatic CH); mass spectrum *m/e* (rel intensity) 81 (32), 67 (39), 55 (42), 43 (38), 41 (100), and 39 (38). A solution of 1-decyne in MeOH was hydrogenated at 22.5° (1 atm) over a 5% Pd/$BaSO_4$ catalyst in the presence of quinoline to yield 67% of a colorless liquid product, bp 170–172.5°, that contained (glpc) *ca.* 80% of 1-decene and *ca.* 20% of other minor components, some of which had retention times corresponding to those of 1-decyne and 1-decane. A pure sample of 1-decene was obtained by collection (glpc): $n^{25}D$ 1.4200 (lit.[26] bp 171–173°, $n^{20}D$ 1.4259); ir (CCl_4) 1645 (C=C) and 925 cm^{-1} ($CH{=}CH_2$); uv (95% EtOH) end absorption (ε 130 at 210 mμ); nmr (CCl_4) δ 4.7–6.0 (3 H m, vinyl CH), 1.7–2.2 (2 H m, allylic CH_2), and 0.7–1.7 (15 H m, aliphatic CH); mass spectrum *m/e* (rel intensity) 140 (M^+, 5), 70 (27), 69 (25), 57 (34), 56 (47), 55 (57), and 41 (100).

Preparation of the 4-Decenes 20 and 21. *n*-Butyltriphenylphosphonium bromide, mp 240–241° (lit.[27] mp 242–243°), was converted to its ylide with *n*-BuLi in an ether–hexane mixture. The red solution of the phosphorus ylide was cooled to −15° and then treated with *n*-hexanal in Et_2O. After reaction at 0° for 10 min and subsequent isolation, 51% yield of a mixture of stereoisomeric 4-decenes **20** and **21**, bp 170° [lit.[28] bp 170.6° (761 mm), $n^{20}D$ 1.4243], was obtained. This product contained (glpc, 20% $AgNO_3$ in ethylene glycol on Chromosorb P) *ca.* 40% of the trans olefin **20** (retention time 6.6 min) and *ca.* 60% of the cis olefin **21** (retention time 8.9 min). Samples were collected (glpc) for spectral characterization. The trans isomer **20** has the following properties: ir (CCl_4) 985 cm^{-1} (trans CH=CH); nmr (CCl_4) δ 5.1–5.5 (2 H m, vinyl CH), 1.7–2.4 (4 H m, allylic CH_2), and 0.7–1.7 (14 H m, aliphatic CH); mass spectrum *m/e* (rel intensity) 140 (M^+, 5), 70 (22), 68 (35), 56 (40), 55 (91), 43 (31), 42 (26), 41 (100), and 39 (36). The cis isomer **21** shows the following peaks: nmr (CCl_4) δ 5.29 (2 H t, J = 5 Hz, vinyl CH), 1.8–2.3 (4 H m, allylic CH_2), and 0.7–1.8 (14 H m, aliphatic CH); mass spectrum *m/e* (rel intensity) 140 (M^+, 5) 70 (23), 69 (33), 56 (42), 55 (91), 43 (35), 42 (28), 41 (100), and 39 (37). Although the ir spectra (neat) of the cis isomers **19** and **21** and of the trans isomers **18** and **20** differ slightly from one another in the fingerprint region, most spectroscopic properties of each pair are sufficiently similar that quantitative analysis would be difficult. We were unable to resolve mixtures of **19** and **21** or mixtures of **18** and **20** with any of the glpc columns we examined.

Properties of the C_6 Olefins and Acetylenes. Commercial samples of the following olefins and acetylenes were purchased from the sources indicated: **8**,[29] **32**,[30] **9**,[29] **25**,[30] **24**,[31] **29**,[30] **28**,[31] and **27**.[31] The structure and purity of each of these samples were confirmed by glpc, ir, and mass spectral analysis. The nmr spectra of the various olefins **24**, **25**, **28**, **29**, and **30** were also determined to confirm the structures and purity of these materials.

On a 4.2-m glpc column, packed with a solution of 20% $AgNO_3$ in $HOCH_2CH_2OH$ suspended on Chromosorb P, the retention times of the various components follow: *n*-hexane, 1.8 min; methylcyclohexane (one internal standard used), 2.1 min; trans olefin **28**, 5.1 min; trans olefin **24**, 6.3 min; olefin **27**, 15.5 min; cis olefin **29**, 14.8 min; cis olefin **25**, 17.8 min; pinacolone (a second internal standard used), 25.8 min; acetylene **32**, 39.8 min; and acetylene **9**, 41.8 min. The terminal acetylene **8** was not eluted from this column. The retention times of other components employed as solvents in the subsequently described reactions follow: pentane (a mixture), 1.2–1.8 min; *n*-octane, 3.9 min; and THF, 35.6 min. On a second glpc column (Carbowax 20 M on Chromosorb P) used for analysis of the acetylene **8**, the retention times of the various components were: pentane (a mixture), 1.9–3.4 min; olefin **27**, 3.2 min; acetylene **8**, 13.9 min; THF, 18.6 min; pinacolone (an internal standard), 38.9 min; and *n*-BuOH, 21.0 min. On this column, the retention times of the other C_6 hydrocarbons follow: *n*-hexane, 3.2 min; acetylene **9**, 12.5 min; acetylene **32**, 16.2 min; olefin **24**, 3.6 min; olefin **25**, 3.6 min; olefin **28**, 3.7 min; olefin **29**, 4.1 min. The glpc apparatus was calibrated with known mixtures of the internal standards and the various C_6 hydrocarbons.

Cyclononyne (11). From a sample of this acetylene[8] containing several minor impurities, a pure sample of the acetylene **11** was collected (glpc, Carbowax 20 M on Chromosorb P) as a colorless liquid: $n^{25}D$ 1.4872 (lit. $n^{23}D$ 1.4880;[32] $n^{20}D$ 1.4890[33]); ir (CCl_4) 2260 and 2220 cm^{-1} (C≡C); nmr (CCl_4) δ 2.0–2.4 (4 H m, $CH_2C{\equiv}CCH_2$) and 1.5–1.9 (10 H m, CH_2); mass spectrum *m/e* (rel intensity) 122 (M^+, 4), 121 (23), 107 (45), 94 (87), 93 (93), 91 (69), 81 (87), 80 (90), 79 (100), 77 (71), 67 (67), 54 (53), 53 (46), 41 (49), and 39 (47).

Polarography. Either a conventional dropping Hg electrode or a stationary spherical Hg-coated Pt electrode, a saturated calomel reference electrode with intermediate salt bridges of aqueous 1 *M* $NaNO_3$ and 0.5 *M* Et_4NBF_4 in DMF, and a Pt wire counter

electrode were employed with the previously described[34] apparatus. With 0.5 *M* n-Bu_4NBF_4 in purified DMF, the background current for either polarographic measurements or cyclic voltammetry became significant in the range −2.95 to −3.00 V (*vs.* sce) corresponding to the reduction of the n-Bu_4N^+ cation. The addition of the various acetylenes **7**, **8**, **9**, **10**, **11**, or 1-decyne to this solution (concentrations *ca.* 10^{-2} *M*) produced no visible reduction wave. When HC≡CH was passed through the solvent-electrolyte mixture, the resulting polarographic scans differed from the background in that appreciable current began to pass through the cell at *ca.* −2.80 V (*vs.* sce) rather than at 3.00 V when no HC≡CH was present. However, no separate reduction wave could be resolved from the background current. Attempts[23] to reduce the acetylenes **7** or **10** with solutions of Cr(II) reagents[35] [either $CrSO_4$ in aqueous MeOH or $(en)_2CrClO_4$[36] in aqueous DMF] for 1 hr at 25° resulted in the recovery of the acetylenes, and none of the olefinic product **22** or **18** was detected (glpc analysis).

Preparation and Standardization of Solutions of Na in HMP–THF. The solvents were purified by distilling the THF from $LiAlH_4$ and distilling the HMP under reduced pressure from a blue solution of Na in HMP. The HMP was collected as a colorless liquid, bp 85–87° (3 mm). The Na solutions were prepared by stirring purified HMP with excess Na slices until the solution became blue (*ca.* 1 min). Then sufficient purified THF was added so that a 3:2 (v/v) ratio of HMP to THF was present and the resulting mixture was stirred at 25° for 1.5–2 hr. The deep blue solution, maintained continuously under an anhydrous condition and a nitrogen atmosphere, was transferred with a stainless steel cannula from the original flask (containing excess Na) to other flasks. Aliquots of this blue solution were titrated at 25° to a colorless end point by the dropwise addition of either pinacolone (distilled from CaH_2, bp 106°) or freshly distilled propionic acid. Each of these materials reacts with 1 g-atom of Na/mol of compound.[9] When aliquots of the blue Na solution were titrated at 25° to a yellow end point with a THF solution of the enone, *trans*-*t*-BuCH=CHCOBu-*t*,[9] 1.3 g-atoms of Na was consumed per mole of the enone. The concentrations of these Na solutions were in the range 0.192–0.236 mg-atom of Na per gram of solution.

When aliquots of this blue Na solution were titrated at 25° with 5-decyne (**7**) to a red end point, 2.2 g-atoms of Na/mol of acetylene **7** was consumed. Similarly, titration with 3-hexyne (**9**) to a red end point consumed 2.0 g-atoms of Na/mol of acetylene **9** and titration with 1-hexyne (**8**) to a colorless end point consumed 0.70 g-atom of Na/mol of acetylene **8**. An attempted titration with the acetylene **10** was not successful because addition of excess acetylene **10** did not decolorize the blue Na solution.

Reduction of 3-Hexyne (9). A. With Na in Liquid NH_3. To 33 ml of liquid NH_3 (freshly distilled from Na) was added 7.0 g (0.31 g-atom) of Na slices. To the resulting bronze-colored, cold (−33°) solution was added, dropwise and with stirring during 1 hr, a solution of 10.0 g (0.122 mol) of the acetylene **9** in 22 ml of THF. The resulting solution was stirred under reflux for an additional 2 hr and diluted with a solution of 0.4 mol of NH_3 in 50 ml of H_2O and then the NH_3 was allowed to evaporate. The organic layer was separated and the aqueous phase was extracted with pentane. The combined organic solutions were washed successively with aqueous 3 *M* HCl, with aqueous $NaHCO_3$, and with H_2O and then dried over K_2CO_3. After methylcyclohexane (2.45 g) had been added as internal standard, glpc analysis ($AgNO_3$ in $HOCH_2CH_2OH$ on Chromosorb P) indicated the only product to be the trans olefin **24** (87% yield).

The reduction was repeated by adding to a cold (−33°) solution of 0.2 g (8.7 mg-atoms) of Na in 25 ml of liquid NH_3, dropwise and with stirring during 30 min, a solution of 263 mg (3.2 mmol) of the acetylene **9** and 2.8 g (38 mmol) of *t*-BuOD (from *t*-BuOK and D_2O[9,12b]) in 5 ml of THF. The resulting mixture was stirred under reflux for 30 min and then subjected to the previously described isolation procedure. The only product detected (glpc analysis) was the trans olefin **24** (71% yield). A collected (glpc) sample of the trans olefin **24** contained 99% d_0 and 1% d_1 species which indicated rapid equilibration among the protons in NH_3 and *t*-BuOH.

B. With Na in HMP–THF. Solutions of Na in 24 ml of HMP and 16 ml of THF were prepared as previously described employing the amount of Na indicated in Table I. After the Na solution had been brought to the temperature specified, the acetylene **9** was added, dropwise and with stirring, and the resulting mixture was stirred for the time and at the temperature specified in Table I. Then the solution was quenched by the addition of either H_2O or D_2O and the resulting mixture was extracted with either pentane (for analysis of the olefin yields) or, in one case, *n*-octane (to determine the yield of *n*-hexane). Known amounts of an internal standard (either methylcyclohexane or pinacolone) were added and the mixtures were subjected to glpc analysis. For analysis of the olefins and *n*-hexane, a glpc column containing $AgNO_3$ in $HOCH_2CH_2OH$ on Chromosorb P was employed and a Carbowax 20 M on Chromosorb P glpc column was used to establish the absence in the reaction mixtures of 1-hexyne (**8**) and higher molecular weight (*i.e.*, C_{12}) products. In cases where certain products were examined for deuterium content, that product was collected (glpc) and then subjected to mass spectrometric analysis. The product yields, determined with previously calibrated glpc equipment, are summarized in Table I. The identities of the olefinic products were established by comparison of glpc retention times and the mass spectra of collected (glpc) samples with the corresponding properties of authentic samples.

C. With Na and *t*-BuOH in HMP–THF. To solutions containing the amounts of Na and *t*-BuOH (or *t*-BuOD) indicated in Table I was added, dropwise and with stirring, either the pure acetylene **9** or a solution of the acetylene **9** in THF. The total amounts of solvents used were 24–30 ml of HMP and 16–20 ml of THF so that the ratio of HMP–THF was 3:2 (v/v). After the acetylene **9** had been added at the temperature indicated, the resulting solution was stirred at the temperature and at the time indicated and then quenched with H_2O and extracted with pentane. An internal standard was added and the glpc analysis was performed as previously described to allow calculations of the product yields summarized in Table I. In one case where the yield of *n*-hexane was determined, *n*-octane was used as the extraction solvent. The identities of the reaction products were established by comparison of glpc retention times and the mass spectra of collected (glpc) samples with the corresponding properties of authentic samples. Where deuterium contents are indicated, they were determined by mass spectrometric analysis of collected (glpc) samples.

In certain cases noted in Table I, the *t*-BuOH (or *t*-BuOD) was added with the acetylene **9** in THF solution to the reaction mixture. In other cases noted in Table I involving an inverse addition procedure, standardized solutions of Na in HMP–THF were added to a solution of the acetylene **9** and *t*-BuOH (or *t*-BuOD) in THF. In these additions, the Na solution was added dropwise at such a rate that the blue color (from excess Na) was discharged before the next drop of Na solution was added. Approximately a 4-hr period was required for these additions.

A number of representative product mixtures were examined (glpc, Carbowax 20 M on Chromosorb P) for higher molecular weight C_{12} products; one product mixture from an inverse addition procedure was also examined by mass spectrometric analysis. In no case were any C_{12} products detected.

The following experiment was performed to establish the relative rates of reduction of the cis (**25**) and trans (**24**) olefins to *n*-hexane with Na and *t*-BuOH in HMP–THF. A solution (22.7 g) containing 5.49 mg-atoms of Na in HMP–THF (3:2 v/v) was added, dropwise and with stirring during 30 min, to a cold (0°) solution of 195 mg (2.38 mmol) of olefin **24**, 147 mg (1.79 mmol) of olefin **27** contained only undeuterated material and a collected dard) in 3 ml of THF. The resulting solution was partitioned between H_2O and *n*-undecane and the organic phase was analyzed (glpc, $AgNO_3$ in $HOCH_2CH_2OH$ on Chromosorb P). The yield of *n*-hexane was 41%. The ratio of cis olefin **25**/trans olefin **24** changed from the initial value, 0.75, to a final value of 0.78. Thus, the trans olefin **24** is reduced to *n*-hexane only slightly more rapidly than the cis olefin **25**.

Reduction of 1-Hexyne (8). A. With Na in HMP–THF. To 35.33 g of a solution containing 6.82 mg-atoms of Na in HMP–THF (3:2 v/v) at 25° was added, dropwise and with stirring, 802 mg (9.78 mmol) of the acetylene **8** which just discharged the blue color. After the solution had been quenched by the addition of 5 ml of D_2O, the mixture was extracted with pentane and an internal standard (pinacolone) was added to the organic solution. Analysis (glpc) indicated the product yields to be 31% of olefin **33** and 63% recovery of acetylene **8**. A collected (glpc) sample of the olefin **27** contained only undeuterated material and a collected (glpc) sample of the acetylene **8** contained (mass spectrometric analysis) 87% d_0 species and 13% d_1 species.

B. With Na in HMP–THF–*t*-BuOH. To a solution of 0.69 g (30 mg-atoms) of Na and 0.96 g (13 mmol) of *t*-BuOH in 30 ml of HMP and 18 ml of THF at 25° was added, dropwise and with stirring, a solution of 0.96 g (13 mmol) of *t*-BuOH and 162 mg (1.97 mmol) of the acetylene **8** in 2 ml of THF. The resulting solution was immediately partitioned between H_2O and *n*-decane. After the addition of an internal standard (methylcyclohexane),

analysis (glpc) indicated that all the starting acetylene **8** had been consumed and that the product yields were 53% *n*-hexane and 28% 1-hexene (**27**).

Reduction of the Acetylene 10. Although the previously described titration data indicated that reaction of the acetylene **10** with Na in HMP–THF was very slow, the acetylene could be reduced in the presence of *t*-BuOH. To a solution of 0.40 g (17 mg-atoms) of Na in 30 ml of HMP was added a mixture of 0.58 g (4.2 mmol) of the acetylene **10** and 0.5 g (7 mmol) of *t*-BuOD. The resulting solution was stirred at 25° and additional 0.5-g portions of *t*-BuOD were added after 1.5 and after 3 hr. The reaction mixture was diluted with H_2O and then partitioned between pentane and H_2O. The organic layer was concentrated and the residue was distilled in a short-path still (128° bath) to separate 0.51 g (88%) of the product as a colorless liquid containing (glpc, silicone SE-30 on Chromosorb P) 98% of the trans olefin **22** and 2% of the hydrocarbon **26**. A collected (glpc) sample of the olefin **22** contained (mass spectrometric analysis) 12% d_0, 42% d_1, and 46% d_2 species. In another comparable experiment where excess water was added to quench the reaction mixture immediately after the addition of the acetylene **10** and *t*-BuOD, the crude product contained (glpc analysis with *n*-nonane as an internal standard) the recovered acetylene **10** (47% recovery) and the trans olefin **22** (22% yield). A collected (glpc) sample of the olefin **22** contained 22% d_1 species and 78% d_2 species. In another experiment a cold (0°) solution of Na in 20 ml of HMP was treated with 2 ml of *t*-BuOH and then sufficient acetylene **10** (170 mg) was added to just discharge the blue color of the sodium. The colorless solution was diluted with 20 ml of D_2O and then subjected to the usual isolation and analysis procedure. The calculated yields (glpc) were 68% olefin **22** and 9% acetylene **10**. A collected sample of the olefin **22** contained <2% d_1 species.

Reduction of the Acetylene 7. After 3.508 g of a blue solution containing 1.11 mg-atoms of Na in HMP–THF (3:2 v/v) at 25° had been titrated to a red end point with 71 mg (0.52 mmol) of the acetylene **7**, the reaction mixture was quenched with H_2O, an internal standard (isopropylbenzene) was added, and the mixture was extracted with pentane. Analysis (glpc, $AgNO_3$ in $HOCH_2CH_2CH$ on Chromosorb P) indicated the presence of one or both of the trans olefins **18** and **20** (retention time 6.0 min, 23% yield), isopropylbenzene (16.5 min), and the acetylene **7** (31% recovery). The reaction was repeated adding 78 mg (0.56 mmol) of the acetylene **7** to a solution of 2.0 g (87 mg-atoms) of Na and 1.2 g (15 mmol) of *t*-BuOH in 24 ml of HMP and 16 ml of THF at 25°. The product yields were *ca.* 52% trans olefins **18** and/or **20**, *ca.* 14% cis olefins **19** and/or **21**, and 3% *n*-decane.

Reduction of the Chloro Olefin 40. Following previously described[17d,37] procedures, *trans*-3-hexene (**24**) was converted to *meso*-3,4-dichlorohexane, bp 60–63° (16 mm), $n^{25}D$ 1.4490 [lit.[17d] bp 55° (15 mm), $n^{20}D$ 1.4508], and this dichloride was dehydrochlorinated[17d] with KOH in *t*-BuOH to yield the chloro olefin **40** as a colorless liquid, bp 118–120°, $n^{25}D$ 1.4340 (lit.[17d] bp 119.6°, $n^{20}D$ 1.4360). This product contained (glpc, Carbowax 20 M on Chromosorb P) the chloroolefin **40** (retention time 4.1 min) accompanied by *ca.* 3% of the stereoisomeric olefin **43** (3.6 min): ir (CCl_4) 1650 cm^{-1} (C=C); nmr (CCl_4) δ 5.52 (1 H t, J = 7.6 Hz, vinyl CH), 1.8–2.6 (4 H m, allylic CH_2), and 0.8–1.3 (6 H, m, CH_3); mass spectrum *m/e* (rel intensity 120 (14, M^+ for ^{37}Cl), 118 (40, M^+ for ^{35}Cl), 89 (45), 83 (73), 75 (25), 67 (48), 55 (100), 53 (36), 41 (71), and 39 (40).

The reductions of the chloro olefin **40** with Na–HMP–THF solutions were performed by adding the chloro olefin **40**, dropwise and with stirring, to solutions of Na (and in most cases *t*-BuOD) in HMP–THF (3:2 v/v) employing the quantities and reaction times and temperatures given in Table II. In one experiment involving an inverse addition, a standardized solution of Na in HMP–THF was added, dropwise and with stirring, to a solution of the chloro olefin **40** and *t*-BuOD in THF. The reaction solutions were then quenched with H_2O and extracted with pentane (or undecane if an analysis for *n*-hexane was desired). After the organic solutions had been mixed with a known weight of internal standard (methylcyclohexane), they were analyzed (glpc, $AgNO_3$ in $HOCH_2CH_2OH$ in Chromosorb P) as previously described to give the yield data listed in Table II. Collected (glpc) samples of the trans olefin **24** were analyzed for deuterium content by mass spectrometry. For reductions in liquid NH_3, solutions of the chloro olefin **40** in a cosolvent (THF or methylcyclohexane) were added, dropwise and with stirring, to a solution of Na in liquid NH_3. After the reaction time indicated (Table II), the reaction mixture was quenched with aqueous NH_4OH, partitioned between H_2O and pentane, and then subjected to the previously described analytical procedure to provide the yields (or compositions) listed in Table II. To examine the possibility that the cis chloro olefin **40** was isomerized to the trans chloro olefin **43** more rapidly than it was reduced, 208 mg (1.79 mmol) of the chloro olefin **40** and 1.3 g (17.5 mmol) of *t*-BuOH in 4 ml of THF was added to a cold (−33°) solution of 0.69 g (30 mg-atoms) of Na in 30 ml of HMP and 20 ml of THF and the solution was quenched with H_2O within 30 sec. However, even after this short reaction period, analysis (glpc, $AgNO_3$ in $HOCH_2CH_2OH$ on Chromosorb P) of a pentane solution of the reaction product indicated that reduction of the chloro olefin **40** (retention time 5.2 min) was complete to give a mixture of the trans olefin **24** (4.5 min, 82% of the olefin product) and the cis olefin **25** (11.9 min, 18% of the olefin product). Consequently, the reaction was repeated with insufficient Na for complete reduction by adding a solution of 453 mg (3.84 mmol) of the chloro olefin **40** and 1.70 g (23 mmol) of *t*-BuOH in 4 ml of THF to a cold (−33°) solution of 40.7 mg (1.77 mg-atoms) of Na in 30 ml of HMP and 20 ml of THF. The resulting pale yellow solution was partitioned between pentane and H_2O and the organic solution was analyzed (glpc, $AgNO_3$ in $HOCH_2CH_2OH$ on Chromosorb P and Carbowax 20 M on Chromosorb P). Approximately 75% of the unchanged chloro olefin **40** remained and the cis chloro olefin **40** was contaminated with only *ca.* 4% of the trans isomer **43**.

Registry No.—**7**, 1942-46-7; **8**, 693-02-7; **9**, 928-49-4; **10**, 17530-24-4; **11**, 6573-52-0; **18**, 7433-56-9; **19**, 7433-78-5; **20**, 19398-89-1; **21**, 19398-88-0; **22**, 692-48-8; **23**, 692-47-7; **24**, 13269-52-8; **25**, 7642-09-3; **28**, 4050-45-7; **29**, 7688-21-3; **30**, 1522-16-3; **31**, 17553-43-4; **40**, 17226-35-6; **43**, 17226-34-5; 1-decyne, 764-93-2; 1-decene, 872-05-9; *n*-butyltriphenylphosphonium ylide, 3728-50-5.

References and Notes

(1) (a) This research has been supported by Public Health Service Grant 9-RO1-GM-20197 from the National Institute of General Medical Sciences. The execution of this research was also assisted by an Institutional Research Grant from the National Science Foundation for the purchase of a mass spectrometer. (b) This work is part of the Ph.D. thesis of E. F. Kinloch done *in absentia* from the Department of Chemistry, Massachusetts Institute of Technology.

(2) For reviews and leading references, see (a) H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, Menlo Park, Calif., 1972, pp 205–209; (b) M. Smith in "Reduction," R. L. Augustine, Ed., Marcel Dekker, New York, N. Y., 1968, p 116; (c) H. Smith, "Organic Reactions In Liquid Ammonia," Vol. I, Part 2, Wiley-Interscience, New York, N. Y., 1963, pp 213–216; (d) A. J. Birch and G. Subba Rao, *Advan. Org. Chem.*, **8**, 38 (1972).

(3) (a) R. A. Benkeser, G. Schroll, and D. M. Sauve, *J. Amer. Chem. Soc.*, **77**, 3378 (1955); (b) R. A. Benkeser and C. A. Tincher, *J. Org. Chem.*, **33**, 2727 (1968); (c) R. E. A. Dear and F. L. M. Pattison, *J. Amer. Chem. Soc.*, **85**, 622 (1963); (d) B. S. Rabinovitz and F. S. Looney, *ibid.*, **75**, 2652 (1953).

(4) D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965, pp 130–135.

(5) H. O. House, L. E. Huber, and M. J. Umen, *J. Amer. Chem. Soc.*, **94**, 8471 (1972).

(6) (a) R. E. Sioda, D. O. Cowan, and W. S. Koski, *J. Amer. Chem. Soc.*, **89**, 230 (1967); (b) H. E. Zimmerman and J. R. Dodd, *ibid.*, **92**, 6507 (1970); (c) A. G. Evans, J. C. Evans, P. J. Emes, and T. J. Phelan, *J. Chem. Soc. B*, 315 (1971); (d) W. M. Moore and D. G. Peters, *Tetrahedron Lett.*, **No. 5**, 453 (1972); (e) Z. Csuros, P. Caluwe, and M. Szwarc, *J. Amer. Chem. Soc.*, **95**, 6171 (1973).

(7) (a) A. J. Fry, "Synthetic Organic Electrochemistry," Harper and Row, New York, N. Y., 1972, pp 238–239; (b) A. P. Tomilov, *Russ. Chem. Rev.*, **31**, 569 (1962).

(8) We are grateful to Professor W. R. Moore for providing us with a sample of the cyclic acetylene **11**.

(9) K. W. Bowers, R. W. Giese, J. Grimshaw, H. O. House, N. H. Kolodny, K. Kronberger, and D. K. Roe, *J. Amer. Chem. Soc.*, **92**, 2783 (1970).

(10) (a) G. Levin, J. Jagur-Grodzinski, and M. Szwarc, *J. Amer. Chem. Soc.*, **92**, 2268 (1970); *J. Org. Chem.*, **35**, 1702 (1970); (b) G. Levin and M. Szwarc, *Chem. Commun.*, **No. 17**, 1029 (1971); (c) D. A. Dadley and A. G. Evans, *J. Chem. Soc. B*, 418 (1967); 107 (1968).

(11) For a review of the properties of this solvent, see H. Normant, *Angew. Chem., Int. Ed. Engl.*, **6**, 1046 (1967).

(12) (a) M. Larchevêque, *Ann. Chim. (Paris)*, 129 (1970); (b) G. M. Whitesides and W. J. Ehmann, *J. Org. Chem.*, **35**, 3565 (1970).

(13) (a) The difficulty of separating the structural isomers of *n*-decene by glpc analysis has been described elsewhere: B. Blouri, J.-E. Fauvet, and P. Rumpf, *Bull. Soc. Chim. Fr.*, 1855 (1963). (b) The analysis of mixtures of the structurally isomeric *n*-octenes presents similar problems: N. C. G. Campbell, J. R. P. Clarke, R. R. Hill, P. Oberhänsli, J. H. Parish, R. M. Southham, and M. C. Whiting, *J. Chem. Soc. B*, 349 (1968).

(14) For discussions of the base-catalyzed acetylene–allene isomerization, see (a) R. J. Bushby, *Quart. Rev., Chem. Soc.*, **24**, 585 (1970); (b) M. D. Carr, L. H. Gan, and I. Reid, *J. Chem. Soc., Perkin Trans. 2*, 668, 672 (1973); (c) M. Sovoboda, J. Zavada, and J.

Sicher, *Collect. Czech. Chem. Commun.*, **30**, 413, 421 (1965); (d) G. Nagendrappa, R. K. Srivastava, and D. Devaprabhakara, *J. Org. Chem.*, **35**, 347 (1970).
(15) (a) For examples of the reaction of THF with organometallic and anion radical intermediates, see R. B. Bates, L. M. Kroposki, and D. E. Potter, *J. Org. Chem.*, **37**, 560 (1972); M. H. Hnoosh and R. A. Zingaro, *J. Amer. Chem. Soc.*, **92**, 4388 (1970). (b) The reaction of MeLi with HMP to form methane[9] and the base-catalyzed exchange of H for D in HMP [H. Normant, T. Cuvigny, and G. J. Martin, *Bull. Soc. Chim. Fr.*, 1605 (1969)] both indicate that HMP can donate a proton to strong bases.
(16) As the first antibonding π orbital of acetylene is populated, the geometry of the molecule is expected to change from a linear to a trans-bent geometry. See B. M. Gimarc, *J. Amer. Chem. Soc.*, **92**, 266 (1970); G. W. Schnuelle and R. G. Parr, *ibid.*, **95**, 8974 (1973).
(17) (a) For a recent review see L. A. Singer, *Selec. Org. Transform.*, **2**, 239 (1972); (b) G. D. Sargent and M. W. Browne, *J. Amer. Chem. Soc.*, **89**, 2788 (1967); (c) A. J. Fry and M. A. Mitnick, *ibid.*, **91**, 6207 (1969); (d) M. C. Hoff, K. W. Greenlee, and C. E. Boord, *ibid.*, **73**, 3329 (1961). (e) The rate of inversion of vinyl radicals has also been studied by examining the stereochemistry of the reduction of the isomeric 2-bromo-2-butenes to the 2-butenes with *n*-Bu_3SnH in a reaction involving an intermediate 2-buten-2-yl radical. H. G. Kuivila [*Accounts Chem. Res.*, **1**, 299 (1968)] found that at −75°, 2-bromo-*cis*-2-butene gave an olefin mixture containing 57% of *cis*-2-butene where the trans bromo olefin gave a mixture containing 15% *cis*-2-butene. G. M. Whitesides and C. P. Casey [*J. Amer. Chem. Soc.*, **88**, 4541 (1966)] studied the same reaction at 25° and found that each isomeric bromo olefin gave the same mixture of 2-butenes containing 65% of the trans isomer and 35% of the cis isomer.
(18) All melting points are corrected and all boiling points are uncorrected. Unless otherwise stated $MgSO_4$ was employed as a drying agent. The ir spectra were determined with a Perkin-Elmer Model 237 or Model 257 infrared recording spectrophotometer fitted with a grating. The uv spectra were determined with a Cary Model 14 or a Perkin-Elmer Model 202 recording spectrophotometer. The nmr spectra were determined at 60 MHz with Varian Model A-60 or Model T-60 nmr spectrometer. The chemical shifts are expressed in δ values (parts per million) relative to a Me_4Si internal standard. The mass spectra were obtained with an Hitachi Perkin-Elmer mass spectrometer, Model RMU-7, or a Varian Model M-66 mass spectrometer. All reactions involving strong bases or organometallic intermediates were performed under a nitrogen atmosphere.
(19) P. D. Bartlett and L. J. Rosen, *J. Amer. Chem. Soc.*, **64**, 543 (1942).
(20) The procedure of W. H. Puterbaugh and M. S. Newman [*J. Amer. Chem. Soc.*, **81**, 1611 (1959)] was modified as described by H. O. House and M. J. Umen, *J. Org. Chem.*, **38**, 3893 (1973).
(21) P. Pomerantz, A. Fookson, T. W. Mears, S. Rothberg, and F. L. Howard, *J. Res. Nat. Bur. Stand., No. 2*, **52**, 51 (1954).
(22) G. F. Hennion and T. F. Banigan, Jr., *J. Amer. Chem. Soc.*, **68**, 1202 (1946).
(23) This experiment was done in our laboratories by Dr. Norton D. Peet.
(24) (a) K. N. Campbell and B. K. Campbell, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 117; (b) K. N. Campbell and L. T. Eby, *J. Amer. Chem. Soc.*, **63**, 216 (1941); (c) R. A. Benkeser, G. Schroll, and D. M. Sauve, *ibid.*, **77**, 3378 (1955).
(25) F. D. Rossini, K. S. Pitzer, R. L. Arnett, R. M. Braun, and G. C. Pimentel, "Selected Values of Physical and Thermodynamic Properties of Hydrocarbons and Related Compounds," API Research Project 44, Carnegie Press, Pittsburgh, Pa., 1953, p 66.
(26) H. I. Waterman, P. Van't Spijker, and H. A. Van Westen, *Recl. Trav. Chim. Pays-Bas*, **48**, 1097 (1929).
(27) R. Mechoulam and F. Sondheimer, *J. Amer. Chem. Soc.*, **80**, 4386 (1958).
(28) K. Ziegler, E. Eimers, W. Hechelhammer, and H. Wilms, *Justus Liebigs Ann. Chem.*, **567**, 43 (1950).
(29) Purchased from Columbia Organic Chemicals Co., Inc.
(30) Purchased from Chemical Samples Co.
(31) Purchased from Aldrich Chemical Co., Inc.
(32) V. Prelog, K. Schenker, and W. King, *Helv. Chim. Acta*, **36**, 471 (1953).
(33) A. T. Blomquist, L. H. Liu, and J. C. Bohrer, *J. Amer. Chem. Soc.*, **74**, 3643 (1952).
(34) H. O. House, D. Koepsell, and W. Jaeger, *J. Org. Chem.*, **38**, 1167 (1973).
(35) C. E. Castro and R. D. Stephens [*J. Amer. Chem. Soc.*, **86**, 4358 (1964)] have found that solutions of $CrSO_4$ will reduce both HC≡CH and certain substituted acetylenes.
(36) For a discussion of this reagent with leading references, see H. O. House and E. F. Kinloch, *J. Org. Chem.*, in press.
(37) R. C. Fahey and D.-J. Lee, *J. Amer. Chem. Soc.*, **90**, 2124 (1968).

Complex Metal Hydride Reduction of Carbon–Carbon Unsaturation. I. Sodium Borohydride Reduction of α-Phenylcinnamates and Related Systems[1a]

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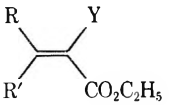
Received August 10, 1973

The substituted methyl cinnamates **4** and **5** have provided a unique system for the study of various mechanistic aspects of the nucleophilic 1,4 addition of sodium borohydride to α,β-unsaturated esters. Competitive rates of reduction for two sets of methyl α-phenyl-*trans*-cinnamates (**4**), para-substituted in the α and β rings, respectively, correlate linearly with Hammett σ_p values. The similarity in ρ_α (1.74) and ρ_β (1.44) indicates that the transition state for hydride transfer occurs before significant change in geometry of the α,β-unsaturated carbonyl system occurs. Competitive rate studies for methyl α-(para substituted phenyl)acrylates (**2**) and methyl α-phenyl-*cis*- and -*trans*-crotonates (**14** and **15**) are corroborated by the data obtained for the cinnamates.

Carbon–carbon double bonds conjugated with strong anion-stabilizing groups (*e.g.*, COR, CO_2R, CN, SO_2R, NO_2) have occasionally been observed to undergo reduction with sodium borohydride.[2-11] Although it is recognized that sodium borohydride exhibits nucleophilic behavior,[3,4] little is known concerning the mechanism or even the general structural requirements for the occurrence of such reactions.

This paper presents preliminary studies on the scope and mechanism of the borohydride reductions of carbon–carbon double bonds in α,β-unsaturated esters. Although esters are less prone to undergo this type of reduction than are more electrophilic systems such as ketones or nitro compounds, reduction of the carbon–carbon unsaturation was not complicated (in the cases studied) by significant reduction of the ester function or by other side reactions.

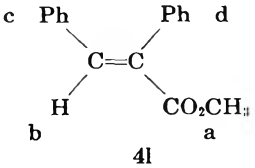
α,β-Unsaturated esters having an additional electron-withdrawing substituent at the α position (*e.g.*, **1a–f**) are known to undergo facile carbon–carbon double bond re-



1

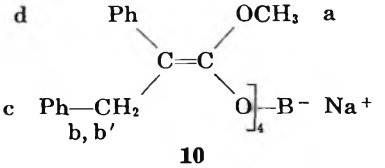
a, R = CH_3; R′ = H; Y = $CO_2C_2H_5$
b, R = R′ = CH_3; Y = $CO_2C_2H_5$
c, R = Ph or substituted Ph; R′ = H; Y = $CO_2C_2H_5$
d, R, R′ = $(CH_2)_5$; Y = CN
e, R = R′ = H; Y = Ph
f, R = R′ = Ph; Y = CN
g, R = R′ = Ph; Y = $CO_2C_2H_5$

Table I
Nmr Data for the Intermediate from the Reaction of Sodium Borohydride with Methyl α-Phenyl-*trans*-cinnamate[a,b]



4l

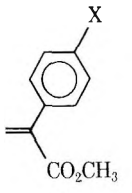
a, δ 3.75 (s)
b, δ 7.88 (s)
c, d, δ 6.83–7.60 (m)



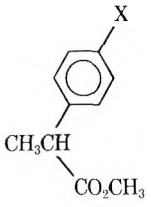
10

a, δ 3.52 (s)
b, b′, δ 3.00 and 3.33 (d, d, J = 14 Hz)
c, d, δ 6.72–7.62 (m)

[a] Similar results were obtained with the α-(*p*-chlorophenyl)cinnamate (**4o**). [b] Shifts (parts per million) were obtained in DMSO-d_6 solution, relative to TMS.

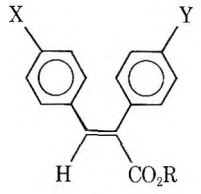


2



3

a, X = NO_2; b, X = Cl; c, X = F; d, X = H; e, X = OCH_3



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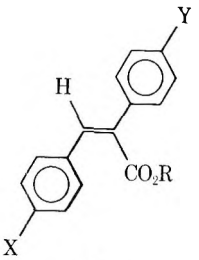
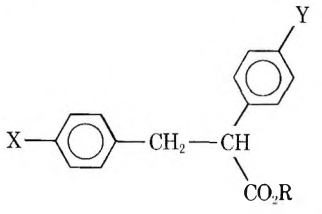


5



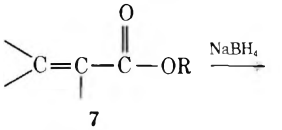
6

a, R = X = Y = H
b, R = X = H; Y = NO_2
c, R = X = H; Y = CO_2H
d, R = X = H; Y = Cl
e, R = X = H; Y = OCH_3
f, R = Y = H; X = NO_2
g, R = Y = H; X = CO_2H
h, R = Y = H; X = Cl
i, R = Y = H; X = OCH_3
j, R = H; X = OCH_3; Y = NO_2
k, R = H; X = OCH_3; Y = OCH_3
l, X = Y = H; R = CH_3
m, X = H; Y = NO_2; R = CH_3
n, X = H; Y = CO_2CH_3; R = CH_3
o, X = H; Y = Cl; R = CH_3
p, X = H; Y = OCH_3; R = CH_3
q, X = NO_2; Y = H; R = CH_3
r, X = CO_2CH_3; Y = H; R = CH_3
s, X = Cl; Y = H; R = CH_3
t, X = OCH_3; Y = H; R = CH_3
u, X = OCH_3; Y = NO_2; R = CH_3
v, X = OCH_3; Y = OCH_3; R = CH_3

duction with sodium borohydride in solvents such as alcohols, dimethoxyethane, or diglyme.[12-15]

We have examined a number of α,β-unsaturated esters in order to find systems of lower electrophilicity than the alkylidene cyanoacetates and malonates, but which would still be susceptible to borohydride reduction. As expected, simple α- or β-alkyl acrylates such as methyl methacrylate, methyl crotonate, or methyl cyclopentene-1-carboxylate and β-aryl acrylates such as methyl cinnamate and methyl *p*-nitrocinnamate were not reduced by sodium borohydride in methanol at room temperature.[16,17] However, under similar conditions, the series of methyl α-(para substituted phenyl)acrylates (**2a–c**) were reduced cleanly to the dihydro esters **3a–e**.[18] Methyl α-(*p*-nitrophenyl)acrylate (**2a**) was completely reduced in 1 min at −5°. This rate was qualitatively 100 times that observed for reduction of the *p*-methoxy ester **2e**. The α-(para substituted phenyl)-*trans*-cinnamates (**4l–p**) were also prepared and all were found to undergo reduction with sodium borohydride in dimethoxyethane at room temperature. The time required for complete reduction ranged from 10 min for **4m** to more than 1 week for **4p**. The stoichiometry of the reductions were shown to be 4:1 (ester:borohydride).

These reductions in aprotic solvent apparently occur by 1,4 addition of borohydride to provide intermediates of type **8**[19] which undergo successive 1,4 additions to give the enol boronates (**9**) in which all four hydride hydrogens have been utilized.



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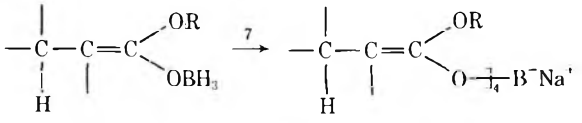


8 **9**

The nmr spectrum for the product obtained by reaction of a 4:1 molar ratio of methyl α-phenyl-*trans*-cinnamate (**4l**) to sodium borohydride in anhydrous DMSO-d_6 solution is consistent with the enol boronate structure **10**. A comparison of the proton nmr data for this intermediate with that for the cinnamate **4l** is presented in Table I. The methylene protons (b, b′) in structure **10** might be expected to exhibit magnetic nonequivalence owing to the conformational restraint placed on the benzyl group as a result of phenyl c to boronate and phenyl c to phenyl d interactions. The 14-Hz coupling observed for the pair of doublets at 3.00 and 3.33 ppm is within expectation for a geminally coupled methylene group adjacent to a π bond.[20] The alternate *E* geometry for **10** was excluded from consideration owing to the steric strain which would be imposed by a phenyl group cis to the alkoxyboronate function.

Table II
Nmr Data for Methyl 2-(*p*-Nitrophenyl)-3-phenylpropionates

Compd[a]	Chemical shift,[b,c] ppm	Coupling constant, Hz
$PhCH_2CHAr$ $\vert$ CO_2CH_3 **6m**	H_a 3.02 H_b 3.38 H_c 3.97	J_{ab} = 15 J_{ac} = 8 J_{bc} = 6–7
$PhCH_2CDAr$ $\vert$ CO_2CH_3 **11**	H_a 2.98 H_b 3.45	J_{ab} = 14
$PhCHDCHAr$[d] $\vert$ CO_2CH_3 **12**	H_a 3.03 H_b 3.42 H_c 4.00	J_{ac}[e] = 8 J_{bc}[e] = 8

[a] Ar = *p*-nitrophenyl. [b] Shifts were determined in CCl_4 solutions relative to TMS. [c] The methoxyl singlet appeared at 3.62 ppm. [d] Diastereomers. [e] Peaks were broadened owing to geminal deuterium coupling.

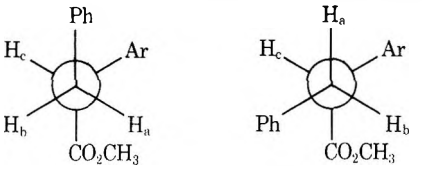
Table III
Relative Rate Data for Sodium Borohydride Reductions

Compd[a]	Relative rate[b]	Reduction time, min	ρ
	Methyl α-(Para substituted phenyl)-*trans*-cinnamates (**4l–p**)		
NO_2/Cl	12.77	3	
CO_2CH_3/Cl	2.63	15	
Cl/H	5.40[c]	42, 50	+1.74[d]
OCH_3/H	0.49	70, 100	
	Methyl α-Phenyl(para substituted phenyl)-*trans*-cinnamates (**4l, 4q–t**)		
NO_2/H	14.05[e]	25	
CO_2CH_3/H	4.05[e]	60	
NO_2/Cl	4.77[e]	60	
CO_2CH_3/Cl	1.63	60	+1.44[f]
Cl/H	3.08	95, 60	
OCH_3/H	0.38	90	
	Methyl α-(Para substituted phenyl)acrylates (**2b–e**)		
Cl/H	4.31[e]	20	
Cl/F	2.39[e]	20	+2.33
OCH_3/H	0.25[e,g]	45	

[a] Pairs were selected on the basis of relative rates of reduction and separability of reactants and products by glpc. [b] Average for two runs. The relative rate for each run was determined from an average of five glpc injections. Response factors were very close to 1:1. Deviations between runs were <3% of lower value. [c] The difference between runs was 6.8%. [d] The standard error was 0.148; the correlation coefficient was 0.978. [e] Results for a single run. [f] The standard error was 0.116, with a correlation coefficient of 0.978. [g] Relative rate was determined by nmr.

It is evident that enol boronates derived from α-aryl cinnamates might exhibit color due to the auxochromic effect of the divalent oxygen functions attached to the styrene type chromophore. However, it is also possible that these compounds would be colored due to the enolate ions which would be present due to some dissociation of the boronates. Johnson and Rickborn[3] have provided evidence for dissociation of similar proposed intermediates obtained by reduction of α,β-unsaturated aldehydes and ketones with sodium borohydride in isopropyl alcohol. A deep burgundy-colored intermediate was formed when sodium borohydride was added to a solution of methyl α-(*p*-nitrophenyl)-*trans*-cinnamate (**4m**) in anhydrous dimethoxyethane or dimethyl sulfoxide solution. Colored intermediates were also observed for **4n** (orange) and **2a** (red) in dimethoxyethane. The intermediates from other α-aryl cinnamates were colorless to pale yellow, except for that from **4q** which was pale orange. These intermediates were stable for weeks in sealed tubes; however, the colors faded quickly in moist air or when water was added. Such intermediates were not observed for reductions carried out in methanol owing to rapid solvolysis to the dihydro esters.

Chemical shifts and coupling constants for the aliphatic proton absorptions in the nmr spectrum of methyl 2-(*p*-nitrophenyl)-3-phenylpropionate (**6m**) (obtained by the sodium borohydride reduction of **4m** in dimethoxyethane solution with subsequent hydrochloric acid work-up) are listed in Table II. Referring to the pertinent Newman projections (**6m**), it is apparent that H_a and H_b are diastereo-



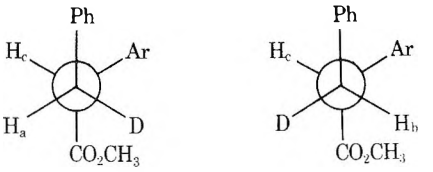
Ar = *p*-nitrophenyl

6m

topic; however, as a consequence of rapid rotamer interconversion, they give rise to simple geminal AB coupling and vicinal coupling with H_c.[21]

Reduction of **4m** with sodium borohydride in anhydrous dimethoxyethane, followed by deuterolysis with 2 *N* deuterium chloride in deuterium oxide and a parallel reaction employing sodium borodeuteride, followed by hydrochloric acid work-up, afforded the propionates **11** and **12** (Table II) deuterated in the α and β positions, respectively. The α-deuteriopropionate (**11**) exhibited the expected simple geminal AB coupling. The β-deuterio compound (**12**) showed the expected H_c doublet, but the β-proton resonance appeared as two AB doublets, indicating the presence of diastereomers **12a** and **12b** (only one conformer of each is shown) in equal amounts. The same mixture of diastereomers was obtained from borodeuteride reduction

of methyl α-(*p*-nitrophenyl)-*cis*-cinnamate (**5m**). Similarly, identical mixtures were obtained from borodeuteride reduction of methyl α-phenyl-*p*-nitro-*cis*- and -*trans*-cinnamates (**5q** and **4q**). Diastereomers are, of course, expected to result from hydrolysis of the proposed enol boronate intermediates.



(+ the enantiomers)

12a **12b**

The α-aryl cinnamates provided an ideal system for mechanistic studies, since the electron availability at the α and β positions could be varied by use of substituents on either the α or β phenyl group. Hammett σ_p correlations were obtained on two series of methyl α-phenyl-*trans*-cinnamates. In one series, the α phenyl group was unsubstituted while the para substituents on the β ring were varied (**4l, 4q–t**). In the second series, the β phenyl group was held constant while the α ring was altered (**4l–p**). Competitive reductions of these cinnamates with sodium borohydride were carried out in anhydrous dimethoxyethane and the reaction mixtures were quenched with dilute hydrochloric acid to provide the corresponding propionates (**6**). Since quenching occurred instantly, the yields of propionates indicated the rates of formation of the boronate intermediates.

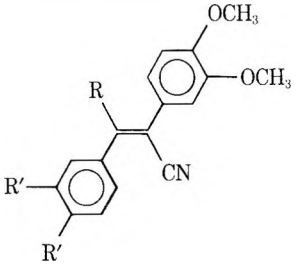
Table III lists relative rate data for the competitive reductions of the methyl α-(para substituted phenyl)-*trans*-cinnamates (**4l–p**). A Hammett plot of this data *vs.* σ_p[22] was linear; ρ was +1.74. The data obtained from competitive reduction of the methyl α-phenyl-*trans*-cinnamates (**4l, 4q–t**) are also given in Table III. The ρ value for this series was +1.44. Although it has not been determined whether the first hydride transfer in the reduction of cinnamates is rate determining, as has been observed in the borohydride reduction of ketones,[23] it appears likely that this is the case. In any event, the linear Hammett correlations obtained are indicative of a constancy of mechanism for the range of substituents employed in both cases.[24] This was further demonstrated by competitive reduction of methyl α-(*p*-nitrophenyl)-*trans*-*p*-methoxycinnamate (**4u**) *vs.* methyl α-(*p*-nitrophenyl)-*trans*-cinnamate (**4m**), which showed a linear $\sigma_\alpha + \sigma_\beta$ contribution.[25] The rate factor (CH_3O/H) was 0.381, comparing favorably to the predicted value of 0.357 (Table III).

Correlation of both sets of relative rate data with σ_p are consistent with a rate-determining step involving hydride transfer to the carbon–carbon double bond in the cinnamate. The magnitudes of ρ are indicative of substantial negative charge stabilization during this step.[25,26] The remarkable similarity in magnitudes of the ρ values suggests that the transition state for hydride transfer is attained before a considerable change in geometry of the cinnamate occurs.

Competitive rate studies on the methyl α-(para substituted phenyl)acrylates (**2a–e**) were quite problematic owing to difficulty in obtaining a sufficient number of compounds in this series and their tendencies to polymerize. On the basis of three reactions carried out in methanol solution at −5° (Table III), a linear Hammett plot was obtained, ρ = +2.3. This value was in line with that anticipated from the ρ value of 1.74 obtained for the α-(para substituted phenyl)-*trans*-cinnamates. The decreased ρ values observed for the cinnamates are explained by a *cis*-stilbene type interaction of the aryl groups[27] which prevents them from achieving maximum resonance interaction with the developing anion.

In the α-phenyl-*trans*-cinnamates, steric hindrance forces the α and β phenyl groups out of plane with the carbon–carbon π bond, but has little effect on the carbomethoxyl group, which can still achieve maximum conjugative overlap. In the *cis*-cinnamate system, however, interaction between the carbomethoxyl and β-phenyl groups forces the ester function out of conjugation.[27] The decreased ability of the carbomethoxyl group to achieve coplanarity and thus stabilize incipient anion formation appears to be the prime factor governing the differences in rates of reduction of *cis*- *vs.* *trans*-α-phenyl cinnamates. Reduction of methyl α-phenyl-*trans*-cinnamate (**4l**) was slow (5.5% in 90 min); however, the cis isomer was not detectably (less than 0.1%) reduced under similar conditions. The methyl α-(*p*-nitrophenyl)cinnamates exhibited similar behavior. The trans isomer (**4m**) was completely reduced in less than 10 min, while the cis isomer required about 8 hr for complete reduction. Analogously, Truce and coworkers[9] report that *trans*-1-mesityl-2-(mesitylsulfonyl)ethylene was reduced to the dihydrosulfone by sodium borohydride in diglyme. The cis isomer was inert to these conditions. In view of these results, the reported failure of diethyl diphenylmethylidenemalonate (**1g**) to undergo borohydride reduction appears to be as much a consequence of steric hindrance to anion development as the proposed decreased electrophilicity of the β carbon atom due to conjugation of the double bond with the β phenyl group.[13]

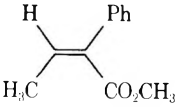
In contrast to the failure of methyl α-phenyl-*cis*-cinnamate to undergo reduction, α-phenyl-*cis*-cinnamonitrile was easily reduced (40% in 90 min) by sodium borohydride in dimethoxyethane. Likewise, Knabe and coworkers[7] have reported that the substituted α-phenylcinnamonitriles **13a–c** undergo double-bond reduction in good



13a, R = R′ = H
b, R = H; R′ = OCH_3
c, R = CN; R′ = OCH_3

yield upon heating with sodium borohydride in tetrahydrofuran solution. In the cinnamonitrile cases, the symmetrical nitrile function is not conformationally restricted to overlap.[27] The nitrile function is, however, a somewhat better anion-stabilizing moiety than the ester function.[28]

Steric restraint of coplanarity of the carbomethoxyl function by a cis β-methyl group is expected to be much less dramatic than that observed with a cis β-phenyl group. Thus both the cis (**14**) and trans (**15**) isomers of methyl α-phenylcrotonate were found to undergo slow reduction with sodium borohydride in methanol to yield methyl α-phenylbutyrate. Competitive rate studies in methanol showed the trans crotonate to be 2.6 times more reactive than the cis isomer.



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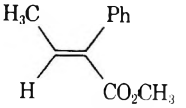

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Experimental Section[29]

Reagents. Sodium borohydride (SBH) and sodium borodeuteride were obtained from Matheson Coleman and Bell and from Stohler Isotopes, Inc., respectively. α-Phenyl-*trans*-cinnamic acid was purchased from Aldrich Chemical Co. Dimethoxyethane (DME) was refluxed over freshly cut sodium for several days and distilled from calcium hydride under nitrogen just prior to use. Solutions of SBH in anhydrous DME were standardized by titration with hydrochloric acid to a Methyl Orange endpoint.[30]

Preparation of Methyl α-(Para substituted phenyl)acrylates (2a–e). Preparation of **2a** was reported previously;[31] **2b–e** were prepared by the procedure of Dutta and Biswas[32] for the preparation of ethyl α-(*p*-methoxyphenyl)acrylate, except that the appropriate methyl para-substituted phenyl acetates, sodium methoxide in methanol, and dimethyl oxalate were employed instead of the corresponding ethyl compounds. Nmr and glpc analysis of the crude products after short-path distillation indicated 25–40% yields of acrylates **2b–e** contaminated with 15–20% of the methyl para-substituted phenyl acetates. Small samples of pure **2b–e** were obtained by distillation of the crude products through a 60-cm platinum spinning band column. The boiling points follow: **2b,** 78° (0.10 mm); **2c,** 57° (0.11 mm); **2d,** 69° (0.76 mm); **2e,** 89° (0.10 mm). The nmr spectra were conclusive for the assigned structures.[33]

Reduction of Acrylates 2a–e. SBH (1 mmol) was dissolved in 5 ml of methanol at −65° under nitrogen. A solution of 1 mmol of the acrylate in 5 ml of methanol at −65° was added and the solution was allowed to warm to room temperature and was stirred for 2 hr longer. Cold 0.4 *N* HCl (25 ml) was added and the mixture was extracted four times with 25-ml portions of ether. The combined ether extract was washed with $NaHCO_3$ solution and twice with 25-ml portions of water, then dried ($MgSO_4$), filtered, and evaporated through a Vigreux column. The propionates **3a–e** were purified by evaporative distillation (bath temperature, pressure): **3a,** 116° (0.15 mm); **3b,** 82–86° (1.2 mm); **3c,** 57–65° (0.2 mm); **3d,** 65° (0.25 mm); **3e,** 100–120° (2.1 mm). Small amounts (5–10%) of residues were obtained in each case. Nmr and glpc analysis indicated 95–100% carbon–carbon double bond reduction and the absence of other products. Preparative glpc was employed to obtain analytical samples of **3a–e.**[33]

Competitive Reductions of the Acrylates 2b–e. Three reactions were conducted with the pairs of acrylates indicated in Table III. Methyl α-(*p*-nitrophenyl)acrylate was omitted since its rate of reduction was too fast to permit quantitative comparison with the other acrylates available.

A solution of 0.35 mmol of each of the indicated pair of acrylates in 27.5 ml of methanol was prepared under nitrogen. The solution was cooled to −5°. SBH solution (prepared by stirring 0.80 mmol of SBH in 2.5 ml of methanol at −5° for 2 min) was added in one portion to the stirred acrylate solution. After stirring at −5° for the time indicated in Table III, the reaction was quenched with 30 ml of cold 1 *N* HCl. Work-up was carried out as described above for reduction of the individual acrylates. The relative rates for Cl/H and Cl/F were determined by glpc analysis. The CH_3O/H ratio could not be determined in this manner owing to unsatisfactory resolution of all four peaks. Since the vinyl proton peaks in the nmr spectrum of a mixture of **2d** and **2e** were completely separated, the relative rate was determined from the rate of disappearance of these peaks. Mesitylene was employed as an internal concentration standard to determine the amounts of **2d** and **2e** remaining after partial reduction.

α- and β-(Para substituted)-α-phenyl-*cis*- or -*trans*-cinnamic Acids. The *trans*-cinnamic acids **4b,**[34] **4c, 4d,**[35] **4e,**[34] **4f,**[34] **4g, 4h,**[36] **4i,**[34] **4j,**[34] and **4k**[34] were prepared by triethylamine-catalyzed condensation of the appropriate para-substituted benzaldehyde and phenylacetic acid in acetic anhydride solution according to the procedure of Buckles and coworkers (recrystallized from methanol).[37,38] Compounds **4c,** mp 191–192°, and **4g,** mp 304° (both obtained in ~80 yield), apparently have not been reported previously. The assigned structures were confirmed by microanalyses on the corresponding methyl esters[33] and by nmr and ir spectroscopy.

The *cis*-cinnamic acids **5a, 5b,** and **5f** were isolated from the equilibrium mixtures obtained by refluxing the corresponding trans acids in triethylamine–acetic anhydride solution for 3 hr.[34]

Preparation of the Methyl Esters of the *cis*- or *trans*-Cinnamic Acids (4a–j, 5a, 5b, and 5f). An ice-cold solution of diazomethane in ether[39] was added slowly to a cold suspension or solution of the appropriate α- or β-(para-substituted)-α-phenylcinnamic acid in 25 ml of anhydrous ether until evolution of nitrogen ceased and excess diazomethane was visibly present. After stirring for 0.5 hr (ice bath), the ether solution was allowed to warm to room temperature and excess diazomethane was destroyed by addition of a little acetic acid. The ether solution was extracted with 50 ml of 10% Na_2CO_3 solution, dried ($MgSO_4$), and evaporated.

The crude cinnamates were recrystallized from hexane or methanol. The yields ranged from 89 to 96%. The melting points follow: **4l,** 72–73°; **5l,** liquid; **4m,** 102–103° (lit.[40] 104°); **4n,** 126°; **4o,** 87–88°; **4p,** 82.5–83°; **5m,** 101–103°; **4q,** 139–140°; **5q,** 149–150°; **4r,** 104–105°; **4s,** 105–106°; **4t,** 73–74°; **4u,** 113–114°; **4v,** 96–97°. The assigned structures were confirmed by elemental analysis[33] and by nmr and ir spectroscopy.

Sodium Borohydride Reduction of the Cinnamates 4l–v, 5l, 5m, and 5q. A mixture of 1.0 mmol of the particular methyl α-phenylcinnamate, 1.0 mmol (37.8 mg) of SBH, and 10 ml of anhydrous DME was stirred at room temperature. After sufficient time for complete reduction (ranging from about 10 min for **4m** to more than 1 week for **4p** or **4t**) the mixture was neutralized with 1 *N* HCl and the solvent was removed *in vacuo*. Saturated aqueous NH_4Cl solution (5 ml) was added and the mixture was extracted three times with a total of 20 ml of chloroform. The combined extract was dried over $MgSO_4$, concentrated, and sublimed or evaporatively distilled at 100–110° (0.1 mm). These dihydroesters were all liquids except **6m,** mp 60–61°; **6q,** mp 78–80°; **6r,** mp 63–64°; **6t,** mp 60–61°; **6u,** mp 73–78°. Reduction of **4v** was extremely slow—gc analysis indicated that **6v** was formed in only 1% yield after 2 weeks reduction time. The dihydrocinnamate structures were verified by microanalysis[33] and nmr (data in Table II are typical) spectroscopy. Glpc indicated that these compounds were the only reaction products in all cases. This was confirmed by tlc.

Competitive Reductions of Methyl α- or β-(Para-substituted)-α-phenyl-*trans*-cinnamates. Five milliliters of a standardized solution containing 5.67 mg (0.15 mmol) of SBH in anhydrous DME was added to a stirred solution of 0.33 mmol each of the two cinnamates (Table III) in 2 ml of dry DME at 25°. After the reaction time indicated, the reaction was quenched with a few drops of 2 *N* HCl. The solvent was removed *in vacuo*, 5 ml of saturated NH_4Cl solution was added, and the mixture was extracted three times with a total of 25 ml of ether; the combined extract was dried ($MgSO_4$) and evaporated before glpc analysis.

Preparation of Intermediates for Nmr Analysis (Table I). Samples were prepared in a glove box under nitrogen. A solution of 4.33 mmol of methyl α-phenyl-*trans*-cinnamate (**4l**) or the *p*-chlorophenyl ester (**4o**) in 2 ml of anhydrous DMSO-d_6 (1% TMS) was prepared in a dry 4-ml septum-capped vial. Sodium borohydride (1.08 mmol) was added and the sample was sealed and stirred magnetically to effect solution. Samples were then transferred to oven-dried nmr tubes fitted with conventional polyethylene caps.

Preparation of Methyl 2-Deuterio-2-(*p*-nitrophenyl)-3-phenylpropionate (11). One millimole (283 mg) of **4m** was dissolved in 20 ml of dry DME under nitrogen and 1 mmol of SBH was added. The mixture was stirred for 10 min, then quenched with a few drops of 2 *N* DCl in D_2O solution. The solvent was evaporated *in vacuo* at room temperature. The residue was extracted twice with 5-ml portions of ether, and the combined extract was dried over $MgSO_4$ and evaporated *in vacuo*. The crude product was recrystallized from hexane to yield 206 mg (76% yield) of **11,** mp 58–59°. Nmr data for **11** are given in Table II.

Preparation of Methyl 2-(*p*-Nitrophenyl)-3-deuterio-3-phenylpropionate (12). A solution of 0.5 mmol of methyl α-(*p*-nitrophenyl)-*cis*- or -*trans*-cinnamate (**4m** or **5m**) was dissolved in 10 ml of dry DME under nitrogen. An equimolar amount of sodium borodeuteride was added and the mixture was stirred at room temperature (10 min for **4m,** overnight for **5m**). A few drops of water was then added and the solvent was evaporated *in vacuo* at room temperature. Work-up was carried out as described for the preparation of the 2-deuterio compound (**11**). Nmr on the crude product (Table II) indicates that both reactions gave 1:1 mixtures of the diastereomers of **12**.

Borohydride Reduction of α-Phenyl-*cis*-cinnamonitrile. Reduction of α-phenyl-*cis*-cinnamonitrile (K and K Laboratories) was carried out for 1.5 hr at room temperature, using the amounts and procedure described for the cinnamates. The crude product was examined by glpc and by nmr and found to contain ~40% 2,3-diphenylpropionitrile.

Preparation of Methyl α-Phenyl-*cis*- and -*trans*-crotonates (14, 15). A 15-g sample of α-phenylcrotonic acid[41] was esterified by refluxing for 22 hr with 100 ml of a 10% solution of concentrated H_2SO_4 in methanol. The crude product was poured into ice

water and extracted into ether. The ether extract was washed with water, dried ($MgSO_4$), evaporated, and distilled at 70–73° (0.3 mm) to give 6.8 g (42% yield) of a 9:91 mixture of methyl α-phenyl-*cis*- and -*trans*-crotonates (**14** and **15**, respectively). These isomers were separated by preparative glpc. The nmr spectrum of the *trans*-crotonate **15** had peaks at 1.68 (d, J = 7 Hz, CH_3), 3.58 (s, OCH_3), 7.08 ppm (q, J = 7 Hz, =CH), partly obscured by the phenyl absorptions (7.05–7.40, m). Peaks for the *cis*-crotonate **14** were at 1.96 (d, J = 7 Hz, CH_3), 3.65 (s, OCH_3), 6.14 (q, J = 7 Hz, =CH), 7.05–7.40 ppm (m, phenyl).

Borohydride Reduction of the Crotonates 14 and 15. A solution of 189 mg (5 mmol) of SBH in 20 ml of methanol was prepared under nitrogen at −78°. A solution of 881 mg (5 mmol) of methyl phenyl-*cis*- and -*trans*-crotonates (9:91) in 5 ml of methanol was added, the cooling bath was removed, and the mixture was stirred for 2 hr at room temperature (29°). Work-up with dilute HCl, etc., as described for the acrylate reductions, followed by glpc analysis, indicated that ~20% reduction had occurred. The crude product was redissolved in methanol at 0° under nitrogen, 0.5 g of SBH was added, and the mixture was allowed to warm to 25° over 1.25 hr. The solution was again cooled to 0° and another 0.5-g portion of SBH was added. The mixture was allowed to warm to 25° over 1.5 hr. Work-up with dilute HCl, etc., as before, gave 775 mg of colorless liquid. Glpc indicated that 15–20% unreacted crotonates (cis:trans ratio *ca.* 2:3) remained as well as a major and minor (<5%) product. Samples of these products were collected by glpc. The major product was methyl α-phenylbutyrate (**16**), confirmed by ir, uv, and microanalysis.[33] The minor product was 2-phenylbutanol (nmr).

Competitive Reduction of the Crotonates. A solution of 21 mg (0.12 mmol) of a mixture of methyl α-phenyl-*cis*- and -*trans*-crotonate (41.7% cis, 58.3% trans) in 1 ml of methanol at 28° was treated with a total of 28.7 mg (0.75 mmol) of SBH, added in three portions at 1.25-hr intervals. After addition of a few drops of cold dilute HCl, work-up was carried out as described for the acrylate reductions. Glpc analysis on the crude product indicated that the *trans*-crotonate (**15**) was reduced 2.6 times faster than the cis isomer. Only a trace of 2-phenylbutanol was observed. Reduction of a sample of *cis*-crotonate under similar conditions ruled out the possibility of cis–trans isomerization of starting material.

Registry No.—**2a**, 28042-27-5; **2b**, 50415-59-3; **2c**, 50415-66-2; **2d**, 1865-29-8; **2e**, 50415-68-4; **3a**, 50415-69-5; **3b**, 50415-70-8; **3c**, 50415,71-9; **3d**, 31508-44-8; **3e**, 50415-73-1; **4c**, 50415-74-2; **4g**, 50415-75-3; **4l**, 36854-27-0; **4m**, 23848-96-6; **4n**, 50415-78-6; **4o**, 50415-79-7; **4p**, 42443-25-4; **4q**, 42443-21-0; **4r**, 50415-82-2; **4s**, 42307-43-7; **4t**, 36854-29-2; **4u**, 50415-61-7; **4v**, 50415-62-8; **5l**, 41366-87-4; **5m**, 42443-20-9; **5q**, 31499-32-8; **6m**, 50415-50-4; **6q**, 50415-51-5; **6r**, 50415-52-6; **6t**, 5448-41-9; **6u**, 50415-54-8; **10**, 50404-58-5; **11**, 50415-55-9; **12a**, 50415-56-0; **12b**, 50415-83-3; **14**, 50415-84-4; **15**, 50415-85-5; **16**, 2294-71-5; sodium borohydride, 16940-66-2.

References and Notes

(1) (a) Presented at the Middle Atlantic Regional Meeting of the American Chemical Society, Dover, Del., April 1970. (b) Abstracted in part from the Ph.D. Thesis of G. J. W., Villanova University, May 1970. (c) NASA Fellow, 1966–1969. (d) M.A. degree recipient, Villanova University, August 1973.

(2) A survey of the literature on these reductions is presented in the Ph.D. Thesis of G. J. W. (ref 1b); representative studies are cited in ref 3–11.

(3) M. R. Johnson and B. Rickborn, *J. Org. Chem.*, **35**, 1041 (1970).

(4) W. R. Jackson and A. Zurqiyah, *J. Chem. Soc.*, 5280 (1965).

(5) K. Iqbal and W. R. Jackson, *J. Chem. Soc.*, 616 (1968).

(6) M. S. Brown and H. Rapoport, *J. Org. Chem.*, **28**, 3261 (1963).

(7) J. Knabe, P. Herbort, and N. Ruppenthal, *Arch. Pharm. (Weinheim)*, **299**, 534 (1966).

(8) D. C. Dittmer and M. E. Christy, *J. Amer. Chem. Soc.*, **84**, 399 (1962).

(9) W. E. Truce, H. G. Klein, and R. B. Kruse, *J. Amer. Chem. Soc.*, **83**, 4636 (1961).

(10) H. Schechter, D. E. Ley, and E. B. Roberson, Jr., *J. Amer. Chem. Soc.*, **78**, 4984 (1956).

(11) A. I. Meyers and J. S. Sircar, *J. Org. Chem.*, **32**, 4134 (1967).

(12) J. A. Meschino and C. H. Bond, *J. Org. Chem.*, **28**, 3129 (1963).

(13) S. B. Kadin, *J. Org. Chem.*, **31**, 620 (1966).

(14) J. A. Marshall and R. D. Carroll, *J. Org. Chem.*, **30**, 2748 (1965).

(15) D. Cabaret and Z. Welvart, *C. R. Acad. Sci., Ser. C*, **274**, 1200 (1972).

(16) Owing to solvolysis of sodium borohydride by methanol [H. C. Brown and K. Ichikawa, *J. Amer. Chem. Soc.*, **83**, 4372 (1961)], reductions which proceeded very slowly would not have been detected.

(17) Brown and Rapoport (ref 6) have observed partial reduction of double bonds in certain β-aryl acrylates under forcing conditions (tenfold excess of sodium borohydride in refluxing methanol).

(18) During the course of this work, Kadin (ref 13) reported the analogous reduction of ethyl α-phenylacrylate (**1e**) with sodium borohydride in ethanol.

(19) Jackson and Rickborn and coworkers (ref 3–5) have proposed similar intermediates for borohydride reductions of α,β-unsaturated ketones.

(20) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, Elmsford, N. Y., 1969, p 274. The proton nmr data are also compatible with the alternate 1,2-addition product, $[PhCH_2C(PhCO_2CH_3)]_4B^-Na^+$; however, this structure would appear to be excluded on the basis of the severe steric hindrance which would result during the third and fourth hydride transfers required for its formation.

(21) Reference 20, p 372.

(22) Substituent constants were obtained from the tables of C. D. Ritchie and W. F. Sager, *Progr. Phys. Org. Chem.*, **2**, 323 (1964).

(23) H. C. Brown, O. H. Wheeler, and K. Ichkawa, *Tetrahedron*, **1**, 214 (1957).

(24) H. H. Jaffe, *Chem. Rev.*, **53**, 191 (1953).

(25) *Cf.* T. I. Crowell, G. C. Helsley, R. E. Lutz, and W. L. Scott, *J. Amer. Chem. Soc.*, **85**, 443 (1963), who observed that base-catalyzed addition of methanol to a series of *trans*-*p,p'*-disubstituted dibenzoylethylenes gave a Hammett plot linear in $\sigma_p + \sigma_{p'}$ (ρ = 1.00).

(26) The ρ value for Michael addition of barbiturate ion to β-nitrostyrene is 0.74: M. J. Kamlet and D. J. Glover, *J. Amer. Chem. Soc.*, **78**, 4556 (1956).

(27) H. E. Zimmerman and L. Ahramjian, *J. Amer. Chem. Soc.*, **81**, 2086 (1959).

(28) R. G. Pearson and R. L. Dillon, *J. Amer. Chem. Soc.*, **75**, 2439 (1953).

(29) Glpc was carried out on a Hewlett-Packard F & M Model 700 instrument equipped with 12 ft × 0.125 or 0.25 in. stainless steel columns packed with 15% SE-30 on acid- and base-washed, silanized Chromosorb W. Analytical glpc for the crotonate reduction was done on a Wilkins Instrument Co. Hi Fi chromatograph equipped with a 12 ft × 0.125 in. TCEP column. Nmr spectra were obtained with a Varian A-60 spectrometer using TMS as the internal reference. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn. Melting points are uncorrected.

(30) W. D. Davis, L. S. Mason, and G. Stegeman, *J. Amer. Chem. Soc.*, **71**, 2775 (1949).

(31) J. H. Schauble, E. H. Freed, and M. D. Swerdloff, *J. Org. Chem.*, **36**, 1302 (1971).

(32) J. Dutta and R. N. Biswas, *J. Indian Chem. Soc.*, **40**, 629 (1963).

(33) *Microanalysis (C, H, N, or halogen) for* **2b**, **2d**, **2e**, **3a–e**, **4l–v**, **5l**, **5m**, **5q**, **6l–v**, and **16** were all within ±0.25% of the calculated values. Repetitive analyses for **2c** were erratic, apparently owing to incomplete combustion.

(34) R. Ketcham and D. Jambotkar, *J. Org. Chem.*, **28**, 1034 (1963).

(35) J. F. Codington and E. Mosettig, *J. Org. Chem.*, **17**, 1027 (1952).

(36) P. Schmid, *U. S. At. Energy Comm.*, UCRL-8883 (1959); *Chem. Abstr.*, **54**, 7647 (1960).

(37) R. E. Buckles, M. P. Bellis, and W. D. Coder, Jr., *J. Amer. Chem. Soc.*, **73**, 4972 (1951).

(38) R. E. Buckles and K. Bremer in "Organic Syntheses," Collect. Vol. IV, N. Rabjohn, Ed., Wiley, New York, N. Y., 1963, p 777.

(39) T. J. DeBoer and H. J. Backer in "Organic Syntheses," Collect. Vol. IV, N. Rabjohn, Ed., Wiley, New York, N. Y., 1963, p 250.

(40) G. Drefahl, G. Heublein, and G. Tetzlaff, *J. Prakt. Chem.*, **23**, 318 (1964).

(41) P. Pfeiffer, I. Engelhardt, and W. Alfuss, *Justus Liebigs Ann. Chem.*, **467**, 181 (1928).

The Addition of Unsaturated Carbenes to Cyclic Dienes. Intramolecular Trapping of Trimethylenemethane Diradicals[1]

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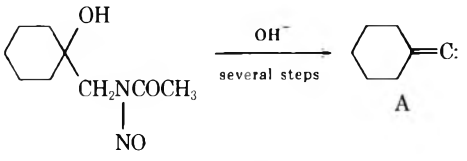
Received August 16, 1973

The addition of cyclohexylidenecarbene (A) generated *in situ* by alkaline treatment of 1-(*N*-nitrosoacetylaminomethyl)cyclohexanol (1) to cyclopentadiene (2), 1,4-cyclohexadiene (3), and bicyclo[2.2.1]heptadiene (4) yields 4-cyclohexylidenebicyclo[3.1.0]hex-2-ene (5), 7-cyclohexylidenebicyclo[4.1.0]hept-3-ene (8), and 3-cyclohexylidenetricyclo[3.2.1.$0^{2,4}$]oct-6-ene (9), respectively, in 65–76% yields. On heating at 150° 9 rearranges to 3-cyclohexylidenetetracyclo[3.3.0.$0^{2,8}$.$0^{4,6}$]octane (10). Oxidation of 10 yields tetracyclo[3.3.0.$0^{2,8}$.$0^{4,6}$]octan-3-one (16).

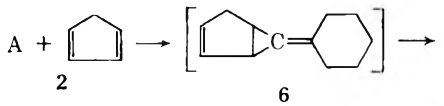
The tendency of methylenecyclopropanes to afford a trimethylenemethane diradical on heating represents a phenomenon long of interest.[3] Methods of preparing the requisite precursors, methylenecyclopropanes, have been summarized.[4] In addition to the methods mentioned, the addition of unsaturated carbenes, generated from nitrosoxazolidones, to olefins provides another route.[5] We undertook the work herein described to see whether an unsaturated carbene would react in a 1,2 (or other) manner with cyclic dienes and to observe any thermal rearrangements of the addition products.

In order to generate an unsaturated carbene, A, we chose the procedure in which a solution of the diene and 1-(*N*-nitrosoacetylaminoethyl)cyclohexanol (1) containing a catalytic amount of Aliquat 336[6] is treated with aqueous sodium hydroxide.[7] The dienes were cyclopentadiene (2), 1,4-cyclohexadiene (3), and bicyclo[2.2.1]heptadiene (4).

In the reaction involving 2 (eq 1) there was obtained a 76% yield of 4-cyclohexylidenebicyclo[3.1.0]hex-2-ene (5),[8] a compound which cannot be initially formed by a 1,2 or a 1,4 addition to the diene. We believe 5 is formed by a 1,2 addition to yield 6-cyclohexylidenebicyclo[3.1.0]hex-2-ene (6), which is thermally unstable and rearranges readily to 5. In our first experiment no attempt was made to keep the temperature down during distillation of the product. On repetition involving a work-up in which the temperature was never higher than about 30°, the product was still entirely 5. Thus 6 rearranges readily to 5. The driving force for this trimethylenemethane diradical type rearrangement undoubtedly stems both from the steric strain in 6 and from the formation of the conjugated diene system in 5. We see no route by which the reactants can go directly to 5.[9]



1 A



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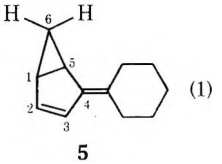
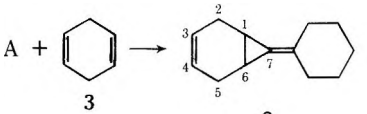


(1)

5

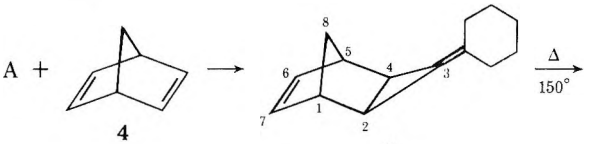
In the reaction involving 3 (eq 2) there was obtained a 65% yield of 7-cyclohexylidenebicyclo[4.1.0]hept-3-ene (8),[8] a compound which proved stable thermally at temperatures as high as 185°. At higher temperatures a complex mixture of hydrocarbons which was not studied in detail resulted.[10] If a trimethylenemethane diradical is formed, the olefinic bond present is not well enough oriented for homoallylic participation to allow for rearrangement.



(2)

3 8

In the reaction involving 4 (eq 3) there was obtained a 69% yield of 3-cyclohexylidenetricyclo[3.2.1.$0^{2,4}$]oct-6-ene (9).[8] On heating to 150° for 20 min rearrangement of 8 to 3-cyclohexylidenetetracyclo[3.3.0.$0^{2,8}$.$0^{4,6}$]octane (10) resulted. No change in 10 resulted on longer heating at 190–200°.



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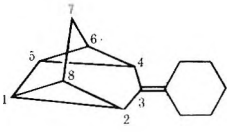
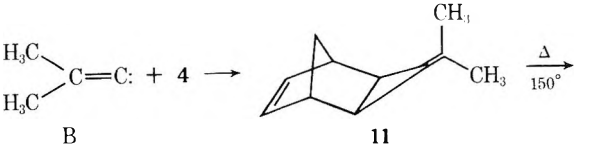


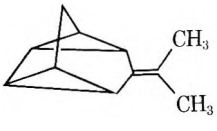
(3)

10

While our work was in progress the synthesis of 3-isopropylidenetricyclo[3.2.1.$0^{2,4}$]oct-6-ene (11) in 12% yield by the addition of isopropylidenecarbene (B) to 4 as well as the flash thermolysis of 11 at 400° to give 3-isopropylidenetetracyclo[3.3.0.$0^{2,8}$.$0^{4,6}$]octane (12) was reported.[11] We had also prepared 11 in 35% yield (not maximized) and shown that heating at 150° for 20 min converted 11 smoothly to 12 (eq 4).



B 11



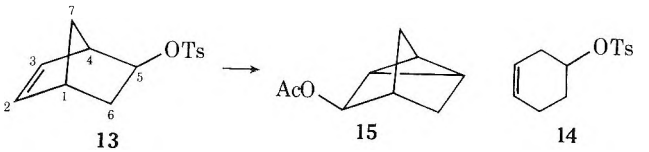
(4)

12

We believe the rearrangements of 9 to 10 and of 11 to 12 occur by trimethylenemethane diradical paths as the con-

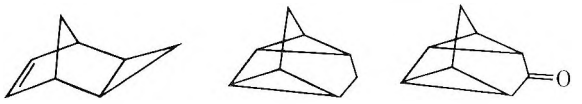
certed cycloaddition alternative would involve a forbidden $\sigma 2_s + \pi 2_s$ process.[12]

The facile participation of the 6,7-double bond of **9** in the trimethylenemethane diradical type rearrangement of **9** to **10** as contrasted to the lack of participation of the 3,4-double bond of **8** may be parallel to the acetolysis of *exo*-bicyclo[2.2.1]hept-2-en-5-yl tosylate (**13**), which occurs considerably more rapidly[13] than the acetolysis of cyclohexen-4-yl tosylate[14] (**14**). That the double bond in **14** does not assist in the acetolysis is supported by the fact that the corresponding brosylate and cyclohexyl brosylate acetolyze at about the same rate.[15] Furthermore the main product obtained from acetolysis of **13** is *exo*-7-acetoxytricyclo[2.2.1.$0^{2,6}$]heptane (**15**), whereas only acetoxycyclohexenes and cyclohexadienes are obtained from **14**.[15,16] Thus, a consideration of the kinetics of solvolysis and the structure of the products obtained may be used as a criterion to determine if participation of an isolated double bond with a trimethylenemethane diradical will occur in structures comparable to **6**, **9**, and **11**.



13 **15** **14**

Our results with the rearrangement of **9** to **10** may be compared with similar studies of intramolecular trapping of 1,3 diradicals[17] as pointed out by a referee. Interestingly, the rearrangement of tricyclo[3.2.1.$0^{2,4}$]oct-6-ene (**16**) to **17** takes place only on photolysis and not on pyrolysis,[17b] in contrast to the thermal rearrangement of **9** to **10**. On pyrolysis **16** gave three products,[17b] none of which was **17**.



16 **17** **18**

On oxidation **10** yields tetracyclo[3.3.0.$0^{2,8}$.$0^{4,6}$]octan-3-one (**18**), a ketone previously prepared[18] by an entirely different route.

In conclusion we would like to emphasize that by the reaction of cyclic dienes with unsaturated carbenes of type A products in the polycyclic hydrocarbon area may readily be synthesized in one step. Furthermore, since such methylenecyclopropyl structural units undergo thermal homolytic cleavage to trimethylenemethane diradicals, new complex polycyclic hydrocarbons may easily be obtained. The combination of these two steps allows for the elaboration of molecules which otherwise would require multiple step synthesis. Many interesting products may be predicted by proper choice of dienic and polyenic systems.

Experimental Section

Product Analysis. Glpc analyses were performed on a Wilkens Aerograph Model A-700; column (10 ft × ¼ in.): 30% SE-30, 45/60 a/w Chromosorb A, helium flow 25 ml/min. Proton magnetic resonance (pmr) spectra were recorded on an A-60 nmr spectrometer, Varian Associates, Palo Alto, Calif. All samples were dissolved in carbon tetrachloride (CCl_4); tetramethylsilane (TMS) was used as an internal standard; chemical shifts are reported in δ values (TMS = 0.0). Melting and boiling points are uncorrected. Melting points were taken with a Thomas-Hoover melting point apparatus. All boiling points are approximate since the material was rapidly distilled in order to avoid unwanted thermal rearrangements.

The *in situ* generation of all alkylidenecarbenes described here follows a general procedure which begins with the nitrosation of 1-(acetylaminomethyl) alcohols.

1-(*N*-Nitrosoacetylaminomethyl)cyclohexanol (1). A solution prepared by bubbling gaseous nitrosyl chloride into 100 ml of cooled glacial acetic acid until 13.2 g (0.2 mol) had been absorbed was added dropwise during 45–60 min to a solution of 17.1 g (0.1 mol) of 1-(*N*-acetylaminomethyl)cyclohexanol,[7] 20 g of freshly fused potassium acetate, and 2 g of phosphorus pentoxide in 100 ml of glacial acetic acid cooled to part crystallization. After 2 hr the mixture was allowed to warm to room temperature and was then poured onto ice and methylene chloride. The organic layer was separated and washed thrice with ice–water. The combined aqueous fractions were neutralized with sodium bicarbonate and back-extracted with methylene chloride. The organic portions were combined and washed with cold saturated $NaHCO_3$ solution, cold saturated NaCl solution, and filtered through a cone of anhydrous Na_2SO_4 into a flask immersed in an ice bath. The methylene chloride was removed under reduced pressure at or below room temperature to afford 19 g (95%) of **1** as a yellow oil which had no NH absorption in the ir spectrum and a strong band at 5.75 μ. These nitroso compounds should be used immediately or stored for up to 1 week in methylene chloride solution in the freezing compartment of a refrigerator.

Generation of Cyclohexylidene Carbene A; Isolation of Addition Products. In a typical reaction a stirred solution held at −10 to −5° of **1** prepared from 4.3 g (25 mmol) of 1-(*N*-acetylaminomethyl)cyclohexanol and 1 g of Aliquat 336[6] in 50 ml of olefin was treated dropwise over 30 min with a solution of 1.2 g (30 mmol) of sodium hydroxide in 3 ml of water. The theoretical volume of nitrogen was collected over water during the addition of the base. The reaction mixture was diluted with ether and shaken with saturated NaCl. The organic layer was filtered through a cone of anhydrous Na_2SO_4, and the solvent was fractionally distilled at atmospheric pressure in a small total-reflux partial-takeoff column in order to recover excess olefin. The residue was chromatographed through 50 g of Woelm neutral alumina (column 250 × 23 mm) with 250 ml of pentane to remove Aliquat 336. The solvent was then fractionally distilled at atmospheric pressure, and the residue was distilled at reduced pressure to afford the carbene adduct. Yields are based on isolated material obtained after distillation and calculated from the amount of 1-(acetylaminomethyl) alcohol used.

When addition products from alkylidene carbenes and valuable olefins are required, moderate yields (40–50%) may be obtained by using only 2 equivalents of olefin in pentane as the solvent. Furthermore since all solvent removal processes involve fractional distillation, the excess olefin may be recovered.

4-Cyclohexylidenebicyclo[3.1.0]hex-2-ene (5). The above procedure[19] [from 50 mmol of 1-(*N*-acetylaminomethyl)cyclohexanol] afforded 6.1 g (76%) of **5**; bp 125–130° (25 mm); uv max (cyclohexane) 260 mμ (ϵ 24,500) [lit.[20] uv max (ethanol) 257 mμ (ϵ 12,780)]; pmr 6.00 (m, 2, vinyl), 2.22 and 2.05 (m, 6, allylic), 1.58 (m, 6, aliphatic), 0.82 (triplet of doublets, 1, exo cyclopropyl), and 0.15 (q, 1, endo cyclopropyl); mass spectrum *m/e* 160.

Anal.[21] Calcd for $C_{12}H_{16}$: C, 90.0; H, 10.0. Found: C, 90.3; H, 10.0.

The above procedure was repeated except that the cyclopentadiene was diluted with an equal volume of pentane (to reduce dimerization) and the reaction mixture was never warmed above 30°. The solvents were evaporated at reduced pressure at or below room temperature. The final product (5.2 g, 65%), which was not distilled (pmr analysis showed no dicyclopentadiene), was identical with the **5** obtained above. The lower yield is due to the loss incurred when the fractional distillation of solvent and excess cyclopentadiene was omitted. Since the primary adduct is apparently not stable at room temperature or somewhat lower we made no further efforts to elucidate its structure.

The structure of **5** was elucidated[22] by recording the pmr spectrum on an HA 100 nmr in frequency sweep mode, locked internally on chloroform. Since irradiation at 0.82 and 0.15 had no effect on the vinyl hydrogens (6.00), structure **6** is eliminated. Furthermore, the cyclopropyl hydrogens of **6** are allylic and are not expected to display such high-field signals as those observed. Structure **7** (in ref 9) is eliminated by the lack of symmetry observed in the pmr and by the fact that it has no cyclopropyl hydrogens.

7-Cyclohexylidenebicyclo[4.1.0]hept-3-ene (8). The above general procedure was used (for a 25-mmol run) to afford 2.8 g (65%) of **8**: bp 85–95° (1 mm); pmr 5.38 (m, 2, vinyl), 2.30 and 2.19 (m, 8, allylic), 1.50 and 1.38 (m, 8, aliphatic and allylic cyclopropyl); mass spectrum *m/e* 174.

Anal. Calcd for $C_{13}H_{18}$: C, 89.7; H, 10.4. Found: C, 89.7; H, 10.3.

3-Cyclohexylidenetricyclo[3.2.1.0^{2,4}]oct-6-ene (9). The above general procedure was used (for a 25-mmol run) to afford 3.2 g (69%) of **9**: bp 75–80° (<1 mm); pmr 6.20 (t, 2, H_6 and H_7, see numbering in **9**, eq 3), 2.83 (m, 2, H_1 and H_5), 2.12 (m, 4, allylic on the cyclohexylidene fragment), 1.51 (m, 6, aliphatic on the cyclohexylidene fragment), 1.38 (d, 2, H_2 and H_4), and 0.93 (m, 2, H_8). Further structure proof was based on the product obtained from the thermal rearrangement and subsequent oxidation to LeBel and Liesemer's ketone.[18]

3-Isopropylidenetricyclo[3.2.1.0^{2,4}]oct-6-ene (11) was prepared according to the general procedure (50-mmol run) except 5,5-dimethyl-*N*-nitrosooxazolidone[5a] was used as the isopropylidenecarbene precursor to afford 2.90 g (35%) of **11**: bp 35° (<1 mm); pmr 6.28 (t, 2, H_6 and H_7), 2.88 (m, 2, H_1 and H_5), 1.75 (t, 6, allylic methyls), 1.40 (broad singlet, 2, H_2 and H_4), 0.98–0.88 (m, 2, H_8); these data agree with those reported.[11]

Thermal Treatment of 8. Heating **8** neat for 10 min or 1 hr below 180° had no effect on the pmr spectrum. When **8** was heated at 195°, it quickly darkened. After 10 min the vinyl and allylic signals in the pmr spectrum changed, the vinyls moved to δ 5.95–5.80 and the allylic signals became very broad. Glpc indicated that a good portion of the material was no longer volatile and the volatile material contained several components.

3-Cyclohexylidenetetracyclo[3.3.0.0^{2,8}.0^{4,6}]octane (10). A sample of **9** was heated for 20 min at 150° to afford **10** (quantitative by glpc): bp 110–115° (1 mm); pmr 2.3 (m, 4), series of peaks between 2.0 and 1.2 (14 H), no signals below 2.4; mass spectrum *m/e* 186.

Anal. Calcd for $C_{14}H_{18}$: C, 90.3; H, 9.7. Found: C, 90.6; H, 9.5.

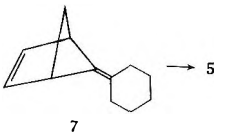
Tetracyclo[3.3.0.0^{2,8}.0^{4,6}]octan-3-one (18). To a well-stirred mixture of 186 mg (1 mmol) of **10** and 6 drops of Aliquat-336[6] in 2 ml of benzene and 4 ml of water was added 634 mg (4 mmol) of potassium permanganate. The suspension was stirred for 2 hr at room temperature, excess sodium sulfite was added, and the suspension was diluted with ether and vacuum filtered through Celite (analytical filter aid) to remove manganese dioxide. The organic layer was washed with water, saturated sodium chloride solution, and filtered through a cone of anhydrous sodium sulfate. Fractional distillation of the solvents afforded an oil which contained 72 mg of **18** (60%) and cyclohexanone. The tetracyclic ketone was shown to be identical with an authentic sample provided by Dr. LeBel: mp 68–70°; mmp 67–69°; ir (CCl_4) 1730 cm^{-1} (C=O); mass spectrum *m/e* 120 [lit. mp 69–71°; ir (CCl_4) 1730 cm^{-1}]; both ketones had identical fragmentation patterns in the mass spectrum.

3-Isopropylidenetetracyclo[3.3.0.0^{2,8}.0^{4,6}]octane (12). A sample of **11** was heated for 20 min at 150° to afford **12** (quantitative by glpc): pmr 1.70 (s, 6, allylic methyls), series of multiplets from 2.09 to 1.35 (8 H), no absorption below δ 2.10; these data compare with those in the literature;[11] mass spectrum *m/e* 146; the compound decolorizes Br_2 in CCl_4.

Registry No.—**1**, 37150-64-4; **2**, 542-92-7; **3**, 628-41-1; **4**, 121-46-0; **5**, 50277-68-4; **8**, 50277-69-5; **9**, 50277-70-8; **10**, 50277-71-9; **11**, 50277-72-0; **12**, 42038-54-0; **18**, 873-36-9; A, 20693-98-5; B, 26265-75-8; 1-(*N*-acetylaminomethyl)cyclohexanol, 37150-63-3.

References and Notes

(1) This work was supported by Grant No. 12445 from the National Science Foundation.
(2) This work formed part of the Ph.D. Thesis of M. C. V. Z., The Ohio State University, 1973.
(3) For reviews, see F. Weiss, *Quart. Rev., Chem. Soc.*, **24**, 278 (1970), and P. Dowd, *Accounts Chem. Res.*, **5**, 242 (1972).
(4) W. Rahman and H. G. Kuivila, *J. Org. Chem.*, **31**, 772 (1966).
(5) (a) M. S. Newman and A. O. M. Okorodudu, *J. Amer. Chem. Soc.*, **90**, 4189 (1968); (b) *J. Org. Chem.*, **34**, 1220 (1969).
(6) Aliquat 336 is methyltricaprylammonium chloride. Our procedure is based on the phase transfer principle of C. M. Starks, *J. Amer. Chem. Soc.*, **93**, 195 (1971).
(7) M. S. Newman and Z. ud Din, *J. Org. Chem.*, **38**, 547 (1973).
(8) The proof of structure is given in the Experimental Section.
(9) An alternate, less likely route involves the 1,4 addition of A to **2** to yield 5-cyclohexylidenebicyclo[2.1.1]hex-2-ene (7), which could undergo a suprafacial [1,3] sigmatropic rearrangement to give **5**.



7

Such a rearrangement has shown to occur in the parent case at about 150° by F. T. Bond and L. Scerbo, *Tetrahedron Lett.*, 2789 (1968); see also W. R. Roth and A. Friedrich, *ibid.*, 2607 (1969), and S. Masamune, S. Takada, N. Nakatsuka, R. Vukov, and E. N. Cain, *J. Amer. Chem. Soc.*, **91**, 4322 (1969), for other examples.
(10) For the formation of dimers from a trimethylenemethane diradical, see J. A. Berson, R. J. Bushby, J. M. McBride, and M. Tremelling, *J. Amer. Chem. Soc.*, **93**, 1544 (1971).
(11) R. Bloch, F. Leyendecker, and N. Toshima, *Tetrahedron Lett.*, 1025 (1973). The exo structure for **11** was established by spin-decoupling experiments. We assume **9** to be exo because of the similarity of the nmr data.
(12) R. B. Woodward and R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **8**, 781 (1969).
(13) The calculated value at 25° is given by S. Winstein and M. Shatavsky, *J. Amer. Chem. Soc.*, **78**, 592 (1956).
(14) M. Hanack and W. Keberle, *Chem. Ber.*, **96**, 2937 (1963).
(15) G. LeNy, *C. R. Acad. Sci.*, **251**, 1526 (1960).
(16) R. L. Thornton, Ph.D. Thesis, Massachusetts Institute of Technology, 1961.
(17) (a) E. Druckery, M. Arguelles, and H. Prinzbach, *Chimia*, **20**, 432 (1966); (b) H. Prinzbach and H. D. Martin, *Helv. Chim. Acta*, **51**, 438 (1968); (c) L. A. Paquette and L. M. Leichter, *J. Amer. Chem. Soc.*, **93**, 5128 (1971).
(18) N. A. LeBel and R. N. Liesemer, *J. Amer. Chem. Soc.*, **87**, 4301 (1965). We thank Dr. LeBel for sending us an authentic sample which proved identical with our ketone, **18**.
(19) The dicyclopentadiene which formed during the course of the reaction and work-up was removed by heating the residue obtained after chromatography at 180° and fractionally distilling the cyclopentadiene formed.
(20) M. Rey, U. A. Huker, and A. S. Driedling, *Tetrahedron Lett.*, 3583 (1968). The difference in the exo and endo protons was pointed out.
(21) Chemical analyses were performed by The M.H.W. Laboratories, Garden City, Mich. 48135.
(22) We would like to thank Mr. Michael Geckle for performing the spin-decoupling experiments and discussing the results.

Cycloadditions of Pentamethyleneketene. Spiro[5.3]nonanes

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Received October 2, 1973

Cycloaddition reactions of pentamethyleneketene to cyclopentadiene, dihydropyran, tetramethylallene, diisopropylcarbodiimide, *N-tert*-butylbenzylimine, and chloral have been investigated as routes to spiro compounds. Pentamethyleneketene is formed *in situ* from the triethylamine dehydrochlorination of cyclohexanecarboxyl chloride and the zinc dehalogenation of α-bromocyclohexanecarboxyl chloride. Dimerization is a serious competing reaction and reactive cycloaddition partners are necessary to successfully compete for the ketene.

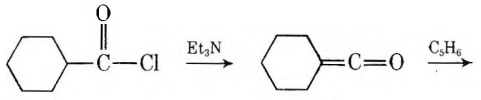
The preparation and dimerization of pentamethyleneketene from cyclohexanecarboxyl chloride was reported about 20 years ago.[1] The preparation of this ketene by cracking cyclohexanecarboxylic acid anhydride and prop-

erties of the ketene have recently been described.[2] There have been several recent reports on the dimerization and trimerization of this ketene and the chemistry of these oligomers.[3-5] However, cycloaddition reactions of the ketene have not received much attention. Wasserman and coworkers have just recently described the cycloaddition of pentamethyleneketene and ethoxyacetylene to yield a thermally unstable cycloadduct.[6] The cycloaddition of this ketene and sulfur dioxide has also been recently reported.[7]

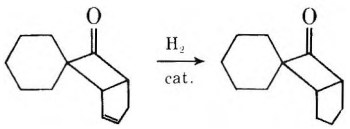
Pentamethyleneketene (I) is quite susceptible to dimerization; *e.g.*, the reaction of cyclohexanecarboxyl chloride with triethylamine produces a good yield of the dimer, dispiro[5.1.5.1]tetradecane-7,14-dione. Therefore, it seemed desirable to effect *in situ* cycloadditions with reactive unsaturated compounds to successfully compete with the dimerization process. This is also the case with β,γ-unsaturated pentamethyleneketene.[8]

We now wish to report on some *in situ* cycloaddition reactions of pentamethyleneketene to yield spiro[5.3]nonanes.

The dehydrochlorination of cyclohexanecarboxyl chloride with triethylamine in the presence of cyclopentadiene resulted in a 65% yield of the spiro[5.3]nonane (II) accompanied by some ketene dimer. The optimum conditions appear to be the dropwise addition of the acid halide to a refluxing solution of triethylamine and cyclopentadiene in benzene and continued refluxing for about 20 hr. A reaction time of this length is necessary because the ketene is slowly formed from the acid halide and amine under these



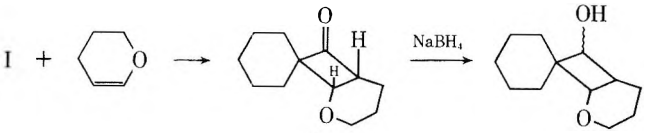
I



II III

conditions. The use of chloroform as a solvent reduces the reaction time to about 8 hr. Complete separation of this cycloadduct from the dimer was not achieved. Consequently, hydrogenation to the corresponding saturated ketone, III, resulted in a compound which could be purified.

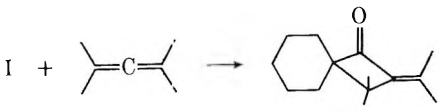
The cycloaddition of pentamethyleneketene with dihydropyran occurred readily and the cycloadduct was isolated in 67% yield (IV). This adduct was also difficult to separate from the ketene dimer and was reduced with sodium borohydride to the corresponding alcohol V, which was easily separated from the ketene dimer and thus com-



IV V

pletely characterized. Although two regioisomers of this cycloadduct are possible, only one was detected. The presence of the bridgehead protons in the nmr at δ 4.1 and 3.3 dictates that the isomer indicated is the one produced.[9] This is quite consistent with numerous other ketene cycloadditions where some charge separation in the transition state is indicated.

Tetramethylallene cycloadded to pentamethyleneketene to yield an α,β-unsaturated spiro[5.3]nonane (VI) in 60% yield which was easily purified by recrystallization. Only one regioisomer was detected and this was the expected

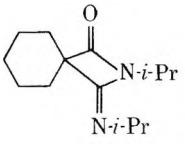


VI

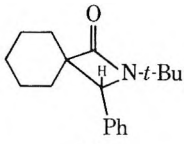
α,β-unsaturated adduct, which is the only regioisomer that has been detected in these cycloadditions.[10]

We also investigated the cycloaddition of ethoxyacetylene with pentamethyleneketene and found that while the cycloaddition occurred the cycloadduct was thermally unstable (decomposition occurred upon vacuum distillation) as reported by Wasserman and coworkers.[6]

The *in situ* cycloaddition of pentamethyleneketene with diisopropylcarbodiimide and *N-tert*-butylbenzylimine was also effected. These reactive imino compounds yielded the expected spiroimino-β-lactam in 51% yield (VII) and the spiro-β-lactam in 48% yield (VIII).

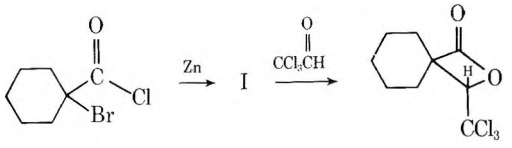


VII



VIII

The dehydrochlorination of cyclohexanecarboxyl chloride in the presence of chloral did not produce the expected spiro 2-oxetanone. Triethylamine readily reacts with chloral, which complicates this *in situ* cycloaddition, and numerous attempts with simultaneous and various orders of additions were unsuccessful. However, the zinc dehalogenation of α-bromocyclohexanecarboxyl chloride in the presence of chloral produced a 45% yield of the spiro-2-oxetanone (IX). This 2-oxetanone was quite resistant to decarboxylation, as are other 4-trichloromethyl-2-oxetanones.[11] This method of generating pentamethyleneketene offers the advantage of not having a reactant which reacts with chloral, and also the by-product in this reaction, zinc halide etherate, activates the carbonyl compound for cycloaddition. The ketene dimer is also produced by this method of generation.



IX

The attempted cycloaddition of cyclohexene with pentamethyleneketene by both the dehydrohalogenation and dehalogenation methods were unsuccessful. It should be emphasized that all the successful cycloadditions described above involve activated unsaturated compounds. Pentamethyleneketene undergoes cycloaddition with activated unsaturated compounds readily but the reaction is always accompanied with ketene dimer. Consequently, if unactivated olefins such as cyclohexene are employed, dimerization occurs completely at the expense of cycloaddition with the olefin. Other unsaturated compounds which were investigated with little or no success included phenylacetylene, 5-methylene-2-norbornene, ethyl thioisocyanate, quinone, *p*-chlorobenzaldehyde, and *N*-phenylbenzalaniline.

In summary, the generation of pentamethyleneketene by the dehydrohalogenation and/or dehalogenation method in the presence of reactive unsaturated compounds gives a good yield of the [2 + 2] cycloaddition product, which is a spiro[5.3]nonane. All cycloadditions are accompanied by ketene dimer. Unactivated or less reactive cycloaddition partners do not successfully compete with the dimerization process.

Experimental Section

Proton nmr spectra were recorded on Jeolco Minimar 60-MHz and Jeolco PS-100 nmr spectrometers employing tetramethylsilane as an internal standard and CCl_4 as the solvent unless otherwise noted. Solvents and triethylamine were distilled from sodium and stored over Linde type 4-A molecular sieve. Tetramethylallene was obtained by the $AlCl_3$-catalyzed rearrangement of the tetramethylcyclobutadiene dimer of dimethylketene followed by pyrolysis over a hot wire. *N*-*tert*-Butylbenzylimine was prepared from benzaldehyde and *tert*-butylamine according to standard procedure.

General Procedure for Preparation of Pentamethyleneketene by the Dehydrohalogenation Method. A solution of 0.1 mol of cyclohexanecarboxyl chloride in 50 ml of dry benzene was added dropwise to a refluxing solution of 0.15 mol of triethylamine and 0.2-0.3 mol of an unsaturated compound in 150 ml of dry benzene. After completion of the addition, refluxing was continued for about 20 hr. The amine salt was removed by filtration and washed with benzene. Concentration afforded the crude cycloadduct. Vacuum distillation or recrystallization resulted in purification of the pentamethyleneketene adduct.

Pentamethyleneketene Cyclopentadiene Adduct (II). This adduct was obtained in 65% yield at 67-69° (0.1 mm): ir 1767 (C=O), and 1601 cm^{-1} (C=C); nmr δ 1.50 (m, 10 H), 2.42 (m, 2 H), 3.15 (m, 1 H), 3.75 (two t or three d, 1 H), and 5.70 (m, 2 H).

After two distillations, this adduct contained a small amount of the ketene dimer as an impurity. Consequently, the cycloadduct was hydrogenated in ethanol under 50 psi of hydrgoen employing platinum oxide as a catalyst. An 80% yield of the saturated spiro ketone (III) resulted at 57-58° (0.08 mm): nmr δ 1.7 (m, 16 H), 2.52 (two t or three d, 1 H), and 3.65 (two t or three d, 1 H).

Anal. Calcd for $C_{12}H_{18}O$: C, 80.89; H, 10.11. Found: C, 80.63; H, 9.75.

Pentamethyleneketene Dihydropyran Cycloadduct (IV). This cycloadduct was produced in 67% yield at 90-92° (0.2 mm): ir 1767 cm^{-1} (C=O); nmr δ 1.60 (m, 14 H), 3.30 (two d or three t, 2 H), 3.80 (two t or three d, 1 H), and 4.10 (d, 1 H).

This compound was also contaminated with the ketene dimer and was reduced with sodium borohydride in ethanol. The corresponding alcohol (V) was recrystallized from ether: mp 53-55°; ir 3450 cm^{-1} (OH); nmr δ 1.42 (m, 14 H), 2.1-2.6 (s, H of OH), 2.43 (m, 1 H), 3.30 (m, 1 H), and 3.80 (m, 3 H).

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.46; H, 10.21. Found: C, 73.28; H, 9.99.

Pentamethyleneketene Tetramethylallene Cycloadduct (VI). A 60% yield of a crystalline solid which was recrystallized from ethanol was obtained: mp 47-48°; ir 1725 (C=O) and 1639 cm^{-1} (C=C); nmr δ 1.28 (s, 6 H), 1.84 (s, 3 H), 2.08 (s, 3 H), and 1.25-2.0 (m, 10 H); the three singlets are out of the multiplet at 1.25-2.0. The chemical shift values for the unequivalent methyl protons attached to the vinyl linkage and the equivalent methyl protons on the β carbon are in excellent agreement with other tetramethylallene ketene cycloadducts.[10,11]

Pentamethyleneketene Diisopropylcarbodiimide Cycloadduct (VII). This adduct was prepared in 51% yield and was recrystallized from ether: mp 83-85°; ir 1818 (C=O) and 1686 cm^{-1} (C=N); nmr δ 1.20 (d, 6 H), 1.48 (d, 6 H), 1.94 (m, 10 H), and 3.80 (m, 2 H).

Anal. Calcd for $C_{14}H_{24}ON_2$: C, 71.19; H, 10.18; N, 11.86. Found: C, 71.31; H, 10.56; N, 11.36.

Pentamethyleneketene *N*-*tert*-Butylbenzylimine Adduct (VIII). The cycloadduct was obtained in 48% yield and was recrystallized from ether: mp 105-106°; ir 1748 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.30 (s)and 1.60 (m) (accounts for 19 H), 4.35 (s, 1 H), and 7.30 (s, 5 H).

Anal. Calcd for $C_{18}H_{25}NO$: C, 79.70; H, 9.22; N, 5.16. Found: C, 80.00; H, 9.03; N, 5.08.

Pentamethyleneketene Chloral Adduct (IX). To a mixture of 0.3 mol of activated zinc and 0.2 mol of freshly distilled chloral in 100 ml of dry ether containing a trace of $AlCl_3$ with vigorous stirring was added dropwise a solution of 0.1 mol of α-bromocyclohexanecarboxyl chloride in 15 ml of ether. After the addition was complete, the reaction mixture was refluxed for 24 hr. The unreacted zinc was removed by filtration and the filtrate was concentrated on a rotatory evaporator. The residue was extracted with three 50-ml portions of CCl_4 to extract the cycloadduct from the zinc halide etherate. The combined extracts were concentrated and distilled under vacuum. The condensate solidified and was recrystallized from ethanol: mp 77-78°; ir 1837 cm^{-1} (C=O); nmr δ 1.80 (m, 10 H) and 4.57 (s, 1 H).

Anal. Calcd for $C_9H_{11}Cl_3O_2$: C, 41.94; H, 4.27. Found: C, 41.78; H, 3.93.

Acknowledgments. The authors wish to express appreciation to the Robert A. Welch Foundation and the North Texas State University Faculty Research Fund for support of this investigation.

Registry No.—I, 22589-13-5; II, 50515-89-4; III, 50515-91-8; IV, 50515-90-7; V, 50515-92-9; VI, 50515-93-0; VII, 50515-94-1; VIII, 50515-95-2; IX, 50515-96-3.

References and Notes

(1) C. M. Hill and M. E. Hill, *J. Amer. Chem. Soc.*, **75**, 2765 (1953).
(2) G. Sioli, R. Mattone, L. Giulfre, R. Trotta and E. Tempesti, *Chim. Ind. (Milan)*, **53**, 133 (1971).
(3) J. L. E. Erickson, F. E. Collins, Jr., and B. L. Owen, *J. Org. Chem.*, **31**, 480 (1966).
(4) M. Regitz and J. Ruter, *Chem. Ber.*, **102**, 3877 (1969).
(5) A. P. Krapcho and F. J. Waller, *J. Org. Chem.*, **37**, 1079 (1972).
(6) H. H. Wasserman, J. U. Piper, and E. V. Dehmlow, *J. Org. Chem.*, **38**, 1451 (1973).
(7) E. Tempesti, L. Guiffre, M. Fornaroli, and G. Airoldi, *Chem. Ind. (London)*, 183 (1973).
(8) A. G. Ismailov, S. A. Musaev, and G. M. Bairamov, *Zh. Org. Khim.*, **7**, 929 (1971); *Chem. Abstr.*, **75**, 63209 (1971).
(9) W. T. Brady and R. Roe, Jr., *J. Amer. Chem. Soc.*, **93**, 1662 (1971).
(10) (a) J. C. Martin, P. G. Gott, V. W. Goodlett, and R. H. Hasek, *J. Org. Chem.*, **30**, 4175 (1965); (b) W. Weyler, L. R. Byrd, M. C. Caserio, and H. W. Moore, *J. Amer. Chem. Soc.*, **94**, 1027 (1972); (c) M. Bertrand, J. L. Gras, and J. Gore, *Tetrahedron Lett.*, 1189 (1972); (d) *ibid.*, 2499 (1972); (e) W. T. Brady, J. D. Stockton, and A. D. Patel, *J. Org. Chem.*, in press.
(11) W. T. Brady and A. D. Patel, *J. Org. Chem.*, **37**, 3536 (1972).

Behavior of *endo*-7-Aminomethylbicyclo[3.3.1]nonan-3-one under Reducing Conditions[1]

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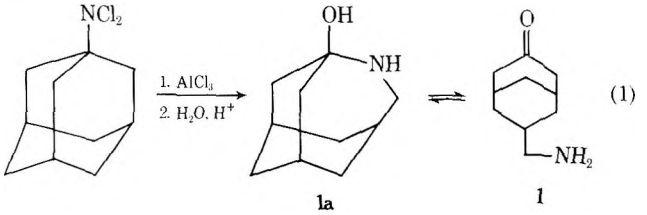
Received October 4, 1973

The behavior of *endo*-7-aminomethylbicyclo[3.3.1]nonan-3-one (1) toward various reducing agents was investigated. Sodium borohydride gave a mixture of endo and exo alcohols (mainly endo) whose ratio varied depending upon the nature of the alcohol used as the medium. Sodium–alcohol reduction provided the exo alcohol as essentially the only product. With hydrogenation in ethanol in the presence of Raney nickel, carbonyl reduction, N-alkylation, and reductive cyclization occurred. Either mono- or dialkylation on nitrogen took place depending upon the temperature. The cyclization reaction produced *N*-ethyl-4-azahomoadamantane. Conversion to the diamine, *exo*-3-amino-*endo*-7-aminomethylbicyclo[3.3.1]nonane, was effected by sodium–ethanol reduction of the oxime of 1. Mechanistic and conformational aspects are also treated.

There are relatively few uncomplicated routes for entry into the bicyclo[3.3.1]nonane series.[4-6] A simple pathway was recently reported[6,7] *via* rearrangement of 1-*N*,*N*-dichloroaminoadamantane in the presence of aluminum chloride. Subsequent exposure to aqueous acid afforded *endo*-7-aminomethylbicyclo[3.3.1]nonan-3-one (1) in 70–80% yield (eq 1). Prior work[6,8] has shown that 1 can serve as a versatile precursor for a variety of derivatives in this series by reactions which generally take place in high yield.



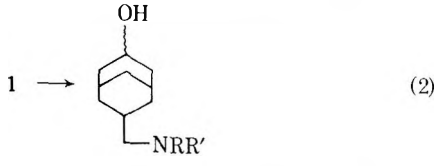
(1)

1a 1

The objective of the present work was to investigate the behavior of 1 under diverse reducing conditions. In addition, attention was given to the stereochemical and mechanistic aspects. In previous, related studies involving 1, Wolff–Kishner reduction[6] provided *endo*-3-bicyclo[3.3.1]nonylmethylamine, and $LiAlH_4$ gave 4-azahomoadamantane.[7]

Results and Discussion

Hydride Reduction. Initially, our attention was focused on reduction of 1 with sodium borohydride in various alcoholic solvents. In all cases, reaction provided an endo–exo mixture of *endo*-7-aminomethylbicyclo[3.3.1]nonan-3-ols, generally in very good yields (eq 2). The ratio of 2 to 3, determined by glpc, was found to vary with change in solvent, but in all cases isomer 2 predominated as expected.



(2)

endo OH 2, R = R′ = H 4, R = H; R′ = C_2H_5 6, R = R′ = C_2H_5

exo OH 3, R = R′ = H 5, R = H; R′ = C_2H_5 7, R = R′ = C_2H_5

From Table I it can be seen that there is a systematic increase in the per cent of 2 as the solvent is changed from isopropyl alcohol to ethanol to methanol. A similar solvent effect was observed earlier for reduction of 3-cholestanone[9] and tropinone.[10] This type of correlation was attributed to formation of methoxyborohydrides *in situ*.

Table I
Reduction of 1 with $NaBH_4$

Solvent	Yield, %	2:3 ratio
MeOH	90–95	95:5
MeOH–H_2O[a]	40–50	95:5
95% EtOH	90–95	75:25
Absolute EtOH	90–95	75:25
i-PrOH	80–85	63:37
Pyridine	60–65	70:30
MeOH[b]	80–85	93:7

[a] 1:1 molar ratio. [b] $NaB(OCH_3)_3H$ as reducing agent.

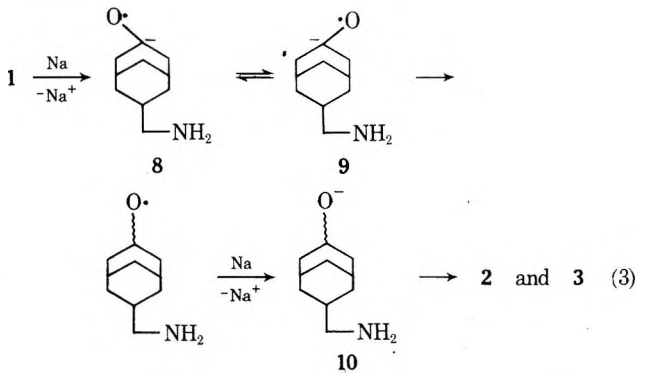
These bulkier reducing entities would favor approach from the less hindered side of the carbonyl group. Thus, the predominance of 2 is rationalized in terms of steric control to attack by hydride resulting in the thermodynamically less stable isomer. The results in Table I are in accord with the relative acidities of *i*-PrOH, EtOH, and MeOH toward sodium borohydride. To test this hypothesis, sodium trimethoxyborohydride was used to reduce 1, giving essentially the same isomer ratio as did sodium borohydride in methanol, in line with the analogous result[9] of Vail and Wheeler with 3-cholestanone. When $NaBH_4$ was allowed to react with methanol for 0.5 hr before addition of 1, no reduction of the amino ketone occurred, indicating that all of the hydrides were replaced by methoxyl groups. This type of exchange is well documented.[11]

A high degree of selectivity was also obtained when the acetamide of 1 was reduced with sodium borohydride in methanol. The resulting product was shown to be essentially 100% endo alcohol by hydrolysis and subsequent glpc analysis. The added bulk on nitrogen would lend additional driving force to exo attack by the reducing species.

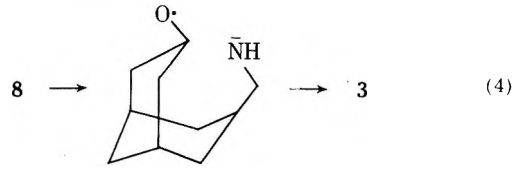
Reduction with Sodium and Alcohols. Reduction of 1 with sodium and ethanol provided 3 contaminated with substantial amounts of unchanged ketone which could be removed by conversion to the oxime followed by a simple extraction procedure. Similar results were obtained with isopropyl alcohol. However, best yields of 3 (75%) were realized with *tert*-butyl alcohol. It is evident that a decreased rate of reaction between sodium and the alcohol (EtOH > *i*-PrOH > *t*-BuOH) produces an overall beneficial effect.

The pronounced selectivity merits comment. Dissolving metal reductions of this type are believed[12] to involve initial formation of an anion radical, which is then protonated (eq 3). Applying this concept to 1, one can visualize

the existence of exo (8) and endo (9) forms of the anion radical.



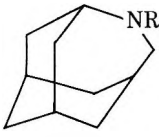
One plausible route would entail intramolecular abstraction of a proton which would be favored in the case of the exo form (8) (eq 4).



Alternatively, prior work[12] has shown that the more stable alcohol is frequently the predominant product. Apparently, the generated alkoxide, *e.g.* **10**, can interact with substrate ketone, similar to the Meerwein–Ponndorf–Verley reduction, to produce the isomeric alkoxide in an equilibrium situation which usually favors the more stable product (eq 5).

10 (endo) + 1 ⇌ **10** (exo) + 1 (5)

Catalytic Hydrogenation. When 1 was hydrogenated in ethanol with Raney nickel catalyst, products were obtained resulting from carbonyl reduction, N-alkylation, and reductive cyclization. At 100° and about 2000 psi, 4 and 5 were isolated in a ratio of 35:65. The ring-closed material was found to be *N*-ethyl-4-azahomoadamantane (**11c**). In addition, a small amount of an unknown substance was present.



11a, R = H
b, R = CH_3
c, R = C_2H_5

Alcohols 4 and 5 were identified by comparison with authentic materials.[13] The structure of **11c** was established by spectral comparison with **11b**,[6] and by alternate synthesis involving reduction by $LiAlH_4$ of the acetyl derivative of **11a**.

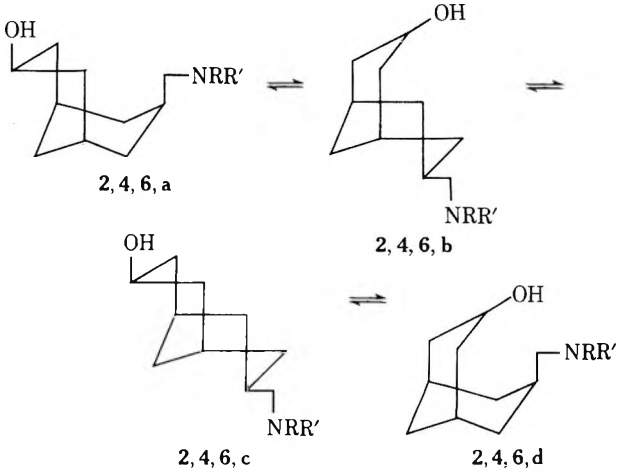
When the temperature of reaction was increased to 130°, **11c** and the minor, unidentified product were again produced. However, the N-alkylated alcohols were found to be a mixture of 6 and 7 in 4:96 ratio, whose structures were assigned on the basis of microanalyses, spectral evidence, and independent synthesis. The mass spectra displayed a weak, parent peak at *m/e* 225 and a base peak at *m/e* 86. The presence of two *N*-ethyl groups and the exo or endo configuration at C-3 are in accord with the nmr spectra. Dialkylation of 3 with ethyl iodide provided an alternate route to 7. Compound 6, as well as 7, was also prepared by acetylation of the *N*-ethyl derivative[13] of 1 with subsequent reduction by $LiAlH_4$. Temperatures of 165–175° produced a complex mixture from hydrogenation.

It has been reported that N-alkylation during hydrogenation of ketones containing primary or secondary amino groups is an undesirable side reaction when low molecular weight alcohols are present with Raney nickel catalyst.[14a] Whereas this type of reaction occurred at 100–130° in our case, previous investigators used temperatures in excess of 150° with their systems.[14] In other, prior work,[15] primary and secondary amines were found to undergo alkylation by alcohols and hydrogen at 180–250° in the presence of Raney nickel or copper chromite. Since tertiary alcohols did not function, the proposal was advanced that dehydrogenation of the alcohol occurs, the resultant carbonyl compound reacts with the amine, and finally hydrogenation to the end product takes place. Excellent yields from reductive alkylation of pyridine bases with alcohols were realized with rhenium sulfide and hydrogen.[16] A related example may be cited in the conversion of 2-amino-2-methyl-1-propanol to 2,2,5,5-tetramethylpiperazine on exposure to hydrogen and Raney nickel.[17]

The mechanistic scheme previously advanced[14-16] serves to rationalize the presence of 4, 5, 6, and 7. Three possible routes can be visualized for formation of **11c**. Hydrogenolysis might occur with **1a** or the *N*-ethyl derivative of **1a**. Alternatively, intramolecular dehydration of 1 could conceivably generate the strained bridgehead imine. Subsequent steps would consist of hydrogenation to **11a** and then N-alkylation.

Stereochemistry. Amino alcohols 2 and 3 were identified by microanalytical and spectral means. The nmr spectra were especially helpful in assigning exo and endo configurations to the hydroxyl functions as described[13] for the corresponding *N*-ethyl derivatives, 4 and 5. As anticipated, 3 displayed a larger vicinal coupling constant for the C-3 carbinyl proton than did the endo isomer.

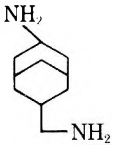
In addition, the nmr spectra indicate that 2 and 3 exist in different conformations. Most notable is the appearance of the CH_2N signal, a singlet for 2 in contrast to a doublet for 3. Similar results were observed for 4 *vs.* 5 and 6 *vs.* 7. Conformational preferences for bicyclo[3.3.1]nonane derivatives have been discussed.[4,13,18,19] Peters and coworkers provided[18] a detailed treatment of the 3,7-disubstituted compounds, which is quite pertinent to the present work. Various conformations for the endo,endo case are illustrated.



The principal contributors appear to be the chair–boat forms **a** and **b**. The double-boat conformation (**c**) seems to play an increasing role as the bulk of the substituents increases, and **d** purportedly participates to only a small extent. For the corresponding exo alcohols, the population would mainly consist of the chair–boat forms.

Possibilities for hydrogen bonding in our case may complicate the conformational picture. For **6** and **7** in chloroform, both free and bonded absorptions (3600 and 3300 cm^{-1}, respectively) are present, whereas a neat sample of **7** showed absorption in this region only at 3300 cm^{-1}. Molecular models indicate that **2** might exist as a hydrogen-bonded monomer in conformation **b** and as a hydrogen-bonded dimer in conformations **a**, **b**, and **c**. The exo isomers **3**, **5**, and **7**, can apparently undergo only linear hydrogen bonding.

Reduction to Diamine. Dissolving metal reduction[20,21] of the oxime of **1** with sodium and ethanol afforded *exo*-3-amino-*endo*-7-aminomethylbicyclo[3.3.1]nonane (**12**) in reasonable yield.



12

Since the free base was quite sensitive to atmospheric exposure, more complete characterization was carried out with the dibenzamide derivative. The rather sharp melting points of the benzamide and the freshly purified amine suggest the presence of essentially one isomeric form. The nmr data, including similarity to the spectra of **3**, **5**, or **7**, indicate an exo configuration for the 3-amino group. Hence, a mechanism analogous to that discussed (see above) for the corresponding reduction of **1** seems plausible.

Attempts to reduce the oxime with $LiAlH_4$ in refluxing ether for periods up to 46 hr gave mostly unchanged starting material. The sluggishness of this type of reducing system has been noted previously.[22] The Leuckart reaction was investigated as a possible direct method. Several runs under various conditions yielded only a small amount (about 10%) of the diamine, in addition to recovered **1**.

Experimental Section

Melting points are uncorrected. Infrared spectra were obtained with Beckman IR-8, IR-20A, and Perkin-Elmer 137 instruments, calibrated with the 1601-cm^{-1} band of polystyrene. Varian T-60 and HA-100 instruments were used to obtain nmr data, which are reported in parts per million relative to tetramethylsilane as internal standard. Gas chromatography was carried out with a Varian Aerograph instrument (A-90-P, 1700, or 1800) with a 15 ft × 0.25 in. column of 15% Carbowax 20M and 10% NaOH on Chromosorb P (30/60), or a 10 ft × 0.25 in. column of 20% Carbowax 20M and 10% NaOH on Chromosorb P (30/60) at 225°.

Solutions were dried over Na_2SO_4. Sodium trimethoxyborohydride was obtained from Alfa Inorganics. Microanalyses were performed by Micro-Tech Laboratories, Skokie, Ill., Baron Consulting Co., Orange, Conn., Mr. A. Gasiecki, and Mr. R. White.

2 and 3 from 1 and Sodium Borohydride. The following procedure is illustrative. A solution of **1** (8 g, 0.48 mol) and $NaBH_4$ (2.3 g, 0.06 mol) in 100 ml of dry methanol was stirred at room temperature for 24 hr. Then 50 ml of 20% saline was added and stirring was continued for a few minutes longer. After the volatile material was removed under reduced pressure, the residue was extracted with methylene chloride. The combined, dried extract was freed of solvent to yield 7.7 g (95%) of a mixture of **2** and **3** as a white solid which can be further purified by recrystallization from cyclohexane and/or sublimation at 70–80° (<1 mm). The ratio of **2**:**3** was found to be 95:5 by glpc. Analytical samples were obtained by preparative glpc followed by sublimation.

Alcohol **2** had mp 93–94.5°; ir ($CHCl_3$) 3650 and 3250 (NH, OH) and 1125 cm^{-1} (CO); nmr ($CDCl_3$) δ 4.12 (m, 1, $J_{AX} \cong J_{BX}$ = 3 Hz, CHOH), 2.54 (m, 2, CH_2N), 1.8 (m, 16, CH, CH_2, NH_2, OH); mass spectrum *m/e* (rel intensity) 169 (3), 152 (2), 151 (5), 30 (100).

Anal. Calcd for $C_{10}H_{19}NO$: C, 70.96; H, 11.31; N, 8.27. Found: C, 71.29; H, 11.42, N, 8.19.

Alcohol **3** had mp 107–108°; ir ($CHCl_3$) 3650 and 3250 (NH, OH) and 1050 cm^{-1} (CO); nmr ($CDCl_3$) δ 3.91 (m, 1, J_{AX} = 5, J_{BX} = 16 Hz, CHOH), 2.48 (d, 2, CH_2N), 1.5 (m, 15, CH, CH_2, NH_2, OH); mass spectrum *m/e* (rel intensity) 169 (2), 151 (6), 30 (100).

Anal. Calcd for $C_{10}H_{19}NO$: C, 70.96; H, 11.31; N, 8.27. Found: C, 70.74; H, 11.40; N, 8.04.

Essentially the same procedure was employed when other alcohols were used as solvents for the reduction of **1**. Lesser quantities of **1** (generally 1–2 g) were used. A drying tube was attached to the apparatus when the solvent was anhydrous. A control experiment showed that the ratio of **2**:**3** was not significantly altered during the work-up and purification procedures.

Reduction of 1 with Sodium Trimethoxyborohydride. To a solution of **1** (1 g, 0.006 mol) in 25 ml of dry methanol was added 2.3 g (0.018 mol) of sodium trimethoxyborohydride in one portion. The mixture was stirred for 12 hr, and then 5 ml of 10% saline was added, followed by a few minutes of stirring. The solvents were removed under reduced pressure, the residue was extracted with CH_2Cl_2, and then solvent was removed from the dried solution to yield crude alcohol product, 0.9 g (90%). Glpc analysis indicated an endo–exo ratio of 93:7 for **2**:**3**.

***endo*-7-Acetamidomethylbicyclo[3.3.1]nonan-3-one from 1.** A mixture of **1** (5 g, 0.03 mol), anhydrous potassium carbonate (6 g, 0.04 mol), and 500 ml of dry benzene was cooled to 0°. Acetyl chloride (5.3 g, 0.07 mol) in 30 ml of dry benzene was added dropwise with stirring during 30 min. The mixture was then stirred for 1 hr at 0–10°, and then for 15 hr at room temperature. The resulting solid was collected by suction filtration and washed thoroughly with hot benzene. The filtrate and benzene washings were combined and washed first with 10% K_2CO_3, next with water, and then dried. Removal of benzene under reduced pressure gave a light yellow oil which crystallized on stirring with 20 ml of petroleum ether (bp 60–90°). The white solid was collected, washed with petroleum ether, and recrystallized from 1:1 benzene–petroleum ether to give 4.2 g (68%) of the amide: mp 113–114°; ir (KBr) 3310 (NH), 1700 (ketone), 1650 (amide), and 1560 cm^{-1} (NH); nmr ($CDCl_3$) δ 1.90 (s, 3, $COCH_3$), 3.0 (t, 2, CH_2N), 7.13 (s, 1, NH).

Anal. Calcd for $C_{12}H_{19}NO_2$: C, 68.86; H, 9.15; N, 6.69. Found: C, 68.86; H, 9.21; N, 6.53.

***endo,endo*-7-Acetamidomethylbicyclo[3.3.1]nonan-3-ol.** A solution of the acetamide of **1** (7 g, 0.033 mol) in 70 ml of absolute methanol was cooled to 0°. Sodium borohydride (2.5 g, 0.067 mol) was added during 10 min. The mixture was stirred at ice-bath temperature for 2 hr and then at room temperature for 15 hr. After addition of water (20 ml), the solvents were removed under reduced pressure, yielding a clear oil which solidified upon addition of 30 ml of water. The solid was collected, dried, and repeatedly crystallized from benzene to yield 6.2 g (88%) of a white solid: mp 165–166°; ir (KBr) 3300–3100 (OH, NH), 1650 (amide), and 1750 cm^{-1} (amide); nmr (CD_3SOCD_3) δ 1.77 (s, 3, $COCH_3$), 2.83 (broad s, 2, CH_2N), 4.0 (broad s, 1, CHOH), 4.27 (d, 1, OH), 7.6 (broad s, 1, NH).

Anal. Calcd for $C_{12}H_{21}NO_2$: C, 68.21; H, 10.02; N, 6.63. Found: C, 68.44; H, 10.21, N, 6.56.

2 from Hydrolysis of the Acetamide of 2. A suspension of the acetyl derivative of **2** (2.1 g, 0.01 mol) in 200 ml of 10% NaOH was heated at reflux until complete solution was attained (1.5 hr). After an additional 1 hr at reflux, the mixture was cooled and extracted in portions with chloroform. Removal of solvent from the combined, dried extract yielded a clear oil which crystallized on standing. Sublimation (80°, 0.3 mm) gave 1.3 g (77%) of white solid, mp 95–96°, which was identical (ir, nmr) with **2** obtained from **1** and $NaBH_4$.

Reduction of 1 with Sodium and Alcohols. 1. Ethanol. In a 1-l. flask with condenser and drying tube were placed **1** (10 g, 0.06 mol) and 400 ml of absolute ethanol. The solution was brought to reflux and kept there by addition of sodium (16 g, 0.69 g-atom) over a 2-hr period. Water (25 ml) was added and the volatile solvents were removed. The residue was refluxed for 8 hr with 28 g of $NH_2OH \cdot HCl$ and about 250 ml of 50% ethanol. The ethanol was removed under reduced pressure, and 100 ml of 15% caustic was added. After the solution was extracted with CH_2Cl_2 in portions, the dried extract was freed of solvent. The residue was sublimed (80–85°, 0.3 mm), yielding 4.5 g (45%) of **3**. Recrystallization from cyclohexane provided a pure sample: mp 114–116°; ir ($CHCl_3$) 3600, 3250 (OH, NH), and 1050 cm^{-1} (CO); nmr ($CDCl_3$) δ 2.46 (d, 2, CH_2N), 3.96 (m, 1, CHOH).

Anal. Calcd for $C_{10}H_{19}NO$: C, 70.96; H, 11.32; N, 8.28. Found: C, 70.70; H, 11.40; N, 8.15.

2. Isopropyl Alcohol. A mixture of **1** (3 g, 0.018 mol) in 70–75 ml of dry isopropyl alcohol was warmed until solution was complete. Sodium (4.1 g) was added in one portion, which caused the reaction mixture to reflux gently. After the initial reaction had subsided, an additional 2 g of sodium and 25 ml of *i*-PrOH were added. The mixture was kept warm until all of the sodium was consumed and a white precipitate had formed. Water (50 ml) was added and the solvents were removed. An additional 100 ml of water was added, and the aqueous solution was extracted with CH_2Cl_2 in portions. Evaporation of solvent left 2.9 g of white solid which was heated at reflux with a 5-molar excess of $NH_2OH \cdot HCl$ and $NaHCO_3$ in 50% ethanol overnight. The volatile solvents were removed and the residue was made basic with 100 ml of 33% caustic. The basic solution was extracted repeatedly with CH_2Cl_2. The dried extract was evaporated to give a white solid, which was sublimed (80–90°, 0.2 mm) to give 1.5 g (50%) of **3**, mp 115–117°. The product was identical (ir and nmr spectra) with that obtained from the sodium–ethanol reduction.

3. *tert*-Butyl Alcohol. Compound **1** (3 g, 0.018 mol) was dissolved in 200 ml of warm *tert*-butyl alcohol. Sodium (6.2 g, 0.27 g-atom) was added in two equal portions at 1-hr intervals. The reaction mixture was agitated with gentle heating until all of the sodium was consumed (4–5 hr). After water (40 ml) was added, volatile material was removed under reduced pressure. Water (100 ml) was added to the residue, and the resulting solution was extracted repeatedly with methylene chloride. Following removal of solvent, the white, solid residue was heated at reflux with a 10-molar excess of hydroxylamine hydrochloride and sodium bicarbonate in 200 ml of 50% ethanol for 8–9 hr. The ethanol was removed under reduced pressure, and then 50 ml of 50% NaOH and 25 ml of water were added. The solution was extracted repeatedly with methylene chloride. The combined, dried extract was freed of solvent, leaving a white solid, which was sublimed (85°, 0.5 mm) to yield 2.1 g (70%) of **3**. Crystallization from cyclohexane gave material melting at 115–118°. The ir and nmr spectra were essentially identical with those of the product from Na–EtOH reduction.

Hydrogenation (Ni-C_2H_5OH) of 1. 1. At 100°. An autoclave was charged with **1** (7 g, 0.04 mol), Raney nickel (10–20 g), and 100–125 ml of absolute ethanol. The reaction mixture was agitated at 100° under a hydrogen pressure of 1800–2000 psi for about 24 hr. The catalyst was removed by gravity filtration and washed with alcohol. Solvent removal afforded an intractable, viscous liquid. After addition of excess 18% HCl, evaporation to dryness yielded 8.4 g of white solid. Glpc analysis (Carbowax 20M), after conversion to the free base, indicated the presence of **4** and **5** (39–41%), **11c** (49–51%), and an unidentified component (8–9%). Compound **4** was identified by glpc peak enhancement with authentic material.[13] Compound **5** had mp 131–132.5° after purification by preparative glpc and vacuum sublimation (lit.[13] mp 131.5–133°). Compound **11c**, purified by preparative glpc, had bp 250° (736 mm) (uncorrected, micro technique); $n^{24}D$ 1.5090; nmr (CCl_4) δ 1.0 (t, 3, CH_2CH_3), 2.58 (q, 2, CH_2CH_3), 2.75 (d, 2, CH_2N), 3.0 (m, 1, CHN), 1.67 (m, 13, rest of H).

Anal. Calcd for $C_{12}H_{21}N$: C, 80.38; H, 11.81; N, 7.81. Found: C, 80.51; H, 11.71; N, 7.63.

11c HCl had mp 258–260°.

Anal. Calcd for $C_{12}H_{22}NCl$: C, 66.80; H, 10.28; N, 6.49. Found: C, 66.56; H, 10.16; N, 6.49.

2. At 130°. The procedure in the preceding section was followed at 130°. After work-up, 6.6 g of hydrochloride salt was obtained (from 5 g of **1**), which was treated with caustic. After extraction with CH_2Cl_2, solvent removal from the dried extract afforded a viscous oil which turned yellow on standing. Glpc analysis revealed the following components (% composition): *N*-ethyl-4-azahomoadamantane (50–52%), unidentified material (about 9%), and a mixture of **6** and **7** (39–41%) in a ratio of 4:96.

Compound **6** was identified by glpc peak enhancement with authentic material. Compound **7**, purified by preparative glpc followed by sublimation at 60–70° (0.1 mm), had mp 69.5–71.5°; ir ($CHCl_3$) 3550, 3350 (OH), and 1050 cm^{-1} (CO); nmr ($CDCl_3$) δ 0.96 (t, 6, CH_2CH_3), 2.21 (s, 1, exchangeable with D_2O), 2.51 (q, 4, CH_2CH_3), 3.95 (m, 1, J_{AX} = 5, J_{BX} = 15 Hz, CHOH), 1.9 (m, rest of H); mass spectrum *m/e* (rel intensity) 22 (1.4), 87 (13), 86 (100), 58 (10.3).

Anal. Calcd for $C_{14}H_{27}NO$: C, 74.61; H, 12.08; N, 6.21. Found: C, 74.58; H, 11.88; N, 6.22.

6 from *N*-Ethyl-7-aminomethylbicyclo[3.3.1]non-3-one. The synthesis was carried out by acetylation (CH_3COCl–C_6H_6–C_5H_5N, room temperature) of the *N*-ethyl derivative[13] of **1**, followed by $LiAlH_4$ reduction. Glpc analysis indicated that **6** and **7** were present in a ratio of 72:28. The endo isomer **6** was separated by preparative glpc and then sublimed under vacuum: mp 69–70°; ir ($CHCl_3$) 3600 and 3300 (OH), 1125 cm^{-1} (CO); nmr ($CDCl_3$) δ 0.99 (t, 6, CH_2CH_3), 1.53 (s, 1, OH, exchangeable with D_2O), 2.50 (q, 4, NCH_2CH_3), 4.13 (m, 1, $J_{AX} \cong J_{BX}$ = 3 Hz, CHOH); mass spectrum *m/e* (rel intensity) 225 (3.5), 87 (13), 86 (100), 58 (9.9), 30 (8.4).

Anal. Calcd for $C_{14}H_{27}NO$: C, 74.61; H, 12.08; N, 6.21. Found: C, 74.35; H, 11.87; N, 6.16.

7 from 3. Crude **3** (4 g) from the sodium–ethanol reduction of **1** (4 g, 0.023 mol) was dissolved in 30 ml of CH_2Cl_2. After the addition of 2,6-lutidine (5.35 g, 0.05 mol) and freshly distilled ethyl iodide (8.6 g, 0.055 mol), the reaction mixture was stirred for about 8 hr at room temperature. Sodium hydroxide (15%, 25 ml) was added, the layers were separated, and the basic portion was extracted with several portions of CH_2Cl_2. The dried, combined organic fraction was freed of solvent. The desired product was separated from the dark brown residue by preparative glpc. Sublimation provided **7** which was identical in all respects with the corresponding product obtained from catalytic hydrogenation of **1** at 130°.

Oxime of 1. A solution of Na_2CO_3 (2.3 g, 0.044 mol) and $NH_2OH \cdot HCl$ (3.1 g, 0.044 mol) in 20 ml of H_2O was refluxed for 5 min to degas the solution. Compound **1** (3.7 g, 0.022 mol) in 20 ml of 95% EtOH was added. After 15 hr at reflux, the solvents were removed under reduced pressure, and the residue was extracted with hot benzene and petroleum ether (bp 30–60°). The solid from filtration of the cooled, combined extract was recrystallized from benzene, 3.4 g (85%), mp 140–141°. The analytical sample was obtained by sublimation at 90–110° (0.1 mm) and recrystallization from benzene, ir (KBr) 3400–3200 (OH, NH) and 1665 cm^{-1} (CN).

Anal. Calcd for $C_{10}H_{18}N_2O$: C, 65.90; H, 9.95; N, 15.37. Found: C, 66.16; H, 10.08; N, 15.48.

12 from Oxime of 1. A solution of the oxime of **1** (4.3 g, 0.023 mol) in 60 ml of absolute ethanol was degassed by boiling for 5 min. After heating was discontinued, sodium (6 g, 0.27 g-atom) was added so as to maintain rapid reflux. The mixture was then stirred for 30 min. Water (30 ml) was added, the solution was stirred for 20–30 min, and then the cooled solution was acidified (litmus) with 18% HCl. After the ethanol was removed under reduced pressure, the remaining aqueous solution was basified with 50% caustic. The product was extracted with $CHCl_3$. Removal of solvent from the dried extract under reduced pressure provided a solid which was purified by sublimation at 40–50° (0.2 mm) to yield 2.4 g (60%) of diamine: mp 40–42°; ir ($CHCl_3$) 3500–3100 (NH) and 1600 cm^{-1} (NH); nmr ($CDCl_3$) δ 1.37 (s, 4, NH, exchangeable with D_2O), 2.48 (d, 2, CH_2N), 3.02 (m, 1, CHN), 1.4 (m, rest of H). Since the product is very sensitive to atmospheric CO_2, it was characterized as the dibenzamide derivative.

Dibenzamide of 12. After freshly sublimed diamine **12** (0.52 g, 0.003 mol) was dissolved in 20 ml of dry pyridine, 1 ml of benzoyl chloride was added dropwise with stirring. The solution was stirred at room temperature for 15 min and then at 60–70° for 45 min. After the cooled mixture was poured into 100 ml of water, the filtered solid was recrystallized from benzene, affording 0.74 g (70%) of the dibenzamide: mp 208–209°; ir (KBr) 3300 (NH), 1650 (C=O), and 1550 cm^{-1} (NH); nmr ($CDCl_3$) δ 3.26 (t, 2, CH_2N), 4.43 (broad s, 1, CHN), 6.10 (broad d, 1, NH), 6.63 (broad m, 1, NH), 7.41 (m, 5, Ar), 7.80 (m, 5, Ar).

Anal. Calcd for $C_{24}H_{28}N_2O_2$: C, 76.55; H, 7.51; N, 7.44. Found: C, 76.45; H, 7.54; N, 7.50.

Acknowledgment. For support of this work we are grateful to the National Science Foundation for a research grant, and to the Undergraduate-Graduate Research Collaboration Program sponsored by the National Science Foundation. We thank Mr. A. Gasiecki and Mr. R. White for some of the microanalyses, Dr. E. M. Levi and Dr. Peter Yates for mass spectral data, and Dr. J.-H. Liu for helpful contributions.

Registry No.—**1**. 34650-78-7; **1** acetamide, 50361-63-2; **1** (*N*-ethyl), 34913-38-7; **1** oxime, 50361-65-4; **2**, 50361-66-5; **2** acetamide, 50361-67-6; **3**, 50361-68-7; **6**, 50361-69-8; **7**, 50361-70-1; **11c**, 50361-71-2; **11c** hydrochloride, 50529-57-2; **12**, 50361-72-3; **12** dibenzamide, 50361-73-4; sodium borohydride, 16940-66-2; sodium trimethoxyborohydride, 16940-17-3.

References and Notes

(1) Paper VIII, "Adamantanes and Related Compounds;" for the preceding publication, see ref 8.
(2) University of Wisconsin—LaCrosse.
(3) University of Wisconsin—Milwaukee.
(4) G. L. Buchanan, "Topics in Carbocyclic Chemistry," Vol. I, D. Lloyd, Ed., Plenum Press, New York, N. Y., 1969, Chapter 3.
(5) R. M. Black and G. B. Gill, *Chem. Commun.*, 972 (1970); H. Stetter and P. Tacke, *Chem. Ber.*, **96**, 694 (1963); F. N. Stepanov and V. D. Sukhoverkhov, *Angew. Chem., Int. Ed. Engl.*, **6**, 864 (1967); W. H. W. Lunn, *J. Chem. Soc. C*, 2124 (1970); H. Hamill, A. Karim, and M. A. McKervey, *Tetrahedron*, **27**, 4317 (1971); A. R. Gagneux and R. Meier, *Tetrahedron Lett.*, 1365 (1969).
(6) J.-H. Liu, G. A. Gauger, and P. Kovacic, *J. Org. Chem.*, **38**, 543 (1973).
(7) P. Kovacic, J.-H. Liu, E. M. Levi, and P. D. Roskos, *J. Amer. Chem. Soc.*, **93**, 5801 (1971).
(8) J.-H. Liu and P. Kovacic, *J. Org. Chem.*, **38**, 3462 (1973).
(9) O. R. Vail and D. M. S. Wheeler, *J. Org. Chem.*, **27**, 3803 (1962).
(10) A. H. Beckett, N. J. Harper, A. D. J. Balon, and T. H. E. Watts, *Tetrahedron*, **6**, 319 (1959).
(11) N. G. Gaylord, "Reduction with Complex Metal Hydrides," Interscience, New York, N. Y., 1956, p 18.
(12) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, New York, N. Y., 1965, pp 54–55.
(13) S. J. Padegimas and P. Kovacic, *J. Org. Chem.*, **37**, 2672 (1972).
(14) M. Freifelder, "Practical Catalytic Hydrogenation," Wiley-Interscience, New York, N. Y., 1971, pp 79, 346; R. L. Augustine, "Catalytic Hydrogenation," Marcel Dekker, New York, N. Y., 1965, pp 42–43.
(15) E. J. Schwoegler and H. Adkins, *J. Amer. Chem. Soc.*, **61**, 3499 (1939).
(16) E. A. Mistryukov, E. L. Ilkova, and M. A. Ryashentseva, *Tetrahedron Lett.*, 1691 (1971).
(17) S. M. McElvain and L. W. Bannister, *J. Amer. Chem. Soc.*, **76**, 1126 (1954).
(18) J. A. Peters, J. D. Remijnse, A. van der Wiele, and H. van Bekkum, *Tetrahedron Lett.*, 3065 (1971).
(19) W. D. K. Macrosson, J. Martin, and W. Parker, *Tetrahedron Lett.*, 2589 (1965).
(20) W. H. Lycan, S. V. Puntambeker, and C. S. Marvel, "Organic Syntheses," Collect. Vol. II, A. H. Blatt, Ed., Wiley, New York, N. Y., 1947, p 318.
(21) H. Lund, "The Chemistry of the Carbon–Nitrogen Double Bond," S. Patai, Ed., Interscience, New York, N. Y., 1970, p 553.
(22) J. March, "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure," McGraw-Hill, New York, N. Y., 1968, p 899.

Studies Related to the Conversion of 9,10-Anthraquinones to Anthracenes

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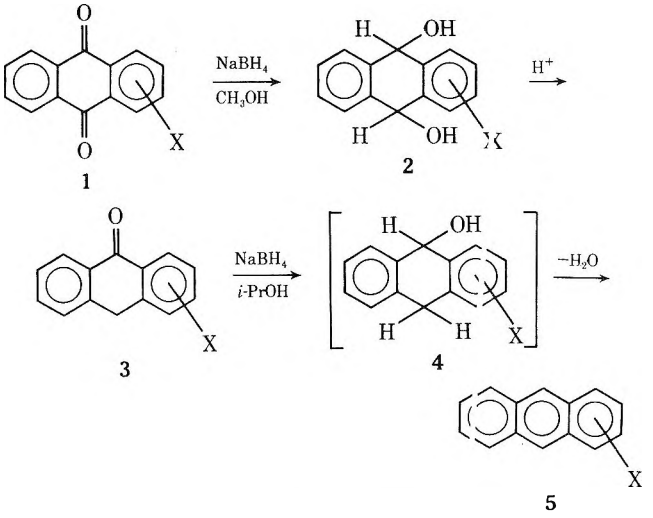
Received August 24, 1973

A facile method for the conversion of certain 9,10-anthraquinones to anthracenes *via* successive heterogeneous alcoholic sodium borohydride reductions and dehydrations has been developed. Several halo- and methyl-substituted anthracenes have been prepared by this procedure and the intermediate 9,10-dihydroxy-9,10-dihydroanthracenes and anthrones have been isolated and characterized. Ir and nmr spectroscopy have been employed for determination of the isomer distribution of 9,10-dihydroxy-9,10-dihydroanthracenes and unsymmetrically substituted anthrones.

The reduction of an appropriately substituted anthraquinone provides a potential route to many anthracene derivatives which are otherwise difficult to obtain. We wish to report that sodium borohydride in a lower alcohol is an effective reagent for this purpose. The intermediates formed during this reduction have been identified and their conformational and keto–enol relationships studied.

Sodium borohydride reduction of anthraquinones in diglyme under widely different reaction conditions has been reported. In one instance,[1] the difficult-to-purify products contained boron, whereas anthrahydroquinone was the product reported in the second case.[2] Later investigators[3,4] claimed 35–50% yields of anthracenes for the reduction of the corresponding anthraquinones in refluxing sodium borohydride–diglyme solutions. Evidence was also given for the formation of some anthracene derivatives (50–70%) when the reduction was run in the presence of boron trifluoride or aluminum chloride. Under these conditions, anthraquinone gave a mixture of anthracene and 9,10-dihydroanthracene. More recently,[5,6] sodium borohydride in methanol has been used to obtain 9,10-dihydroxy-9,10-dihydroanthracenes from the corresponding anthraquinones. Reductions wherein lithium aluminum hydride has been used have given conflicting results.[7,8]

We have found that a three-step procedure involving two reduction–dehydration sequences using sodium borohydride in methanol or 2-propanol converts many anthraquinones (1) to anthracenes (5) in a straightforward fashion, *via* the successive formation of 9,10-dihydroxy-9,10-dihydro intermediates, anthrones, and 9-hydroxy-9,10-dihydro intermediates. The steps are schematically represented wherein X represents one or more substituents on either or both end rings.



Procedures described in the Experimental Section have been generalized and represent a skeletal framework from which one can adapt procedures for specific anthraquinones. Table I lists the pertinent data for a number of anthraquinones. An additional specific procedure for the synthesis of 1,4-dimethoxyanthracene (**5j**) is included, because the literature preparation[9] for **5j** is not readily reproducible in our hands. Compound **5j** has been shown to be a useful diagnostic tool for detecting the presence of benzyne intermediates,[10] and satisfactory yields are not obtained by the general stepwise procedure discussed above.

The yield of 9,10-dihydroxy-9,10-dihydroanthracene (**2a**) was lower than the yields for **2** from substituted anthra-

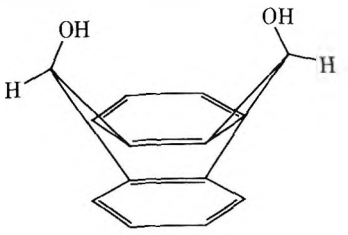
Table I
Sodium Borohydride Reduction of Anthraquinones. Yields and Melting Points of Isolable Compounds

Anthraquinone (1)	9,10-Dihydroxy-9,10-dihydroanthracene (2) Yield, %	Mp, °C[a]	Anthrone (3) Yield, %	Mp, °C	Anthracene (5) Yield, %	Mp, °C
H (**a**)	65	158–165[b]	93	158–170[c]	78	213–215[d]
2-Methyl (**b**)	95	165–176[e]	54	116–124[f]	24	206–207[g]
1,4-Dimethyl (**c**)	87	195–215[h]	n.r.			
2,7-Dimethyl (**d**)	88	195–197[e]	83	185–194[i]	94	233–235[j]
1-Chloro (**e**)	n.r.					
2-Chloro (**f**)	84	178–184[e]	97	184–189[k]	30	219–220[l]
1,5-Dichloro (**g**)	90	215–220[m]	82	175–178[n]	67	178–181[o]
1,8-Dichloro (**h**)	88	180–189[p]	98	223–233[q]	47	151–160[r]
1,2,3,4,6,7-Hexachloro[s] (**i**)	84	230–235[e]	n.r.			
1,4-Dimethoxy (**j**)	95	141–143[t]	52	127–170[e]	62	134–136[u]

[a] There is frequent disparity of melting points for **2** between the literature and the reported values in Table I, as well as between published reports. This may be due to the presence of varying proportions of cis–trans mixtures. See footnotes *g* and *i*. [b] Lit. mp 195°: C. Dufraisse and J. Houpillart, *C. R. Acad. Sci.*, **205**, 740 (1937). [c] Lit. mp 163–170°: W. R. Orndorff and C. L. Bliss, *Amer. Chem. J.*, **18**, 453 (1896). [d] Lit. mp 218°: E. Clar, "Polycyclic Hydrocarbons," Vol. 1, Academic Press, New York, N. Y., 1964, p 290. [e] Satisfactory microanalytical data were obtained for this new compound. [f] Lit. mp 100°: H. Limpricht, *Justus Liebigs Ann. Chem.*, **314**, 237 (1900). [g] Lit. mp 203°: E. Bornstein, *Ber.*, **15**, 1820 (1882). [h] Lit. mp 241–242°: Y. Lepage, *Bull. Soc. Chim. Fr.*, 1759 (1961). [i] Lit. mp 171°: F. Mayer and H. Gunther, *Ber.*, **63**, 1455 (1930). [j] Lit. mp 240°: V. L. Kravtsov, *Ukr. Khim. Zh.*, **29**, 957 (1963). [k] Lit. mp 156°: E. B. Barnett and M. A. Matthews, *J. Chem. Soc.*, **123**, 2549 (1923). [l] Lit. mp 215°: H. Schilling, *Ber.*, **46**, 1066 (1913). [m] Cis isomer lit. mp 205–209°; trans isomer lit. mp 220–224° (ref 12). See also ref 11. [n] Lit. mp 178–180°: A. Eckert and R. Pollak, *Monatsh. Chem.*, **38**, 11 (1917). [o] Lit. mp 185°: footnote *l*. [p] Trans isomer lit. mp 160° yellow, 176° dec; cis isomer lit. mp 215° dec (ref 5). [q] 1,8-Dichloro-9-anthrone lit. mp 167°: footnote *k*. 4,5-Dichloro-9-anthrone lit. mp 198°: E. B. Barnett, J. W. Cook, and M. A. Matthews, *Recl. Trav. Chim. Pays-Bas*, **45**, 68 (1926). [r] Lit. mp 156°: footnote *l*. [s] Preparation similar to that of N. S. Dokunikhin, Z. Z. Moiseeva, and V. A. Mayatnikova, *Zh. Org. Khim.*, **2**, 516, (1966). [t] Lit. mp 192° (ref 9). Value corrected to 152–153°: Y. Lepage, *Ann. Chim. (Paris)*, **4**, 1137 (1959). Compound **2j** was obtained *via* the stepwise reduction procedure outlined in the Experimental Section. A specific preferred preparative scheme for compounds **3j** and **5j** is also contained in the Experimental Section and the data for these compounds are included in Table I. [u] Lit. mp 137° (ref 9).

quinones but notably higher than that from $LiAlH_4$ reduction.[8] The synthetic advantage of sodium borohydride over $LiAlH_4$ is further indicated by the 1,5-dichloroanthraquinone reduction sequence. A 59% yield of **2g** was obtained[11] by $LiAlH_4$ reduction (20 days) of **1g**, while the sodium borohydride method gave **2g** in 90% yield in 24 hr. The Meerwein–Ponndorf reduction of **1** to **2** occurs with poorer yields[12] than those realized *via* sodium borohydride reduction. Also, the identity of the Meerwein–Ponndorf reduction product varied with the aluminum alkoxide used with a given anthraquinone. However, the Meerwein–Ponndorf reduction of **1e** to **2e** was successful, whereas **2e** could not be prepared *via* the sodium borohydride method despite several attempts. Compounds **2c** and **2i** could not be dehydrated to **3**, possibly for steric reasons. Thus the sodium borohydride reduction of anthraquinones described above may be the method of choice for the synthesis of some substituted anthracenes, but other reduction methods such as the zinc and ammonium hydroxide reduction may be preferable for other substituted anthracenes.[13,14] The nature and position of substituents seem to have a large effect upon the relative merits of a given method.

We have studied the isomeric distribution and the axial–equatorial conformation of the hydroxyl groups of **2**, as well as the position of the keto–enol equilibria of **3**. Compound **2** can be considered a dibenzo-1,4-cyclohexadiene and as such exists in the boat conformation with quasi-axial and equatorial hydroxyl groups.[5,15,16] The first treatment of the conformation of **2** employed infrared



2

analysis of C–O stretching frequencies to assign hydroxyl-group orientation.[5] Absorption at 1030–1060 cm^{-1} was assigned to equatorial hydroxyl groups and absorption at 960–1000 cm^{-1} to axial hydroxyl groups.[5] Initially, we attempted to correlate the C–O stretching frequencies as was done previously,[5] but our conclusions were inconsistent. A more recent report[14] mentions the use of the O–H stretching region of infrared spectra for stereochemical analysis. Intramolecular hydrogen bonding indicative of cis isomers was evidenced by lower frequency broad absorption, compared to higher frequency, less broad absorption for nonhydrogen-bonded hydroxyl groups of trans isomers. We then used the O–H stretching frequencies for primary stereochemical assignments, reinterpreted the C–O stretching frequency assignments, and refined the assignments by use of the nmr data as described in the following.

The O–H stretching region of the infrared spectra, obtained from KBr pressings, was used to determine the presence of hydrogen bonding[16] which in turn indicated the presence of diaxial hydroxyl cis isomer, the only isomer in which hydrogen bonding (intramolecular) could occur between the hydroxyl groups. Absence of hydrogen bonding indicated trans isomer because of the impossibility for intramolecular hydrogen bonding. Intramolecular hydrogen bonding would also be impossible for a diequatorial hydroxyl cis isomer; however, ring conversion would give the equally or more stable diaxial hydroxyl cis isomer, especially for those compounds containing peri substituents. The nmr spectra were then used in a more quantitative fashion to indicate the distribution of isomers in solution. A degree of uncertainty is inherent in the interpretation of the nmr spectra in the sense that assignment of the 9,10-proton absorptions to specific isomers is not readily possible, but the larger absorption in each case was given the same assignment as that obtained from the infrared spectra. A detailed discussion of the spectra follows, along with additional comments on the spectral correlations and assignments.

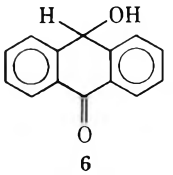
Table II
Nmr[a] and Ir[b] Data for 2

Compd	Aromatic protons	9,10 Protons	9,10 Hydroxyl protons	9,10 Protons after D_2O addition[c]	Major isomer, %	Infrared absorption[d]	Assignment for major isomer[d]
2a[e]	2.40–2.91 (m, 8)	4.80 (s, 2)	4.47 (broad s, 2)	4.47 (s, 0.18) 4.73 (s, 1.82)	91	3220 (s, broad) 1030 (s)	Cis
2b	2.31–2.96 (m, 7)	4.42 (s, 0.55) 4.69 (s, 1.45)	3.82 (broad s, 2)	4.42 (s, 0.55) 4.69 (s, 1.45)	73	3250 (s, broad) 1030 (s)	Cis
2c	2.36–2.95 (m, 6)	4.35 (broad s, 2)[f]	4.67 (broad s, 2)[g]	4.33 (s, 2)	100	3330 (s, broad) 1040 (m) 990 (s)	Trans
2d	2.47–2.98 (m, 6)	4.47 (s, 0.36) 4.73 (s, 1.64)	3.91 (broad s, 2)	4.47 (s, 0.36) 4.71 (s, 1.64)	82	3220 (s, broad) 1030 (s) 1000 (w)	Cis
2f	2.42–2.87 (m, 7)	4.51 (s, 0.25) 4.76 (s, 1.75)	3.71 (broad s, 2)	4.51 (s, 0.25) 4.76 (s, 1.75)	88	3260 (s, broad) 1035 (s) 990 (w)	Cis
2g	2.33–2.65 (m, 6)	4.18 (quartet, 4)		4.38 (s, 2)	100	3310 (s, broad) 985 (s)	Trans
2h	2.33–2.71 (m, 6)	3.55 (d, 1) 4.15 (d, 1)	3.45 (d, 1) 4.30 (d, 1)	3.55 (s, 1)[h] 4.15 (s, 1)	100	3430 (s, broad) 965 (s)	Trans
2i	2.22 (d, 2)	4.23 (s, 1.25) 4.31 (s, 0.75)	5.70 (s, 0.75) 5.71 (s, 1.25)	4.19 (s, 1.25) 4.28 (s, 0.75)	63	3420 (s, broad) 990 (s)	Trans
2j	2.36–2.76 (m, 6)	4.23 (t, 2)	4.84 (t, 2)	4.19 (s, 1.50) 4.27 (s, 0.50)	75	3380 (s, broad) 985 (s)	Trans

[a] Chemical shift in τ units *vs.* TMS, DMSO-d_6 solvent (25° unless otherwise specified) with TMS or hexamethyldisiloxane (HMDSO) used as internal reference. [b] Infrared absorption in cm^{-1}. [c] Addition of D_2O caused elimination of 9,10-hydroxyl proton resonance accompanied by appearance of a DOH resonance in the range τ 6.2–7.0 and did not alter aromatic proton chemical shift. [d] All OH absorption indicates some hydrogen bonding, because the infrared spectra were obtained in the solid state. The differences observed and assignments made relate, therefore, to relative amounts and types (intramolecular *vs.* intermolecular) of hydrogen bonding. [e] Nmr spectra obtained at 110°. [f] Coalesced triplet character. [g] Coalesced doublet character. [h] The 9- and 10-proton absorptions for this compound are nonidentical because of the peri Cl location; therefore, the two absorptions do not represent two isomers. The nmr of 1,8-dichloroanthracene shows the 9 and 10 protons at τ 0.99 and 1.36, respectively.

The infrared spectra for **2a**, **2b**, **2d**, and **2f** showed broad O–H stretch absorption centering below 3300 cm^{-1} (see Figure 1 and Table II), indicative of cis isomers. Trans isomers were assigned to **2c**, **2g**, **2h**, **2i**, and **2j** based on somewhat less broad absorption centering above 3300 cm^{-1}. Obviously, smaller amounts of the other isomer in each case could not be ruled out for these compounds in the solid state based on the infrared spectra. The spectrum for **2g** shows a significant shoulder absorption below 3300 cm^{-1} and may indicate intramolecular hydrogen bonding of the equatorial hydroxyl with the peri chlorine, especially since one hydroxyl of the trans isomer must be equatorial. For **2h**, the equatorial hydroxyl need not be near the peri chlorines, and no hydrogen bonding is indicated. Because of the inconsistencies with the literature concerning the assignment of C–O absorptions as noted above, the appropriate regions of the infrared spectra were examined. Interestingly, with one exception (**2c**), a direct correlation, different from that postulated previously,[5] existed between the cis and trans assignments and the position of absorption in the 1000 cm^{-1} region. The compounds given cis assignments (**2a**, **2b**, **2d**, and **2f**) showed strong absorption between 1020 and 1050 cm^{-1} and little or no absorption between 960 and 1000 cm^{-1}, whereas the compounds given trans assignments (**2c**, **2g**, **2h**, **2i**, and **2j**) gave strong absorption between 960 and 1000 cm^{-1}, and **2c** showed additional significant absorption between 1020 and 1050 cm^{-1}. In light of the rather good correlation, the absorption in the 1000-cm^{-1} region may indicate the "depth" of the boat conformation as reflected in the C–C–O absorption. Thus, for cis isomers the boat form would be "deeper" with the ends drawn somewhat closer due to hydrogen bonding.

Table II gives the nmr data for compounds **2**. The relative shapes and areas of the 9,10-proton absorption and 9,10-hydroxyl proton absorption coupled with the changes observed with the addition of deuterium oxide were useful in obtaining a more quantitative estimate of the relative amounts of cis and trans isomers. Usually, the spectra of the samples treated with deuterium oxide were simpler to evaluate because of the elimination of 9,10-hydroxyl proton absorption. Compounds **2a**, **2b**, **2d**, and **2f** were composed of 73–91% cis isomer. The parent compound (**2a**) with no substituents had 91% cis isomer, compared with 72–88% for the β-substituted compounds (**2b**, **2d**, and **2f**). These observations are in good accord with the complementary observations of Cristol and coworkers,[16] who reported cis diol as the major product for sodium borohydride reduction of some anthraquinones with no peri substituents. A similar correlation was observed for the dihydroxydihydro compounds (**2c**, **2g**, **2h**, **2i**, and **2j**) formed from anthraquinones with peri substituents; trans isomers were obtained as 63–100% of the product. The intermediacy of oxanthrones (**6**) or the corresponding boron esters, as



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suggested by Cristol,[16] and the subsequent stereochemical control by peri substituents nicely explain the stereochemistry of the major product. Note that for the 1,8-dichloro compound, the high stereoselectivity can be obtained only if the carbonyl group peri to the chlorines is reduced first. These arguments assume that isomerizations (*via* a dihydroanthrenyl cation) have not occurred appreciably during work-up conditions.

Anthrones (**3**) are known to exist in solution as keto-enol equilibrium mixtures. The nmr results in Table III show the keto–enol ratios obtained in deuterated dimethyl sulfoxide and chloroform at the indicated temperatures.

Table III
Nmr[a] Data for 3

Compd	Temp, °C	Solvent	Aromatic proton resonance[b]	Methylene proton resonance[c]	Keto:enol ratio
3a	110	DMSO-d_6	1.62–2.77 (m, 9.2)	5.75 (s, 0.8)	40:60
	25	$CDCl_3$	2.42–3.58 (m, 8.4)	6.55 (s, 1.6)[d]	80:20
3b	25	DMSO-d_6	1.55–3.19 (m, 8.5)	5.16 (s, 0.5)	25:75
	25	$CDCl_3$	1.73–3.42 (m, 8.6)	5.42 (s, 0.4)	20:80
3d	25	DMSO-d_6	1.76–3.36 (m, 7.4)	5.36 (s, 0.6)	30:70
	25	$CDCl_3$	1.77–3.39 (m, 7.4)	5.42 (s, 0.6)	30:70
3f	25	DMSO-d_6	1.51–4.27 (m, 8.6)	5.09 (s, 0.4)	20:80
	25	$CDCl_3$	1.67–3.29 (m, 8.5)	5.31 (s, 0.5)	25:75
3g	25	DMSO-d_6	1.24–2.80 (m, 7.5)	4.89 (s, 0.5)	25:75
	25	$CDCl_3$	1.25–2.83 (m, 7.6)	5.86 (s, 0.4)	20:80
3h	110	DMSO-d_6	1.52–2.95 (m, 7.5)[e]	5.91 (s, 0.30)	15:85
	55	$CDCl_3$	1.82–3.02 (m, 7.0)[f]	5.98 (s, 1.0)	50:50
3j	25	DMSO-d_6	2.40–3.29 (m, 7.0)	4.89 (s, 1.0)	50:50
	25	$CDCl_3$	2.18–3.30 (m, 6.9)	4.86 (s, 1.1)	55:45

[a] Expressed in τ units. [b] Addition of D_2O did not in general change aromatic proton resonances. [c] Addition of D_2O caused elimination of methylene proton (in equilibrium with the enol form) resonance accompanied by the appearance of a resonance due to DOH in the range τ 5.71–7.05. [d] Addition of D_2O caused diminution of the intensity of the methylene proton resonance accompanied by the appearance of a resonance due to DOH. [e] In the aromatic region, a multiplet centered at τ 1.60 (1.0 peri H) was assigned to the 10-OH isomer, a multiplet centered at τ 1.96 (0.5 peri H) was assigned to the 10-keto isomer, and a broad singlet at τ 1.52 (0.5 H) was assigned to the 9 H of the 10-OH isomer. Addition of D_2O caused elimination of the latter peak. [f] In the aromatic region, a multiplet centered at τ 1.92 (1.0 peri H) was assigned to the 10-keto isomer.

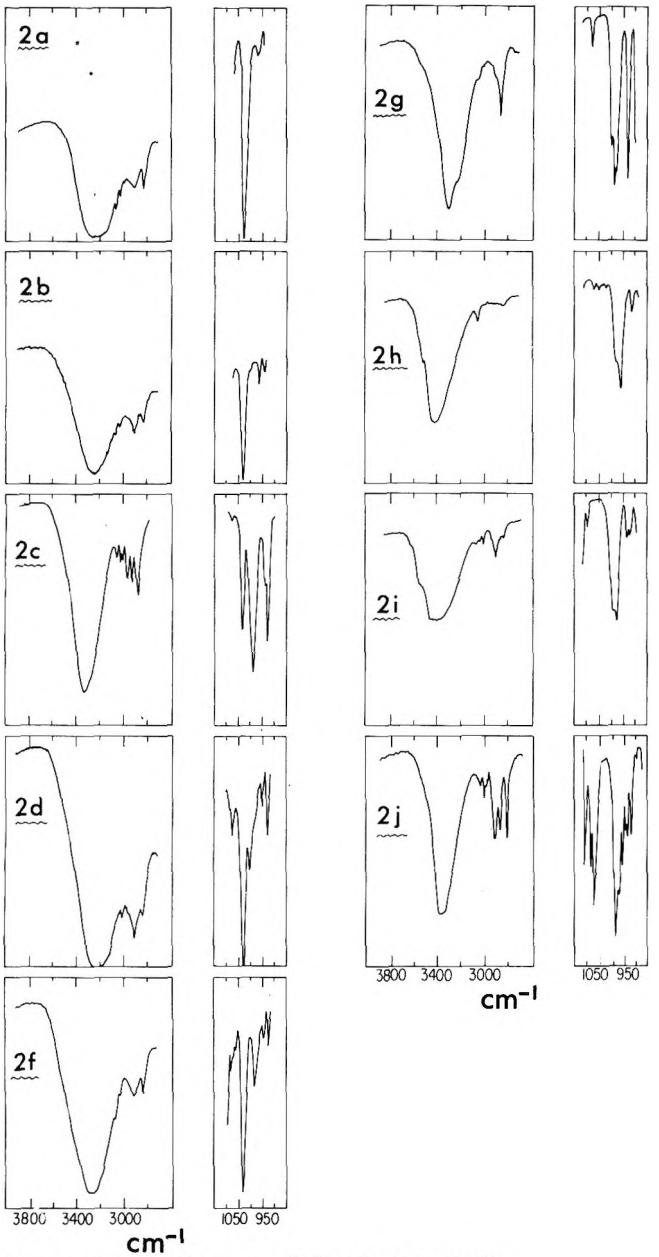
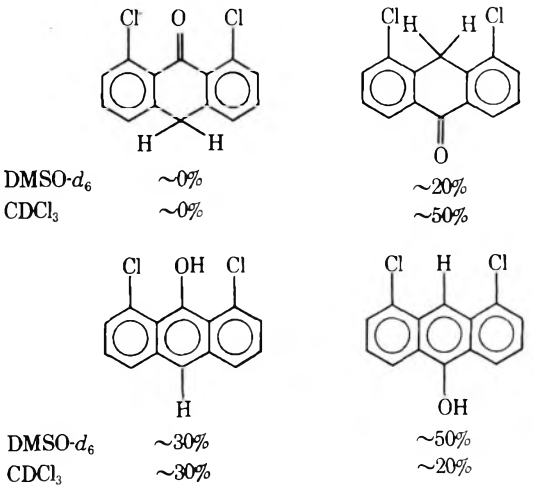


Figure 1. Pertinent regions of infrared spectra for **2**.

Compounds for which the spectra could be obtained at the same temperature in both solvents exhibit keto–enol equilibria ratios that are approximately the same in both solvents for a given compound. However, temperature seems to affect the equilibrium position markedly (**3a** and **3h**). One compound, **3h**, is particularly interesting because two different keto and two different enol forms can arise from the dehydration of **2h**. Chart I indicates the approximate amount of each isomer present in each solvent, based on assignments made with the nmr data in Table III and the footnotes. (The spectra are somewhat ambiguous and the assignments are the most reasonable consistent with certain requirements, for example, the same ratio of structural isomers for each solvent.) Note that one keto form and both enol forms exist in significant amounts for each solvent. The favorable effect of hydrogen bonding for the 9-hydroxyl form is thus demonstrated by the absence of the 9-keto form. Peri substitution has some effect on the mode of dehydration for **2h** to **3h** as is evidenced by the ~1:2 ratio of 9- and 10-substituted anthrones (**3h**).

Chart I



Error: ±10

Experimental Section

Nmr spectra were determined with a Bruker scientific HX-90 spectrometer in DMSO-d_6 or $CDCl_3$ with TMS or HMDS (hexamethyldisiloxane) as internal reference, and all values are nor-

malized with respect to TMS. Infrared spectra were determined with a Beckman IR-12 spectrophotometer; KBr pressings (solid state) were used because most of the materials were not soluble in good solvents for infrared studies.

Generalized Procedure for Anthraquinone Reductions. 1. 9,10-Dihydroxy-9,10-dihydroanthracenes. An anthraquinone (0.08–0.10 mol) was placed in methanol (400–500 ml) and the resulting suspension was stirred while cooling to 0–5° with an ice bath. Solid sodium borohydride (13–15 g, 0.35–0.40 mol) was added in small portions to the suspension at such a rate as to prevent a temperature rise (30–60 min). During continuous stirring at 0–5° (2–4 hr), the reaction mixture assumed an orange color and became nearly homogeneous, and often a white material precipitated. The reaction mixture was poured into an ice–water mixture and stirred. The white precipitate which formed was collected, thoroughly washed with water, and air dried, yield of product 80–90%.

2. Conversion of 9,10-Dihydroxy-9,10-dihydroanthracenes to Anthrones. A suspension of 4 g of 9,10-dihydroxy-9,10-dihydroanthracene in hot 5 *N* HCl (125 ml) was stirred for 3–6 hr. The white, suspended material gradually assumed a yellow color. The anthrone was collected by filtration, thoroughly washed with water, and dried. Recrystallization or trituration afforded material of greater purity, yield of anthrone 80–95%.

3. Conversion of Anthrones to Anthracenes. An anthrone (0.08–0.10 mol) was suspended in 2-propanol (400–500 ml). After addition of sodium borohydride (0.40–0.90 mol), the reaction mixture was refluxed with stirring for 24–36 hr. The reddish-brown reaction mixture was poured with stirring into ice water which had been purged with nitrogen. In most instances, precipitation of the desired anthracene occurred. Addition of dilute acid was necessary in some instances in order to decompose unreacted sodium borohydride and to induce precipitation. The yellow solid was collected, washed thoroughly with water, and air dried. The dehydration of 4 is spontaneous under the reaction conditions, yield of crude anthracene 49–80%. Appropriate recrystallization was necessary for purification (ethanol or dichloromethane–methanol).

1,4-Dimethoxyanthraquinone (1j). Quinizarin (100 g, 0.42 mol), methyl *p*-toluenesulfonate (220 g, 1.18 mol), and sodium carbonate (70 g, 0.66 mol) were combined in o-dichlorobenzene (1.6 l.) and gently refluxed for 20 hr. The reaction mixture was allowed to cool to 95–100°, at which time water (100 ml) was added dropwise (5–10 min). The mixture was steam distilled to remove the solvent, and the precipitate which formed was collected by filtration and recrystallized from ethanol, yield 87.1 g (78%), mp 171–173° (lit.[17] mp 171°).

1,4-Dimethoxyanthracene. To a mixture of 50 g of 1,4-dimethoxyanthraquinone in 750 ml of diglyme at 5° was added sodium borohydride (30 g) in portions (15 min), and the mixture was stirred at 5–15° for 1.75 hr (total) before it was added to approximately 2.5 l. of ice water. An ether layer was added, and 200 ml of acetic acid was then added carefully. The reaction mixture (approximately 4 l.) was heated on a steam bath for 4 hr. Much bubbling occurred as the mixture was heated (at about 50°), and an orange precipitate began to form. The mixture was cooled overnight, and the orange precipitate was filtered off, washed, and dried to give 24.5 g (52%), mp 127–170°, of 1,4-dimethoxyanthrone.

To a mixture of 24.4 g of the anthrone in 375 ml of diglyme at 5–10° was added sodium borohydride (15 g). The mixture was stirred at 5–15° for 2 hr before it was added to approximately 2.0 l. of ice water. An ether layer was added, and 125 ml of acetic acid was then added carefully. Then 50 ml of concentrated hydrochloric acid was added, and the mixture was stirred at room temperature for 2 hr. The yellow precipitate was removed by filtration and washed with water to give 20.7 g, mp 127–132°.

Recrystallization and purification were effected by dissolving the crude product in 100 ml of methylene chloride and adding 400 ml of methanol dropwise. This mixture was cooled and a yellow product was obtained (14 g, 62%), mp 134–136°.

Acknowledgment. We wish to thank Dr. T. H. Regan and Mr. R. L. Young for their aid in interpretation of nmr spectra, Miss T. J. Davis for her discussion of infrared data, Mr. D. P. Maier for mass spectrometric data, Dr. C. V. Wilson for many helpful discussions, and Mr. B. J. Murray for technical assistance; all are from these laboratories.

Registry No.—**1a,** 84-65-1; **1b,** 84-54-8; **1c,** 1519-36-4; **1d,** 3286-01-9; **1e,** 82-44-0; **1f,** 131-09-9; **1g,** 82-46-2; **1h,** 82-43-9; **1i,** 6913-40-2; **1j,** 6119-74-0; **2a,** 35058-16-3; **2b,** 50259-81-9; **2c,** 50259-82-0; **2d,** 50259-83-1; **2f,** 50259-84-2; **2g,** 41187-73-9; **2h,** 50259-86-4; **2i,** 50259-87-5; **2j,** 50259-88-6; **3a,** 90-44-8; **3b,** 50259-89-7; **3d,** 50259-90-0; **3f,** 4887-99-4; **3g,** 50259-92-2; **3h,** 50259-93-3; **3j,** 50259-94-4.

References and Notes

(1) S. W. Chaikin and W. G. Brown, *J. Amer. Chem. Soc.*, **71**, 122 (1949).
(2) G. S. Panson and C. E. Weill, *J. Org. Chem.*, **22**, 120 (1957).
(3) D. S. Bapat, B. C. Subba Rao, M. K. Unni, and K. Venkataraman, *Tetrahedron Lett.*, (5), 15 (1960).
(4) C. J. Sanchorawala, B. C. Subba Rao, M. K. Unni, and K. Venkataraman, *Indian J. Chem.*, **1**, 19 (1963).
(5) M. Toji, Ph.D. Thesis, University of Colorado, 1963.
(6) J. S. Meek and L. L. Koh, *J. Org. Chem.*, **33**, 2942 (1968).
(7) R. F. Nystrom and W. G. Brown, *J. Amer. Chem. Soc.*, **70**, 3738 (1948).
(8) E. Boyland and D. Manson, *J. Chem. Soc.*, 1837 (1951).
(9) A. Etienne and Y. Lepage, *C. R. Acad. Sci.*, **240**, 1233 (1955).
(10) B. H. Klanderman and T. R. Criswell, *J. Amer. Chem. Soc.*, **91**, 510 (1969).
(11) S. J. Cristol, W. Barasch, and C. H. Tieman, *J. Amer. Chem. Soc.*, **77**, 583 (1955).
(12) S. Coffey and V. Boyd, *J. Chem. Soc.*, 2468 (1954).
(13) R. von Perger, *J. Prakt. Chem.*, **23**, 146 (1881).
(14) S. J. Cristol and M. L. Casbar, *J. Org. Chem.* **33**, 2020 (1968).
(15) Molecular models demonstrate that the only reasonable conformation is the boat form. See also ref 16.
(16) S. J. Cristol, *Accounts Chem. Res.*, **4**, 393 (1971).
(17) K. Zahn and P. Ochwat, *Justus Liebigs Ann. Chem.*, **462**, 72 (1928).

Rearrangements of Azidoquinones. XII. Thermal Conversion of 2-Azido-3-vinyl-1,4-quinones to Indolequinones[1]

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Received August 2, 1973

2-Azido-3-vinyl-1,4-quinones (1) thermally undergo a facile ring closure to indolequinones (2). The synthetic utility of this reaction is illustrated in the synthesis of 1,2,5,10-tetrahydro-3*H*-pyrrolo[1,2-*a*]benzo[*f*]indole-5,10-dione (12), the naphthoquinone analog of the mitosene ring system. The mechanism of the thermal ring closure is also discussed and, based upon kinetic data, a concerted process is suggested.

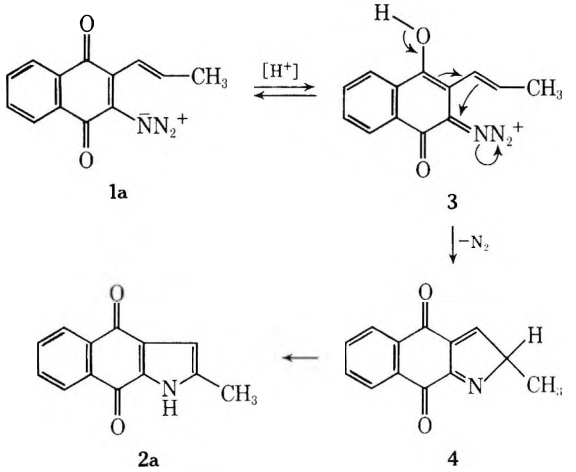
Azidoquinones are uniquely versatile synthetic reagents which are easily prepared and relatively stable under normal laboratory conditions. They are penultamate precursors to a large variety of other compounds, *e.g.*, α-cyanoalkylidene-$\Delta^{\alpha,\beta}$-butenolides,[3] 2-cyano-4-cyclopentene-1,3-diones,[4] azepine-2,5-diones,[5] diacyl cyanides,[6] 3-cyano-2-aza-1,4-quinones,[7] aminoquinones,[8] cyanoketenes,[9] 4-acetoxy-1,2-quinone-2-(*N*-acetyl)imines,[10] *trans,trans*-1,4-

diacetoxy-*cis,cis*-1,4-dicyano-1,3-butadienes[10] and 2-alkenyl-2,3-dihydroindole-4,7-diones.[11] Reported here are the results of an investigation of the thermal decomposition of 2-azido-3-vinyl-1,4-quinones (**1**), a reaction giving high yields of indolequinones (**2**). This transformation constitutes a new nonoxidative route to indolequinones, a ring system whose synthesis has been dominated by the Fremy salt (potassium nitrosodisulfonate)[12] oxidations of variously substituted hydroxy and aminoindoles.[13] Unfortunately, such substituted indoles cannot be obtained in good yields by any published methods and, of course, no substituents can reside on the indole nucleus which are labile to the oxidative conditions employed. These disadvantages are circumvented by the nonoxidative thermal ring closure of the 2-azido-3-vinyl-1,4-quinones (**1a–f**) reported here.

Synthetic Scope. Thermolysis of the azidoquinones (**1a–f**) in refluxing benzene results in their smooth transformation to the respective indolequinones (**2a–f**) (Scheme I). In most cases these products precipitate from the cooled reaction solution in good to excellent yield and in a high state of purity.

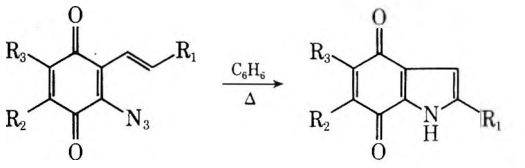
The structures of the indolequinones (**2a–f**) are based primarily upon their analytical and spectral properties which are in good agreement with their formulations (Experimental Section). Their ir spectra show particularly characteristic absorptions at 3400 cm^{-1} (NH) and 1675 and 1645 cm^{-1} (C=O), and their nmr spectra show the proper absorptions and proton counts.

Interestingly, these ring closures can also be accomplished under photolytic or acidic conditions. Photolysis of benzene solutions of the azidoquinones (**1a**, **1b**, and **1d**) with 3600-Å light gave the respective indolequinones (**2a**, **2b**, and **2d**). None of these reactions was allowed to go to completion since the precipitated product nearly filled the reaction tube after a few hours. However, if the recovered starting material is taken into account, the yields are nearly quantitative. When the quinones (**1a**, **1b**, and **1d**) were decomposed in concentrated sulfuric acid at 0° the corresponding indolequinones (**2a**, 67%; **2b**, 93%; and **2d**, 24%) were again isolated. This was a most unanticipated result since *all* other azidoquinones thus far studied rearrange under such acidic reaction conditions to γ-cyanoalkylidene-$\Delta^{\alpha,\beta}$-butenolides.[3] The mechanism of the formation of indolequinones under these acidic conditions is not clear. However, based upon analogy with the mechanism of butenolide formation[3] the following sequence involving the intermediate iminodiazonium ion (**3**) is envisaged.



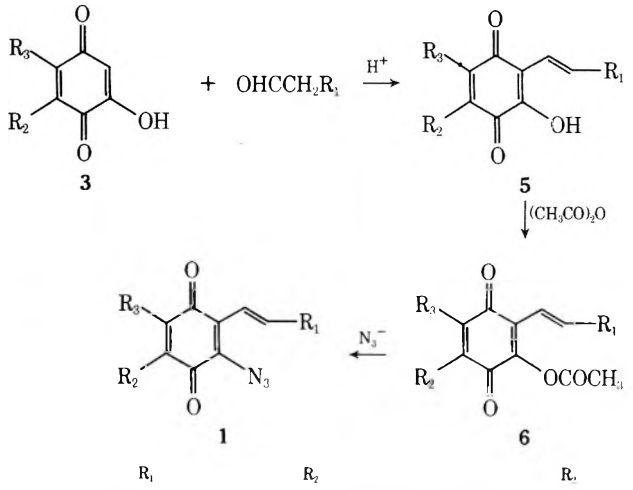
The synthesis of indolequinones as described herein is of particular utility since the starting materials are readily available. Several routes are reported for the construction of vinyl substituted quinones and hydroquinones;[14] these include (1) the decarboxylation of 2,5-dihydroxycinnamic acids,[15] (2) the reduction of 2,5-dihydroxyacetophenone and subsequent dehydration,[15] (3) the reactions of Grignard reagents of hydroquinone diethers and ethylene oxide or acetaldehyde with subsequent dehydration,[15] (4) the reactions of 3-chloromethyl-4-methoxy-2-methyl-1-naphthol pivalate which is converted into the triphenyl phosphonium salt and then to vinyl derivatives by the Wittig reaction,[14] (5) the reactions of 1-hydroxy-4-methoxy-2-methyl-3-naphthaldehyde and an alkylidenetriphenylphosphorane,[14] (6) the condensation of aliphatic aldehydes with 2-hydroxy-1,4-naphthoquinone in the presence of a strong acid.[16] For the study now reported, this last method was employed since the 2-hydroxyl moiety could be converted to the desired azide *via* the corresponding acetate and its subsequent displacement with azide ion (Scheme II). This synthesis provides a general approach to a large variety of 2-azido-3-vinyl-1,4-quinones, from 2-halo-[3,4] or 2-acetoxy-3-vinyl-1,4-benzo- or -1,4-naphthoquinones, and, as a result, to the corresponding indolequinones.

Scheme I



	R_1	R_2	R_3	% yield
2a	$-CH_3$	$-CH{=}CHCH{=}CH-$		90
2b	$-CH_2CH_2CH_3$	$-CH{=}CHCH{=}CH-$		81
2c	$-CH_2(CH_2)_8CH_3$	$-CH{=}CHCH{=}CH-$		87
2d	$-C_6H_5$	$-CH{=}CHCH{=}CH-$		92
2e	$-CH_2-(CH_2)_2-OCOCH_3$	$-CH{=}CHCH{=}CH-$		88
2f	$-C_6H_5$	$-CH_3$	$-CH_3$	66

Scheme II



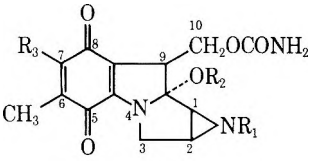
	R_1	R_2	R_3
a	$-CH_3$	$-CH{=}CHCH{=}CH-$	
b	$-CH_2CH_2CH_3$	$-CH{=}CHCH{=}CH-$	
c	$-CH_2(CH_2)_8CH_3$	$-CH{=}CHCH{=}CH-$	
d	$-C_6H_5$	$-CH{=}CHCH{=}CH-$	
e	$-CH_2-(CH_2)_2-OCOCH_3$	$-CH{=}CHCH{=}CH-$	
f	$-C_6H_5$	$-CH_3$	$-CH_3$

Synthetic Utility. The mitomycins (**7**) constitute a synthetically challenging and biologically potent class of naturally occurring antineoplastic antibiotics.[17] Several attempts directed toward their laboratory construction

Table I
Rate of Decomposition of 2-Azido-3-(1-propenyl)-1,4-naphthoquinone as a Function of Temperature and Solvent

Temp, °C	Solvent	Time, sec^{-1}
64.30	Benzene	2.35×10^{-4}
64.30	Chlorobenzene	2.20×10^{-4}
64.30	Chlorobenzene	2.14×10^{-4}
64.30	Chlorobenzene	2.23×10^{-4}
53.65	Chlorobenzene	6.02×10^{-5}
53.65	Chlorobenzene	6.06×10^{-5}
53.65	Chlorobenzene	5.93×10^{-5}
81.38	Chlorobenzene	1.39×10^{-3}
81.38	Chlorobenzene	1.55×10^{-3}
81.38	Chlorobenzene	1.36×10^{-3}
64.30	*o*-Dichlorobenzene	2.04×10^{-4}
64.30	Dimethylformamide	2.13×10^{-4}

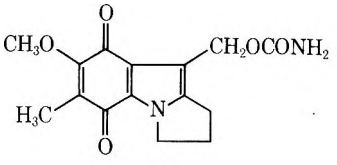
have appeared,[18] but, to date, such an objective has not been achieved.



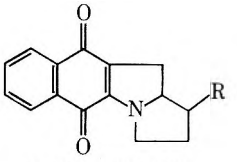
7

	R_1	R_2	R_3
Mitomycin A	H	CH_3	CH_3O
N-Methylmitomycin	CH_3	CH_3	CH_3O
Mitomycin B	CH_3	H	CH_3O
Mitomycin C	H	CH_3	NH_2
Porfiromycin	CH_3	CH_3	NH_2
7-Hydroxyporfiromycin	CH_3	CH_3	OH

One beauty of the mitomycins lies in the fact that a reasonably well-documented mechanism for their biological action has been put forward.[17] Extensive degradative studies have shown that for maximum biological potency the quinone nucleus and alkylating sites at C-1 (aziridine) and C-10 (carbamoyl) are necessary.[19] Therefore, detailed studies leading to versatile new ways in which such structural features can be easily incorporated into the molecular framework of the mitomycin and mitosene ring systems are clearly warrented. Pivotal contributions have been made by the Lederle[18a,b] group who have reported the synthesis of 7-methoxymitosene (8),[18b] a mitomycin analog showing marked *in vivo* activity against gram (+) bacteria. More recently, 1-substituted 7-methoxymitosenes, prepared analogously to the Lederle synthesis, were described.[18c] Also, Carelli, Cardellini, and Morlaichi[18g] have described the synthesis of 1-substituted 1,2,5,10-tetrahydro-3*H*-pyrrolo[1,2-*a*]benzo[*f*]indole-5,10-diones (9) by



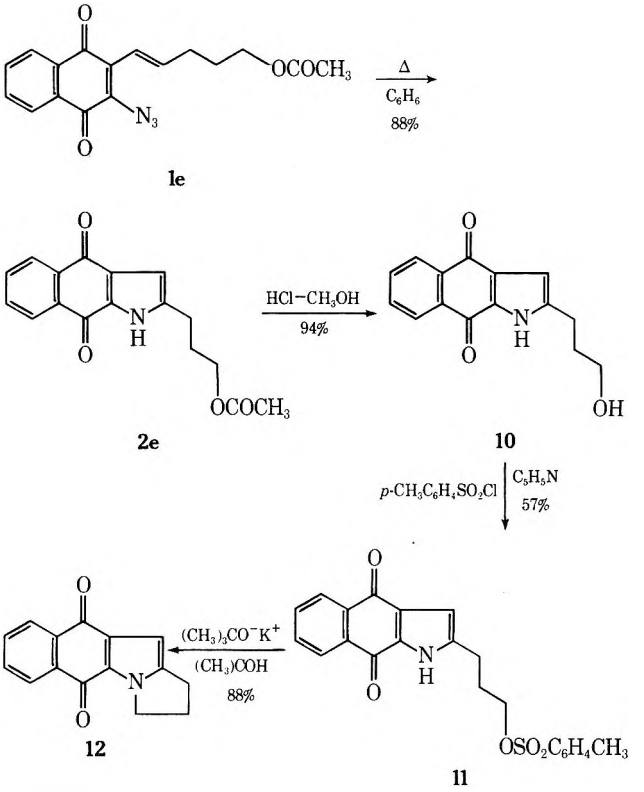
8



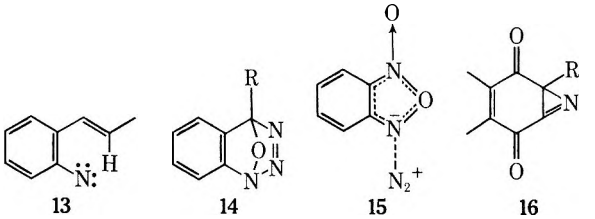
9, R = $NHCOCH_3$
R = NH_2
R = OH

the Friedel–Crafts acylation of 1-acetamido-1,2-dihydropyrrolizine with phthalic anhydride. One fundamental synthetic disadvantage of most of these reported synthetic approaches[18] to the mitomycins and related mitosenes lies in the fact that the quinone nucleus is constructed during the sequence. This often requires oxidative conditions which can cause the transformation to suffer in yields and selectivity.

The thermal ring closure of 2-azido-3-vinyl-1,4-quinones to indolequinones commences with the quinone nucleus intact. The utilization of this procedure for the elaboration of **12**, the naphthoquinone analog of the mitosene ring system, in seven steps from commercially available starting materials is now presented. Hydrolysis of 2-(3-acetoxypropyl)benzo[*f*]indole-4,9-dione (**2e**) in refluxing aqueous methanolic hydrogen chloride gave the alcohol **10** in 94% yield. Reaction of this alcohol with *p*-toluenesulfonyl chloride in pyridine gave the tosylate **11** in 57% yield which upon reaction with potassium *tert*-butoxide in *tert*-butyl alcohol gave **12** in 88% yield.

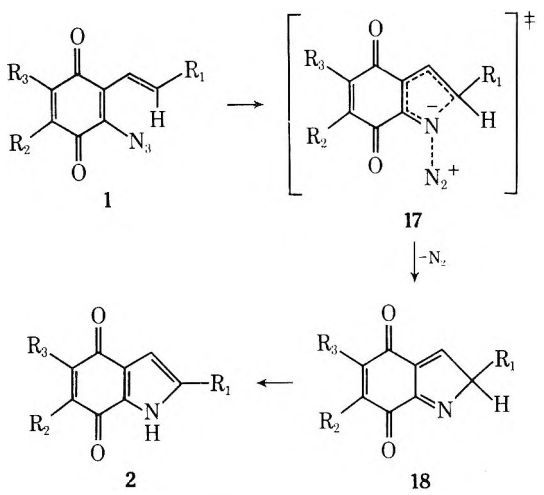


Mechanism. The closest analogies upon which to consider a mechanistic pathway for the pyrolytic conversion of 2-azido-3-vinyl-1,4-quinones to indolequinones are the observed transformations of various ortho-substituted phenyl azides to heterocyclic systems. For those compounds in which the ortho substituent has some type of α,β unsaturation, a variety of mechanistic routes have been suggested. o-Styryl azides efficiently ring close to indoles[20] under thermal conditions and nitrenes have been suggested as intermediates (**13**).[21] On the other hand, 2-azidobenzophenones cyclize to 3-phenylanthranils by a mechanism which apparently involves an initial cycloaddition of the azide group to the carbonyl moiety to give a triazole intermediate (**14**).[22] Finally, a concerted pathway, involving anchimeric assistance, *i.e.*, **15**, is strongly suggested for the thermal conversion of o-nitrophenyl azides to furoxans.[23] Consideration was given to these as well as to the feasibility of an azirine intermediate (**16**) which has



13 14 15 16

Scheme III

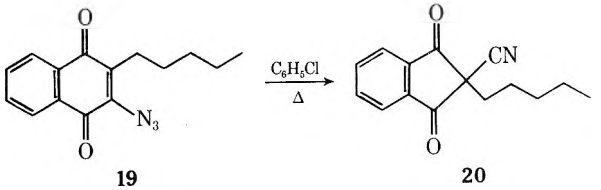


recently been shown to be generated in the thermal rearrangement of 2-azido-3-alkyl-1,4-quinones to 2-cyano-2-alkyl-4-cyclopentene-1,3-diones.[4]

The mechanism for the thermal conversion of 2-azido-3-vinyl-1,4-quinones (**1**) to the corresponding heterocyclic quinones (**2**) which best fits the available data is outlined in Scheme III. This involves anchimeric assistance by the 3-vinyl group in nitrogen loss giving the intermediate (**18**) which then tautomerizes to the observed products (**2**).

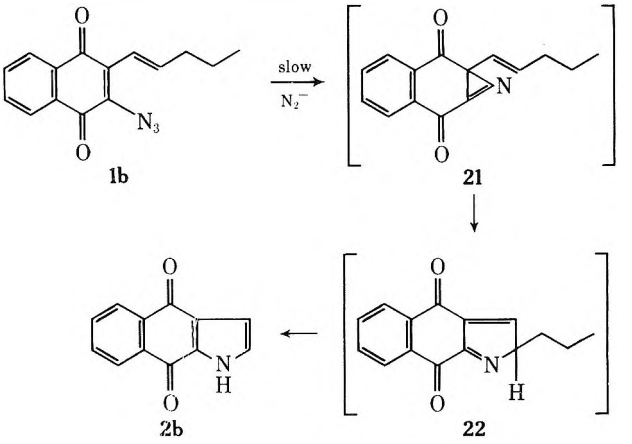
The above mechanism is based primarily upon a kinetic investigation of the thermal conversion of 2-azido-3-(1-pentenyl)-1,4-naphthoquinone (**1b**) to 2-propylbenzo[*f*]indole-4,9-dione (**2b**). The azidoquinone **1b** was thermally decomposed and the rate of nitrogen evolution was measured at three different temperatures and in several different solvents. Virtually no solvent effect was observed on the rate of decomposition of **1b** even though the range in solvent dipole moments varied from 2.30 (benzene) to 37.60 D (dimethylformamide) (Table I). The activation parameters for this clean first-order process follow: ΔH^* = 25.64 kcal mol^{-1}, ΔS^* = +0.43 eu.

For a comparison, the rate of the thermal decomposition of 2-azido-3-pentyl-1,4-naphthoquinone (**19**), the dihydro analog of **1b**, was also measured. This azidoquinone, now having a 3-alkyl substituent rather than a vinyl group, smoothly undergoes the known[4] ring contraction giving 2-cyano-2-pentyl-1,3-indandione (**20**). In chlorobenzene at 72.19° the rate of this reaction is 32 times slower than that for **1b** under the same conditions. The vinyl group in **1b** thus plays a direct role in nitrogen loss, and this participation is envisaged as represented by structure **17**.



The above experimental data are in good agreement with the mechanistic route outlined in Scheme III. A nitrene intermediate cannot account for the rate enhancement of **1b** over **19**. In addition, those reactions known to proceed *via* nitrenes show large positive enthalpies and entropies of activation. For example, the thermal decomposition of *p*-toluenesulfonyl azide, phenyl azide, and cyclohexyl azide show respectively the following activation parameters: ΔH^* = 36.5 kcal mol^{-1}, ΔS^* = +7.0 eu (*p*-toluenesulfonyl azide);[24] ΔH^* = 39.0 kcal mol^{-1}, ΔS^* = +18.7 eu (phenylazide);[25] ΔH^* = 47.5 kcal mol^{-1}, ΔS^* = +32.0 eu (cyclohexyl azide).[25] Comparison of these to ΔH^* = 25.64 kcal mol^{-1} and ΔS^* = 0.43 eu for **1b** argue against a nitrene mechanism for the thermal decomposition of **1b**. The entropy of activation for this reaction is also not in agreement to that which would be expected for a mechanism involving an intramolecular cycloaddition of the azide to the vinyl double bond giving a triazole analogous to **14**. Such a process would be expected to show a large negative entropy of activation. For example, in the addition of phenyl azide to alkenes, values of −30 to −35 eu have been reported.[26] For an intramolecular process ΔS^* would certainly be less negative but not actually positive as is observed here. Indeed, the thermal conversion of 2-azidobenzophenones to 3-phenylanthranils has been shown to involve such an intramolecular 1,3-dipolar cycloaddition giving **14** and the observed entropies of activation range from −6 to −21 eu.[22]

A conceivable mechanism for the cyclization reaction reported here would involve the concerted formation of the azirine **21** followed by ring expansion and subsequent tautomerization to **2b**. There are, in fact, literature precedents for these steps; *i.e.*, 2-azido-3-alkyl-1,4-quinones rearrange to 2-cyano-2-alkyl-4-cyclopentene-1,3-diones *via* an initial rate-determining azirine formation step[4] and 1-azido-1,3-butadienes thermally or photolytically decompose and rearrange to pyrroles *via* an intermediate vinyl substituted azirine.[27] This mechanism would predict that



the activation parameters for the conversion of **1b** to **2b** would be in the same range as those observed for the ring contraction of 2-azido-3-alkyl-1,4-quinones to 2-cyano-2-alkyl-4-cyclopentene-1,3-diones. This is in fact true; the enthalpies of activation for this latter reaction range from 26 to 27.6 kcal mol^{-1} and the entropies of activation from −4.6 to +1.6 eu.[4] However, the above mechanism does not account for the fact that 2-azido-3-pentyl-1,4-naphthoquinone (**19**) decomposes 32 times slower than 2-azido-3-(1-pentenyl)-1,4-naphthoquinone (**1b**), and for this reason the azirine mechanism is disregarded. This leaves as the most reasonable possibility, the mechanism outlined in Scheme III. Such a process would be expected to show a moderate ΔH^* and a very small if not negative ΔS^*. It should show little if any solvent effect and the absolute rate should be enhanced over that observed for the 2-alkyl series **19**. As indicated above, all such criteria were experimentally verified.

Experimental Section

2-Methylbenzo[*f*]indole-4,9-dione (2a). A solution of 103.3 mg (0.432 mmol) of 2-azido-3-(1-propenyl)-1,4-naphthoquinone (**1a**) in 15 ml of anhydrous benzene was refluxed for 1 hr. Upon cooling to 5° the yellow crystalline indole (**2a**) precipitated giving 32.2 mg (90% yield), mp 304–305° dec.

Anal. Calcd for $C_{13}H_9NO_2$: C, 73.92; H, 4.29; N, 6.63. Found: C, 73.81; H, 4.33; N, 6.76.

Characteristic spectral properties for **2a** follow: ir (Nujol, cm^{-1}) 3300, 1675, 1645; nmr (DMSO-d_6, δ) 2.31 s (3), 6.45 s (1), 7.5–8.2 m (4); uv ($CHCl_3$, nm) 261.5 (34.4×10^3).

2-Propylbenzo[*f*]indole-4,9-dione (2b). A solution of 69.2 mg (0.259 mmol) of 2-azido-3-(1-pentenyl)-1,4-naphthoquinone (**1b**) in 10 ml of anhydrous benzene was refluxed for 55 min. The solution was then concentrated to 1 ml *in vacuo* and cooled which resulted in the precipitation of 50 mg (81% yield) of 2-propylbenzo-[*f*]indole-4,9-dione (**2b**), mp, 211–212°.

Anal. Calcd for $C_{15}H_{13}NO_2$: C, 75.31; H, 5.44; N, 5.86. Found: C, 75.05; H, 5.62; N, 5.90.

Characteristic spectral properties for **2b** follow: ir (Nujol, cm^{-1}) 3240, 1655, 1640; nmr (DMSO-d_6, δ) 0.91 t (3) J = 6.5 Hz, 1.3–1.9 m (2), 2.3–2.8 m (2), 6.43 bs (1), 7.5–8.2 m (4); uv ($CHCl_3$, nm) 263.0 (32.4×10^3).

2-Decylbenzo[*f*]indole-4,9-dione (2c). A solution of 103.3 mg (0.283 mmol) of 2-azido-3-(1-dodecenyl)-1,4-napthoquinone (**1c**) in 10 ml of anhydrous benzene was refluxed for 5 hr. The solution was cooled and 10 ml of petroleum ether (bp 60–110°) was added. Upon cooling at 5° for 12 hr, 72.7 mg (76% yield) of the indolequinone **2c** precipitated and was collected. The mother liquor was concentrated *in vacuo* and the residue was recrystallized from petroleum ether giving 10.3 mg of **2c**. This brought the total yield of 2-decylbenzo[*f*]indole-4,9-dione (**2c**) to 83 mg (87% yield), mp 154–155°.

Anal. Calcd for $C_{22}H_{27}NO_2$: C, 78.34; H, 8.01; N, 4.15. Found: C, 78.46; H, 8.01; N, 4.18.

Characteristic spectral properties for **2c** follow: ir (Nujol, cm^{-1}) 3200, 1670; nmr ($CDCl_3$, δ) 0.85 t (3), 1.10–1.47 m (16), 2.41–2.96 m (2), 6.59 bs (1), 7.57–8.34 m (4); uv ($CHCl_3$, nm) 262.0 (31.7×10^3).

2-Phenylbenzo[*f*]indole-4,9-dione (2d). A solution of 536.7 mg (1.78 mmol) of 2-azido-3-(2-phenylvinyl)-1,4-naphthoquinone (**1d**) in 50 ml of anhydrous benzene was refluxed for 2 hr. The solution was then cooled to 5° and 446.8 mg (92% yield) of 2-phenylbenzo-[*f*]indole-4,9-dione (**2d**) was collected, mp 304–305° dec.

Anal. Calcd for $C_{18}H_{11}NO_2$: C, 79.12; H, 4.03; N, 5.13. Found: C, 78.86; H, 4.13; N, 5.03.

Characteristic spectral properties for **2d** follow: ir (Nujol, cm^{-1}) 3220, 1670, 1635; nmr (DMSO-d_6, δ) 7.3–8.2 m; uv ($CHCl_3$, nm) 289.0 (32.8×10^3).

2-(3-Acetoxypropyl)benzo[*f*]indole-4,9-dione (2e). A solution of 100.9 mg (0.31 mmol) of 2-azido-3-(5-acetoxy-1-pentenyl)-1,4-naphthoquinone (**1e**) in 10 ml of anhydrous benzene was refluxed for 75 min and then cooled to 5°. The yellow crystalline precipitate which formed was collected and washed with petroleum ether. The crystals were then dried to give 81.0 mg (88% yield) of 2-(3-acetoxypropyl)benzo[*f*]indole-4,9-dione (**2e**), mp 180–181°.

Anal. Calcd for $C_{17}H_{15}NO_4$: C, 68.69; H, 5.05; N, 4.71. Found: C, 68.46; H, 4.85; N, 4.91.

Characteristic spectral properties of **2e** follow: ir (Nujol, cm^{-1}) 3140, 1730, 1670, 1640; nmr (DMSO-d_6) 1.71–2.24 m (2), 1.99 s (3), 2.71 t (2) J = 7 Hz, 4.00 t (2) J = 6.5, 7.31 s (1), 7.62–8.13 m (4); uv ($CHCl_3$, nm) 261.0 (33.2×10^3).

5,6-Dimethyl-2-phenylindole-4,7-dione (2f). A solution of 66.7 mg (0.24 mmol) of 2-azido-3-(2-phenylvinyl)-5,6-dimethyl-1,4-benzoquinone (**1f**) in 7 ml of anhydrous benzene was refluxed for 2.2 hr. Upon cooling at 5° for several hours 29.8 mg (66% yield) of 5,6-dimethyl-2-phenylindole-4,7-dione (**2e**) was collected, mp 291–292°.

Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.49; H, 5.18; N, 5.58. Found: C, 76.00; H, 5.23; N, 5.47.

Characteristic spectral properties of **2e** follow: ir (Nujol, cm^{-1}) 3260, 1670, 1640; nmr (DMSO-d_6) 1.98 s (6), 7.00 s (1), 7.32–8.07 m (5); uv ($CHCl_3$, nm) 280.5 (36.0×10^3).

Acid-Catalyzed Decomposition of 2-Azido-3-(1-propenyl)-1,4-napthoquinone (1a). Formation of 2-Methylbenzo[*f*]indole-4,9-dione (2a). 2-Azido-3-(1-propenyl)-1,4-naphthoquinone (**1a**) (102.9 mg, 0.4 mmol) was slowly added in very small portions to rapidly stirred cold (0–5°) concentrated sulfuric acid (10 ml). The solution turned dark and gas was evolved upon addition of the azide. After complete addition, the solution was stirred for an additional 5 min and then poured into water. The resulting precipitate (60.4 mg, 67% yield) was collected and shown to be 2-methylbenzo[*f*]indole-4,9-dione (**2a**) by comparison of its spectral properties to those of an authentic sample which was prepared as described above.

Acid-Catalyzed Decomposition of 2-Azido-3-(1-pentenyl)-1,4-napthoquinone (1b). Formation of 2-Propylbenzo[*f*]indole-4,9-dione (2b). 2-Azido-3-(1-pentenyl)-1,4-naphthoquinone (**1b**) (101.2 mg, 0.38 mmol) was slowly added to cold (0–5°) concentrated sulfuric acid (10 ml). Vigorous stirring was maintained throughout the addition. After complete addition, the reaction solution was stirred an additional 5 min and then poured into water. The resulting precipitate (83.9 mg, 93% yield) was collected and shown to be 2-propylbenzo[*f*]indole-4,9-dione (**2b**) by comparison of its spectral properties to those of an authentic sample.

Acid-Catalyzed Decomposition of 2-Azido-3-(2-phenylvinyl)-1,4-naphthoquinone (1d). Formation of 2-Phenylbenzo[*f*]indole-4,9-dione (2d). 2-Azido-3-(2-phenylvinyl)-1,4-naphthoquinone (**1d**) (110.9 mg, 0.37 mmol) was ground in a mortar with 0.4 g of calcium chloride. This mixture was then added in very small portions to 12 ml of rapidly stirred and cold (0–5°) concentrated sulfuric acid. The addition took 40 min and then the solution was allowed to return to room temperature with continued stirring. The solution was then poured into ice and the resulting precipitate recrystallized from benzene to give 24.2 mg (24% yield) of 2-phenylbenzo[*f*]indole-4,9-dione (**2d**), as determined by comparison of its spectral properties to those of an authentic sample.

Photolysis of 2-Azido-3-(1-propenyl)-1,4-naphthoquinone (1a). Formation of 2-Methylbenzo[*f*]indole-4,9-dione (2a). A solution of 130.6 mg (0.5 mmol) of 2-azido-3-(1-propenyl)-1,4-naphthoquinone (**1a**) in 15 ml of anhydrous benzene was irradiated with 3600-Å light for 1 hr while nitrogen was continuously passed through the solution. The solvent was then removed *in vacuo* and the residue analyzed by nmr which showed it to be a mixture of staring azide (30%) and 2-methylbenzo[*f*]indole-4,9-dione (**2a**) (70%). Trituration of the crude residue with benzene gave 51.7 mg (45% yield) of the indolequinone (**2a**).

Photolysis of 2-Azido-3-pentenyl-1,4-naphthoquinone (1b). Formation of 2-Propylbenzo[*f*]indole-4,9-dione (2b). A solution of 102.7 mg (0.39 mmol) of 2-azido-3-pentenyl-1,4-naphthoquinone (**1b**) in 10 ml of anhydrous benzene was irradiated with 3600-Å light for 2.5 hr while nitrogen was continuously passed throeugh the solution. Petroleum ether (4 ml) was then added and the solution cooled for several hours. The resulting precipitate (72.3 mg, 79% yield) was shown to be 2-propylbenzo[*f*]indole-4,9-dione (**2b**) by comparing its physical and spectral properties to those of an authentic sample.

Photolysis of 2-Azido-3-(2-phenylvinyl)-1,4-naphthoquinone (1d). Formation of 2-phenylbenzo[*f*]indole-4,9-dione (2d). A solution of 106.7 mg (0.35 mmol) of 2-azido-3-(2-phenylvinyl)-1,4-naphthoquinone (**1d**) in 11 ml of benzene was irradiated for 45 min with 3600-Å light while nitrogen was continuously passed through the solution. The precipitate which formed during this period was collected to give 29.1 mg (30% yield) of 2-phenylbenzo-[*f*]indole-4,9-dione (**2d**). The mother liquor was concentrated *in vacuo* and analyzed by nmr spectroscopy which showed it to be composed of approximately 50% starting azide and 50% **2d**.

2-Azido-3-(1-propenyl)-1,4-naphthoquinone (1a). To a solution of 380 mg (1.5 mmol) of 2-acetoxy-3-(1-propenyl)-1,4-naphthoquinone (**6a**)[16] in 25 ml of 95% ethanol was added 98 mg (1.5 mmol) of sodium azide dissolved in 2 ml of water. The reaction solution was stirred overnight and then 50 ml of water was added giving an orange precipitate. Recrystallization of this crystalline solid gave 50 mg (14% yield) of 2-azido-3-(1-propenyl)-1,4-naphthoquinone (**1a**), mp 112° dec.

Characteristic spectral properties of **1a** follow: ir (Nujol, cm^{-1}) 2100, 1645; nmr ($CDCl_3$, δ) 1.98 doublet of doublets (3) J = 6.2, 1.4 Hz, 6.57 d (1) J = 17 Hz, 7.10 m (1), 7.6–8.3 m (4).

2-Azido-3-(1-pentenyl)-1,4-naphthoquinone (1b). A solution of 2.1 g (7.4 mmol) of 2-acetoxy-3-(1-propenyl)-1,4-naphthoquinone (**6b**) in 200 ml of 95% ethanol was cooled to 5° and 0.53 g of sodium azide in 5 ml of water was added. The mixture was stirred for 12 hr and then 200 ml of water was added and the mixture cooled at −5° for an additional 12 hr. The resulting precipitate was collected and recrystallized from a chloroform–methanol–water mixture to give 0.51 g (26% yield) of yellow crystalline 2-azido-3-(1-propenyl)-1,4-naphthoquinone (**1b**), mp 70–71° dec.

Anal. Calcd for $C_{15}H_{13}N_3O_2$: C, 67.42; H, 4.87; N, 15.73. Found: C, 67.27; H, 4.77; N, 15.55.

Characteristic spectral properties for **1b** follow: ir (Nujol, cm^{-1}) 2105, 1660, 1625; nmr ($CDCl_3$, δ) 0.94 t (3) J = 6.5 Hz, 1.2–1.9 m (2), 2.0–2.5 m (2), 6.48 bd (1) J = 18 Hz, 6.8–7.4 m (1), 7.5–8.2 m (4); uv ($CHCl_3$, nm) 273.0 (24.8×10^3).

2-(1-Dodecenyl)-3-hydroxy-1,4-naphthoquinone (5c). A solution of 5.0 g (37.0 mmol) of 2-hydroxy-1,4-naphthoquinone in 85 ml of acetic acid was warmed to 75°, and 25 ml of concentrated hydrochloric acid and 41 ml of dodecanal were added. The resulting solution was rapidly stirred at 75–80° for 30 min and then poured into 300 ml of water and allowed to stand at ambient

temperature for 6 hr. The oily mixture was then extracted with 300 ml of benzene. The benzene solution was extracted with 1% sodium hydroxide (500 ml). This basic solution was then washed twice with benzene, acidified, and finally extracted with dichloromethane. The dried ($MgSO_4$) dichloromethane solution was concentrated *in vacuo* to give a brown oil which was absorbed onto 70 g of silica gel. This was then placed in a Soxhlet extraction thimble and extracted with petroleum ether (30–60°) for 14 hr. Evaporation of the solvent gave 34 mg of the crude orange solid 2-(1-dodecenyl)-3-hydroxy-1,4-naphthoquinone, mp 65–77°. This was then recrystallized from benzene–petroleum ether to give the pure product, mp 91–92°.

Characteristic spectral properties of **5c** follow: ir (Nujol, cm^{-1}) 3500, 1670; nmr ($CDCl_3$, δ) 0.87 t (3) J = 7 Hz, 1.12–2.56 m (16), 2.01–2.48 m (2), 6.49 d (1) J = 17 Hz, 6.80–7.27 m (1), 7.46–8.15 m (4).

2-Acetoxy-3-(1-dodecenyl)-1,4-naphthoquinone (6c). A solution of 34 mg (1.0 mmol) of 2-(1-dodecenyl)-3-hydroxy-1,4-naphthoquinone in 12 ml each of acetic anhydride and pyridine was allowed to stand at ambient temperature for 24 hr and then poured into ice. The resulting precipitate was filtered and washed with 5% sulfuric acid and then water to give 20 mg (52% yield) of the acetate (**6c**). Recrystallization from ethanol gave pure 2-acetoxy-3-(1-dodecenyl)-1,4-naphthoquinone (**6c**), mp 74–76°.

Characteristic spectral properties of **6c** follow: ir (Nujol, cm^{-1}) 1770, 1670; nmr ($CDCl_3$, δ) 0.84 t (3) J = 7 Hz, 1.12–2.56 m (16), 2.03–2.49 m (2), 2.36 s (3), 6.79–7.32 m (2), 7.53–8.18 m (4).

2-Azido-3-(1-dodecenyl)-1,4-naphthoquinone (1c). a solution of 1.75 g (4.9 mmol) of 2-acetoxy-3-(1-dodecenyl)-1,4-naphthoquinone in 75 ml of 95% ethanol was treated with 0.5 g (7.7 mmol) of sodium azide in 1 ml of water. The resulting dark solution was stirred at room temperature for 24 hr at −5°. The resulting precipitate was collected and recrystallized from chloroform–methanol (1:3) to give 30 mg (18% yield) of 2-azido-3-(1-dodecenyl)-1,4-naphthoquinone, mp 59–60°.

Characteristic spectral properties of (**1c**) follows: ir (Nujol, cm^{-1}) 2110, 1670; nmr ($CHCl_3$, δ) 0.88 t (3), 1.11–1.50 m (16), 2.05–2.49 m (2), 6.57 d (1) J = 17 Hz, 6.98–7.37 m (1), 7.64–8.22 m (4); uv ($CHCl_3$, nm) 273.0 (19.0 × 10^3).

2-Azido-3-(2-phenylvinyl)-1,4-naphthoquinone (1d). To a solution of 2.0 g (6.3 mmol) of 2-acetoxy-3-(2-phenylvinyl)-1,4-naphthoquinone (**6d**) in 400 ml of 95% ethanol was added 455 mg (7 mmol) of sodium azide in 10 ml of water. The resulting precipitate (1.76 g) was recrystallized from chloroform–methanol to give 1.1 g (58% yield) of red crystalline 2-azido-3-(2-phenylvinyl)-1,4-naphthoquinone (**1d**), mp 119° dec.

Anal. Calcd for $C_{18}H_{11}N_3O_2$: C, 71.76, H, 3.65; N, 13.95. Found: C, 71.56; H, 3.77; N, 13.93.

Characteristic spectral properties of **1d** follow: ir (Nujol, cm^{-1}) 2105, 1655; nmr ($CDCl_3$, δ) 7.1–8.3 m; uv ($CDCl_3$, nm) 290.0 (30 × 10^3).

2-Hydroxy-3-(5-hydroxy-1-pentenyl)-1,4-naphthoquinone (5e). A solution of 10.0 g (75 mmol) of 2-hydroxy-1,4-naphthoquinone in 175 ml of glacial acetic acid was heated to 80° and rapidly stirred while 30 ml of concentrated hydrochloric acid and 40 ml (3.75 mmol) of 5-hydroxypentanal were added. After an initial temperature rise to 85° the solution was maintained at 75–80° for 20 min and then poured into 1 l. of water. The resulting black oil was washed twice with 500-ml portions of 1% sodium hydroxide. This aqueous basic solution was acidified and then extracted twice with ether. Evaporation of the ether extract gave 3.09 g (16% yield) of the yellow-brown 2-hydroxy-3-(5-hydroxy-1-pentenyl)-1,4-naphthoquinone (**5e**). This solid could be used without further purification. However, it could be puried further by Soxhlet extraction using 30–60° petroleum ether to give 2-hydroxy-3-(5-hydroxy-1-pentenyl)-1,4-naphthoquinone as an orange solid, mp 100–110°.

Characteristic spectral properties of **5e** follow: ir (Nujol, cm^{-1}) 3470, 1675; nmr ($CDCl_3$, δ) 1.79 m (2), 2.30 t (2) J = 7 Hz, 3.65 t (2) J = 6.5 Hz, 6.33–7.04 m (2), 7.48–8.07 m (4).

2-Aceetoxy-3-(5-acetoxy-1-pentenyl)-1,4-naphthoquinone (6e). A solution of crude 2-hydroxy-3-(5-hydroxy-1-pentenyl)-1,4-naphthoquinone (3.09 g, 11.9 mmol) in 40 ml of a 1:1 mixture of acetic anhydride–pyridine was allowed to stand at ambient temperature for 24 hr. It was then poured into ice water and the resulting precipitate was chromatographed on 250 g of silica gel using dichloromethane as the eluent giving 2.37 g (58% yield) of 2-acetoxy-3-(5-acetoxy-1-pentenyl)-1,4-naphthoquinone (**6e**), mp 75–76°.

Anal. Calcd for $C_{19}H_{18}O_6$: C, 66.67; H, 5.26. Found: C, 66.93; H, 5.38.

Characteristic spectral properties for **6e** follow: ir (Nujol, cm^{-1}) 1760, 1730, 1670; nmr ($CDCl_3$, δ) 1.80 m (2), 2.02 s (3), 2.29 t (2) J = 6.5 Hz, 2.38 s (3), 4.07 t (2) J = 6.5 Hz, 6.18–7.22 m (2), 7.51–8.13 m (4).

2-Azido-3-(5-acetoxy-1-pentenyl)-1,4-naphthoquinone (1e). A solution of 1.53 g (4.48 mmol) of 2-acetoxy-3-(5-acetoxy-1-pentenyl)-1,4-naphthoquinone (**6e**) in 23 ml of 95% ethanol was treated with 1.45 g (22.4 mmol) of sodium azide in 5 ml of water. The solution was cooled to −5° and allowed to stand for 12 hr. The resulting yellow crystalline solid was collected giving 400 mg (27% yield) of 2-azido-3-(5-acetoxy-1-pentenyl)-1,4-naphthoquinone (**1e**), mp 41–42°.

Characteristic spectral properties of **1e** follow: ir (Nujol, cm^{-1}) 2100, 1725, 1670; nmr ($CDCl_3$, δ) 1.58–2.01 m (2), 2.03 s (3), 2.29 t (2) J = 6.5 Hz, 4.09 t (2) J = 6.5 Hz, 6.30–7.31 m (2), 7.52–8.13 m (4).

2,3-Dimethyl-5-hydroxy-6-(2-phenylvinyl)-1,4-benzoquinone (5f). A solution of 2,3-dimethyl-5-hydroxy-1,4-benzoquinone (4.20 g, 27.6 mmol) in 85 ml of glacial acetic acid was vigorously stirred at 75° while 14.2 ml of concentrated sulfuric acid and a solution of 16.2 ml of concentrated sulfuric acid, 16.2 ml of phenylacetaldehyde, and 16.2 ml of 95% ethanol was added. After 20 min at 75–80° the reaction solution was poured into water (800 ml). The resulting residue was washed several times with water, dissolved in benzene, and then extracted with 500 ml of 1% sodium hydroxide. Upon acidification 3.60 g (51% yield) of purple 2,3-dimethyl-5-hydroxy-6-(2-phenylvinyl)-1,4-benzoquinone (**5f**) was collected. Recrystallization from benzene–petroleum ether gave the pure product, mp 165–167°.

Anal. Calcd for $C_{16}H_{14}O_3$: C, 75.59; H, 5.51. Found: C, 75.71; H, 5.64.

Characteristic spectral properties of **5f** follow: ir (Nujol, cm^{-1}) 3350, 1625; nmr ($CDCl_3$, δ) 2.03 s (6), 5.27 s (1), 7.01–7.98 m (7).

2-Acetoxy-5,6-dimethyl-3-(2-phenylvinyl)-1,4-benzoquinone (6f). A solution of 3.60 g (14.2 mmol) of 2,3-dimethyl-5-hydroxy-6-(2-phenylvinyl)-1,4-benzoquinone (**5f**) in 10 ml of acetic anhydride–pyridine (1:1) was allowed to stand at ambient temperature for 12 hr and then poured into water. The resulting residue was chromatographed on 300 g of silica gel using dichloromethane as the eluent to give 90 mg (12% yield) of 2-acetoxy-5,6-dimethyl-3-(2-phenylvinyl)-1,4-benzoquinone (**6f**), mp 145–146°.

Anal. Calcd for $C_{18}H_{16}O_4$: C, 72.97; H, 5.41. Found: C, 72.64; H, 5.80.

Characteristic spectral properties of **6f** follow: ir (Nujol, cm^{-1}) 1670, 1650; nmr ($CDCl_3$, δ) 2.05 s (6), 2.38 s (3), 6.84–7.91 m (7); uv ($CHCl_3$, nm) 274.5 (19.6 × 10^3).

2-Azido-5,6-dimethyl-3-(2-phenylvinyl)-1,4-benzoquinone (1f). A solution of 942 mg (3.1 mmol) of 2-acetoxy-5,6-dimethyl-3-(2-phenylvinyl)-1,4-benzoquinone (**6f**) in 75 ml of 95% ethanol was treated with 228 mg (3.5 mmol) of sodium azide in 7 ml of water. It was then cooled to −5° and allowed to stand overnight. The precipitate which had formed was collected to give quantitatively the crude azide. Recrystallization from chloroform–methanol–water gave pure 2-azido-5,6-dimethyl-3-(2-phenylvinyl)-1,4-benzoquinone (**1f**), mp 87–88° dec.

Characteristic spectral properties for **1f** follow: ir (Nujol, cm^{-1}) 2100, 1645; nmr ($CDCl_3$, δ) 2.06 s (6), 7.02–8.15 m (7).

2-(3-Hydroxypropyl)benzo[*f*]indole-4,9-dione (10). A suspension of 2-(3-acetoxypropyl)benzo[*f*]indole-4,9-dione (197.3 g, 0.66 mol) in 20 ml of methanol, 4 ml of water, and 8 drops of concentrated hydrochloric acid was refluxed for 2 hr. It was then poured into water and cooled at −5° for 12 hr. The resulting yellow crystalline precipitate was collected to give 158.9 mg (94% yield) of 2-(3-hydroxypropyl)benzo[*f*]indole-4,9-dione (10), mp 214–216°.

Anal. Calcd for $C_{15}H_{13}NO_3$: C, 70.59; H, 5.10; N, 5.49. Found: C, 70.46; H, 5.03; N, 5.22.

Characteristic spectral properties of **10** follows: ir (Nujol, cm^{-1}) 3400, 3200, 1670, 1640; nmr (DMSO-d_6, δ) 1.94–2.37 m (2), 2.82 t (2) J = 7 Hz, 3.66 t (2) J = 6.5 Hz, 6.52 s (1), 7.67–8.28 m (4); uv ($CHCl_3$, nm) 262.5 (33.5 × 10^3).

2-(3-Tosylpropyl)benzo[*f*]indole-4,9-dione (11). A solution of 68.4 mg (0.27 mmol) of 2-(3-hydroxypropyl)benzo[*f*]indole-4,9-dione (**10**) and 108.3 mg (0.57 mmol) of *p*-toluenesulfonyl chloride in 1 ml of anhydrous pyridine was allowed to stand at ambient temperature for 24 hr. The reaction solution was then poured into water and the resulting yellow crystalline precipitate was collected to give 62.8 mg (57% yield) of 2-(3-tosylpropyl)benzo[*f*]indole-4,9-dione (**11**), mp 210–211°.

The infrared spectrum (Nujol) showed characteristic absorptions at 3250, 1645, and 1175 cm^{-1}.

1,2,5,10-Tetrahydro-3*H*-pyrrolo[1,2-α]benzo[*f*]indole-5,10-

dione (12). 2-(3-Tosylpropyl)benzo[*f*]indole-4,7-dione (0.0628 g, 0.000154 mol) was added under nitrogen to a solution consisting of potassium (0.0060 g, 0.000154 mol) dissolved in 1.5 ml of dry *tert*-butyl alcohol. The resulting purple suspension was magnetically stirred for 24 hr. At this time the yellow-green suspension was poured into 10 ml of water. The residue was collected by filtration and washed with water to give 0.0322 g (88% yield) og benzo[*f*]-pyrrolidinyl[1,2-α]indole-4,7-dione, mp 181–184°. An analytical sample, mp 188–189°, was obtained by recrystallization from chloroform–petroleum ether.

Anal. Calcd for $C_{15}H_{11}NO_2$: C, 75.95; H, 4.64, N, 5.91. Found: C, 75.76; H, 4.60; N, 6.02.

Characteristic spectral properties of **12** follow: ir (Nujol, cm^{-1}) 1660; nmr ($CDCl_3$, δ) 2.33–3.07 m (4), 4.33 t (2) J = 6.5 Hz, 6.41 s (1), 7.54–8.35 m (4); uv ($CHCl_3$, nm) 262.0 (33.5 × 10^3).

2-Acetoxy-3-pentyl-1,4-naphthoquinone. 2-Hydroxy-3-pentyl-1,4-naphthoquinone[16] (10.0 g, 0.039 mol) was suspended in 40 ml each of acetic anhydride and pyridine. This solution was allowed to stand overnight at room temperature. It was then poured into ice–water and extracted with ether. The ether layer was washed with 5% sulfuric acid solution and with water and then dried over anhydrous magnesium sulfate. Filtration and evaporation of the solvent gave a red semisolid. This was dissolved in an equal volume (approximately 50 ml) of hot 95% ethanol and cooled in the freezer. The yellow crystals were collected and dried to give 7.0 g. (63% yield) of 2-acetoxy-3-pentyl-1,4-naphthoquinone. This was recrystallized from ethanol to give the clean product, mp 56–57°.

Anal. Calcd for $C_{17}H_{18}O_4$: C, 71.33; H, 6.29. Found: C, 71.27; H, 6.33.

Characteristic spectral properties of 2-acetoxy-3-pentyl-1,4-naphthoquinone follow: ir (Nujol, cm^{-1}) 1670; nmr ($CDCl_3$, δ) 0.89 t (3) J = 6 Hz, 1.08–1.68 m (6), 2.40 s (3), 2.49 q (2) J = 6 Hz, 7.63–8.30 m (4).

2-Azido-3-pentyl-1,4-naphthoquinone (19). 2-Acetoxy-3-pentyl-1,4-naphthoquinone (3.1 g, 0.011 mol) was dissolved in 30 ml of 95% ethanol by heating. When the solution had cooled to room temperature sodium azide (0.72 g, 0.011 mol) in 3 ml of water was added slowly with swirling. The solution turned dark and was allowed to stand at room temperature for 10 min. The solution was then put into the refrigerator for 18 hr. The precipitate which formed was collected, washed with a liitle methanol–water (5:1), and dried. This gave 1.5 g (51% yield) of yellow 2-azido-3-pentyl-1,4-naphthoquinone (**19**). This was recrystallized from ethanol and water to give the clean product, mp 64–66°.

Characteristic spectral properties of **19** follow: ir (Nujol, cm^{-1}) 1670 and 1640; nmr ($CDCl_3$, δ) 0.90 t (3) J = 6 Hz, 1.12–1.74 m (6), 2.58 t (2) J = 7 Hz, 7.64–8.30 m (4).

2-Cyano-2-pentyl-1,3-indandione (20). 2-Azido-3-pentyl-1,4-naphthoquinone (0.1210 g, 0.00045 mol) was refluxed in 15 ml of dry benzene for 18 hr. The solution was then rotary evaporated to a brown-gold oil. This residue was then chromatographed on a silica gel column with benzene as the solvent. A light yellow band came off first and was discarded. This was followed by another yellow band which upon evaporation of the solvent gave 0.0800 g (74% yield) of 2-cyano-2-pentyl-1,3-indandione as a light brown oil. This was recrystallized with great difficulty from petroleum ether to give the clean white product, mp 30.5–31°.

Characteristic spectral properties of **20** follow: ir (neat, cm^{-1}) 2230, 1755, 1730; nmr ($CDCl_3$, δ) 0.85 t (3), 1.06–1.68 m (6), 2.10 q (2), 8.04 s (4). These data are analogous to those reported for 2-cyano-2-methyl-1,3-indandione which was prepared by the thermolysis of 2-azido-3-methyl-1,4-naphthoquinone.[4]

Procedure for the Kinetic Runs of 2-Azido-3-(1-pentenyl)-1,4-naphthoquinone and 2-Azido-3-pentyl-1,4-naphthoquinone. The apparatus used was that described by Martin and Timberlake.[28] The solvent (10 ml) was equilibrated in the constant temperature bath with the system open to the atmosphere and then 0.08 g (0.0003 mol) of 2-azido-3-(1-pentenyl)-1,4-naphthoquinone or 0.06 g (0.0002 mol) of 2-azido-3-pentyl-1,4-naphthoquinone dissolved in 0.5 ml of the solvent was injected. Nitrogen was bubbled through the solution for 90 sec before the system was closed and the rate of the increasing pressure recorded. The reaction was allowed to go to completion in order to obtain a P_∞. The rate constants were obtained by having a computer program plot first the natural logarithm of the quantity ($P_\infty - P$) *vs.* time and then determine the slope of this line. The program also ran a least-squares fit of the points and varied the P_∞ value in order to obtain the smallest deviation. The azidoquinones used were pure as determined by their melting point, and the solvents employed were purified immediately before use.

Registry No.—**1a,** 42244-91-7; **1b,** 42244-92-8; **1c,** 42244-93-9; **1d,** 42244-94-0; **1e,** 42244-95-1; **1f,** 42244-96-2; **2a,** 42244-97-3; **2b,** 42244-98-4; **2c,** 42244-99-5; **2d,** 42207-71-6; **2e,** 42245-00-1; **2f,** 42245-01-2; **5c,** 49827-67-0; **5e,** 49827-68-1; **5f,** 49827-69-2; **6a,** 49827-70-5; **6b,** 49827-71-6; **6c,** 49827-72-7; **6d,** 49827-73-8; **6e,** 49827-74-9; **6f,** 49827-75-0; **10,** 42245-03-4; **11,** 42245-02-3; **12,** 42245-04-5; **19,** 49827-78-3; **20,** 49827-79-4; 2-hydroxy-1,4-naphthoquinone, 83-72-7; dodecanal, 112-54-9; 5-hydroxypentanal, 4221-03-8; 2,3-dimethyl-5-hydroxy-1,4-benzoquinone, 1760-68.5; phenylacetaldehyde, 122-78-1; 2-acetoxy-3-pentyl-1,4-naphthoquinone, 49827-81-8; 2-hydroxy-3-pentyl-1,4-naphthoquinone, 41245-53-8.

References and Notes

(1) A preliminary account of this work has appeared, P. Germeraad and H. W. Moore, *J. Chem. Soc., Chem. Commun.*, 358 (1973).
(2) The authors are grateful to the National Cancer Institute of the Public Health Service for Grant No. CA 11890-03 which partially supported this investigation.
(3) H. W. Moore, H. R. Shelden, D. W. Deters, and R. J. Wikholm, *J. Amer. Chem. Soc.*, **92**, 1675 (1970).
(4) W. Weyler, Jr., D. S. Pearce, and H. W. Moore, *J. Amer. Chem. Soc.*, **95**, 2603 (1973).
(5) H. W. Moore, H. R. Shelden, and W. Weyler, Jr., *Tetrahedron Lett.*, 1243 (1969).
(6) J. A. Van Allen, W. J. Priest, A. S. Marshall, and G. A. Reynolds, *J. Org. Chem.*, **33**, 1100 (1968).
(7) D. S. Pearce and H. W. Moore, unpublished data.
(8) L. F. Fieser and J. L. Hartwell, *J. Amer. Chem. Soc.*, **57**, 1482 (1935); H. W. Moore and H. R. Shelden, *J. Org. Chem.*, 33, 4019 (1968).
(9) W. Weyler, Jr., and H. W. Moore, *J. Amer. Chem. Soc.*, **93**, 2812 (1971).
(10) D. S. Pearce, M. S. Lee, and H. W. Moore, *J. Org. Chem.*, in press.
(11) P. Germeraad, Walter Weyler, Jr., and H. W. Moore, *J. Org. Chem.*, **9**, 781 (1974).
(12) H. Zimmer, D. C. Lankin and S. W. Horgan, *Chem. Rev.*, **71**, 229 (1971).
(13) H. J. Teuber, and G. Thaler, *Chem. Ber.*, **91**, 2253 (1958); H. J. Teuber and G. Staiger, *ibid.*, **87**, 1251 (1954); **92**, 2385, (1959); B. Clifford, P. Nixon, C. Salt, and M. Tomlinson, *J. Chem. Soc.*, 3516 (1961); G. R. Allen, J. F. Poletto, and M. J. Weiss, *J. Amer. Chem. Soc.*, **86**, 3878 (1964); W. A. Remers, P. N. James, and M. J. Weiss, *J. Org. Chem.*, **28**, 1169 (1963); G. R. Allen, J. F. Poletto, and M. J. Weiss, *J. Amer. Chem. Soc.*, **86**, 3887 (1964).
(14) W. E. Bondinell, S. J. DiMari, B. Frydman, I. Matsumoto, and H. Rapoport, *J. Org. Chem.*, **33**, 4351 (1968).
(15) H. C. Cassidy and K. A. Kun, *Polym. Rev.* **11**, 0000 (1965).
(16) S. C. Hooker, *J. Amer. Chem. Soc.*, **58**, 1163, 1168 (1936).
(17) W. Szybalski and V. N. Iyer in "Antibiotics," D. Gottlieb and P. D. Shaw, Ed., Springer-Velag, West Berlin, 1967, pp 211–245.
(18) (a) W. A. Remers, R. H. Roth, and M. J. Weiss, *J. Org. Chem.*, **30**, 2910 (1965); (b) G. R. Allen, Jr., J. F. Poletto, and M. J. Weiss, *ibid.*, **30**, 2997 (1965); (c) D. L. Fost, N. N. Ekwuribe, and W. A. Remers, *Tetrahedron Lett.*, 131 (1973); (d) T. Hirata, Y. Yamada, M. Matsui, *ibid.*, 4107 (1969); (e) R. W. Franck and K. F. Bernady, *J. Org. Chem.*, **33**, 3050 (1968); (f) R. W. Franck and J. Auerbach, *ibid.*, **36**, 31 (1971); (g) V. Carelli, M. Cardellini, and F. Morlacchi, *Tetrahedron Lett.*, 765 (1967); (h) R. J. Friary, J. M. Gilligan, R. P. Szajewski, K. J. Falci, and R. W. Franck, *J. Org. Chem.*, **38**, 3487 (1973).
(19) (a) S. Oboski, M. Matsui, S. Ishii, N. Masago, S. Wakaki, and K. Uzu, *Gann*, **58**, 315 (1967); (b) S. Kinoshita, K. Uzu, K. Nakano, M. Shimizu, and T. Takahashi, *J. Med. Chem.*, **14**, 103 (1971).
(20) R. J. Sundberg, H. F. Russell, W. V. Ligon, Jr., and L. S. Lin, *J. Org. Chem.*, **37**, 719 (1972).
(21) D. V. Banthorpe, "The Chemistry of the Azido Group," S. Patai, Ed., Interscience, New York, N. Y., 1971.
(22) J. H. Hall, F. E. Behr, and R. L. Reed, *J. Amer. Chem. Soc.*, **94**, 4952 (1972).
(23) L. K. Dyall and J. E. Kemp, *J. Chem. Soc. B*, 976 (1968).
(24) D. S. Breslow, M. F. Sloan, M. F. Newburg, and N. B. Renfrow, *J. Amer. Chem. Soc.*, **91**, 2273 (1969).
(25) P. Walker and W. A. Waters, *J. Chem. Soc.*, 1632 (1962).
(26) P. Scheiner, J. H. Schomaker, S. Deming, W. J. Libbey, and G. P. Nowack, *J. Amer. Chem. Soc.*, **87**, 306 (1965).
(27) K. Isomura, M. Okada, and H. Taniguchi, *Chem. Lett.* 1 (7), 629 (1972); *Chem. Abstr.*, **77**, 87555 (1972).
(28) J. C. Martin and J. W. Timberlake, *J. Amer. Chem. Soc.*, **92**, 978 (1970).

Rearrangements of Azidoquinones. XIII. Synthesis of 2-Alkenyl-2,3-dihydroindole-4,7-diones

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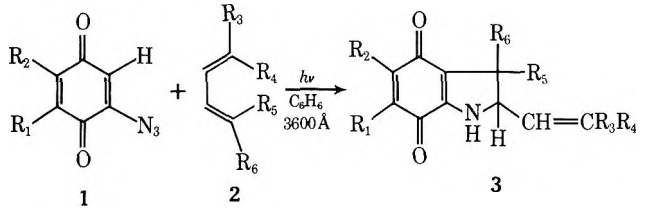
Received August 20, 1973

2-Azido-1,4-quinones which are unsubstituted at position 3 react with acyclic and cyclic dienes upon photolysis with 3600-Å light to give 2-alkenyl-2,3-dihydroindole-4,7-diones. The synthetic scope of this new reaction as well as its mechanism are discussed.

The preceding manuscript describes the facile thermal ring closure of 2-azido-3-vinyl-1,4-quinones to 2-alkyl- (or aryl-) indole-4,7-diones (indolequinones).[3] Described here is a related synthetic transformation which results in the formation of 2-alkenyl-2,3-dihydroindole-4,7-diones. Specifically, photolysis of azidoquinones (**1**) in the presence of various 1,3-dienes (**2**) results directly in the formation of the heterocyclic quinones (**3**), a transformation without precedent in quinone chemistry as well as in the photochemistry of organic azides. The general synthetic scope of this transformation is outlined by the equations shown in Scheme I which describe the reactions of 2-azido-5-*tert*-butyl-1,4-benzoquinone, 2-azido-5-methyl-1,4-benzoquinone and 2-azido-1,4-naphthoquinone with acyclic and cyclic dienes.

Scheme I

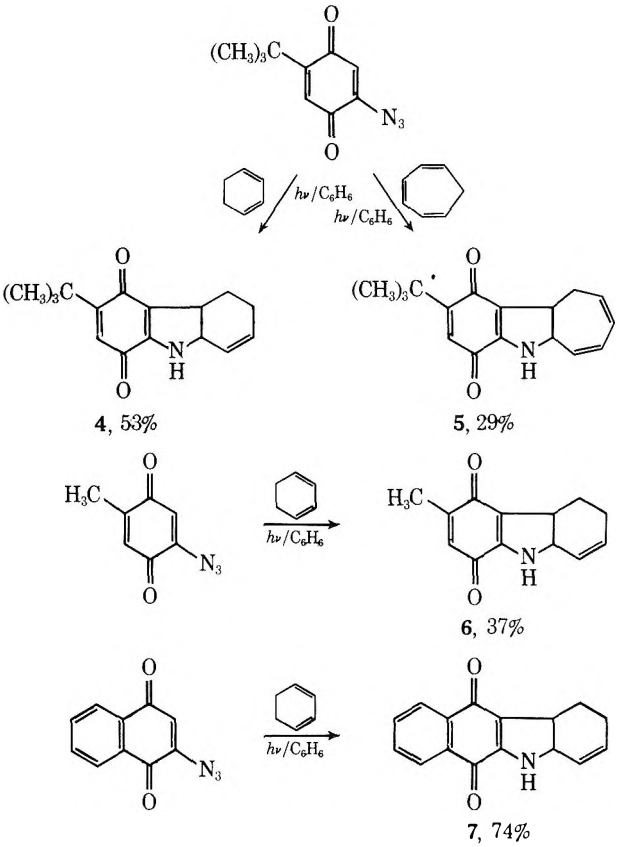


1 **2** **3**

	R_1	R_2	R_3	R_4	R_5	R_6	% yields
3a	H	$C(CH_3)_3$	CH_3	H	H	H	96
3b	H	$C(CH_3)_3$	H	CH_3	H	H	73
3c	H	$C(CH_3)_3$	CH_3	H	H	CH_3	66
3d	H	$C(CH_3)_3$	H	CH_3	CH_3	H	53
3e	H	CH_3	CH_3	H	H	H	40
3f	H	CH_3	H	CH_3	CH_3	H	84
3g			CH_3	H	H	H	72
3h			H	CH_3	CH_3	H	82

The transformation which are shown are conveniently run by irradiating an oxygen-free benzene solution of the azidoquinone and diene (1:10) with 3600-Å light for several hours. The heterocyclic quinone products function as internal filters for the incident irradiation, and, as a result, the reactions were not generally run to completion. The resulting intensely colored dihydroindolequinones were isolated by column chromatography on silica gel using benzene–petroleum ether (5:1) as the eluent. The structures of these products are all based upon their spectral and analytical properties (Experimental Section) which are in good agreement with their formulations.

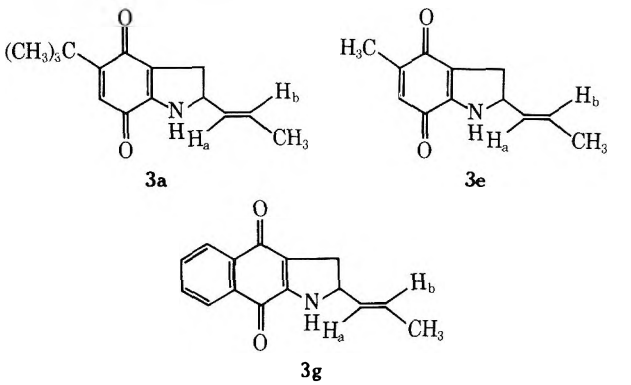
All of the reactions are *regiospecific*, giving only those isomers having the alkenyl group at the 2 position. This assignment is easily made on the basis of the chemical



4, 53% **5**, 29% **6**, 37% **7**, 74%

shifts, spin–spin coupling, and proton count of the absorption due to the proton at position 2 (Experimental Section).

The reaction is stereospecific, with reference to the alkene double bond, only when the acyclic diene employed was *trans*-1,3-pentadiene. In this case, the azidoquinones (**1**) all gave only one detectable isomer, *i.e.*, **3a**, **3e**, and **3g**, respectively, in which the 2-propenyl group maintains its trans geometry. This assignment of trans stereochemistry for the alkene group in **3a**, **3e**, and **3g** is based upon a computer similation of their nmr spectra.[5] The best fit for

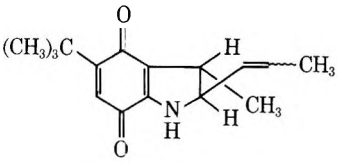


3a **3e** **3g**

the vinyl proton region was obtained when the coupling constant between the alkenyl protons (J_{HaHb}) was 15.47 Hz, which is completely in agreement with the trans geometry.[6]

The reactions of the azidoquinones (**1**) with all other acyclic dienes employed gave the corresponding 2,3-dihydroindole-4,7-diones in a stereoselective manner. That is, 2-azido-5-*tert*-butyl-1,4-benzoquinone photolytically reacts with *cis*-1,3-pentadiene to give **3a** and its cis 2-alkene isomer in a ratio of 1.0:1.3, respectively. Further, the reactions of the above azidoquinones (**1**) with *trans,trans*- and/or *cis,cis*-2,4-hexadiene provide a most interesting dual stereochemical problem which now concerns the geometry of the 2-propenyl group as well as the stereochemical relationship of this moiety to the 3-methyl substituent. Isomerization of the carbon–carbon double bond is again observed. The predominant geometry of this alkene moiety in the product is the same as that of the corresponding alkene bond in the starting diene. More exciting is the fact that *the major isomer(s) always has a cis relationship between the substituents at the 2 and 3 positions, regardless of the stereochemistry of the starting diene.* Concerning this point, 2-azido-5-*tert*-butyl-1,4-benzoquinone reacts with *trans,trans*-2,4-hexadiene to give the isomeric pairs, *trans*-2,3-dihydro-*cis*- and -*trans*-2-propenyl-5-*tert*-butylindole-4,7-dione (**8**) and *cis*-2,3-dihydro-*cis*- and -*trans*-2-propenyl-5-*tert*-butylindole-4,7-dione (**9**) in a relative ratio of 1.0:3.5, respectively. Interestingly, the same azidoquinone gives **8** and **9** in a relative ratio of 1.0:6.7, respectively, when treated with *cis,cis*-2,4-hexadiene under the same conditions. In a like manner, 2-azido-5-methyl-1,4-benzoquinone reacts photolytically with *cis,cis*-2,4-hexadiene giving **10** and **11** in a ratio of 1.0:4.5 and 2-azido-1,4-naphthoquinone reacts with the same diene giving **12** and **13** in a relative ratio of 1.0:1.4, respectively. The ratios of the cis to trans 2-propenyl stereochemistry as determined from their nmr spectra, in each of these respective isomeric pairs, are as follows: **8**–**9**, 1.0:1.6 from *trans,trans*-2,4-hexadiene; **8**–**9**, 1.0:0.16 from *cis,cis*-2,4-hexadiene; **10**–**11**, 1.0:0.48 from *cis,cis*-2,4-hexadiene; **12**–**13**, 1.0:0.81 from *cis,cis*-2,4-hexadiene.

There are conceivably four geometric isomers in each of the above pairs, *i.e.*, cis–cis, cis–trans, trans–cis, and trans–trans. It is assumed that all four isomers are present. However, all attempted separations failed (glc, tlc, recrystallization, sublimation). The nmr spectrum of each purified isomeric mixture did show absorptions for cis and trans 2-propenyl and cis and trans 3-methyl, and the above stereochemical assignments are based upon interpretations of these spectra. For example, a computer simulation of the vinyl region of the nmr spectrum obtained on the mixture of **8** and **9**, shown by nmr to be 86% enriched in the isomer or isomers having one stereochemical form of the 2-propenyl group, gave the best fit when the coupling constant was 10.51 Hz. Such a value is in good accord with cis geometry.[12] Also, decoupling experiments were carried out on this same mixture which was shown by the ratio of the two 3-methyl absorptions to be 87% enriched in the isomer or isomers having either a cis or a trans 2,3 relationship. These decoupling experiments indicate a cis 2,3 configuration in the major isomer(s). That is, irradiation of the 3-methyl absorption revealed that the coupling constant between the protons at the 2 and 3 positions in the major isomer(s) was equal to 7 Hz. A coupling constant of this magnitude is consistent for adjacent protons having a dihedral angle of 20 or 150°[8] which is in accord for only the cis relationship. Analogous decoupling of the mixture of **8** and **9**, obtained from the reaction of 2-azido-5-*tert*-butyl-1,4-benzoquinone with *trans,trans*-2,4-hexadiene again showed the major isomer(s) to also have the cis configuration between the 2,3 substituents. The trans 2-propenyl methyl group in the **8** and **9** isomeric mixture absorbs at 0.25 ppm upfield from that of the cis. Also, the 3-methyl in the major cis 2,3 isomer(s) absorbs 0.1 ppm downfield from that of the trans. Analogous differences were observed in the spectra of the **10** and **11** and **12** and **13** mixtures, and it is upon these data that their indicated stereochemical assignments have been made.



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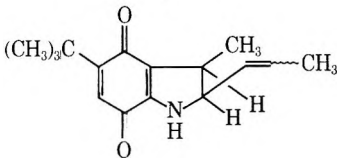
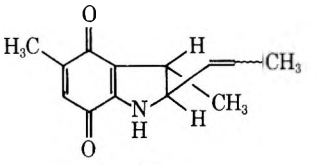


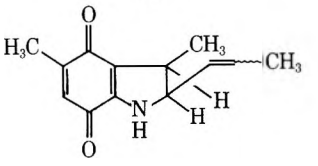
9

1.0[7a] : 3.5[7a]

1.0[7b] : 6.7[7b]

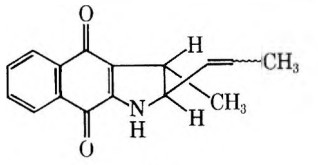


10

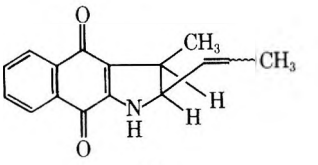


11

1.0 : 4.5



12

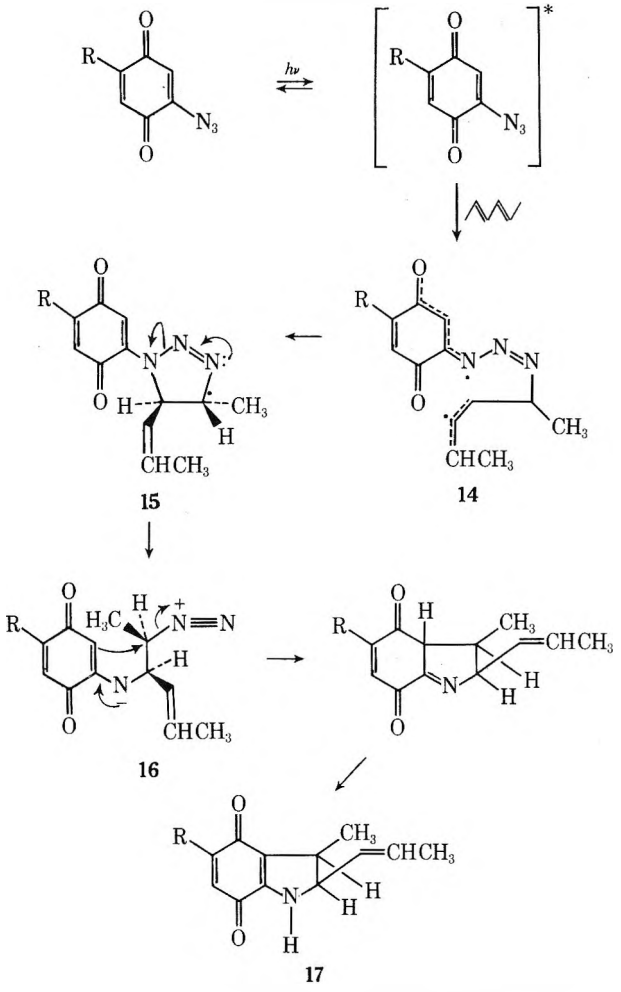


13

1.0 : 1.4

Not all attempts to extend the synthetic scope of this reaction have met with success. Electron rich alkenes such as dihydropyran, furan, and cyclopentene failed to react. The electron deficient alkene, diethyl maleate, also was unreactive. The same was true for the electron poor dienes such as *trans,trans*-1,4-dicarbomethoxy-1,3-butadiene and *trans,trans*-1,4-diacetoxy-1,4-dicyano-1,3-butadiene.[9] Concerning the quinone component, the reaction appears to be limited to those azidoquinones which are unsubstituted at the position adjacent to the azide group. For example, photolysis of 2-azido-3-methyl-1,4-naphthoquinone in the presence of excess 1,3-pentadiene gave only 2-cyano-2-methyl-1,3-indandione.[10] This intramolecular

Scheme II



rearrangement can be induced either thermally or photolytically and has previously been discussed.[10]

Mechanism. A mechanism for the formation of the 2-alkenyl-2,3-dihydroindole-4,7-diones, which is generally consistent with the available data, is outlined in Scheme II. Such a mechanism describes an unsensitized, photolytic, nonconcerted cycloaddition of the azidoquinone to the diene to give the intermediate Δ^2-triazoline (**15**), which collapses to product *via* the betaine intermediate **16**. This mechanism nicely accounts for the observed stereoselectivity of the reaction. That is, the diradical (or zwitterion) intermediate **14** could allow for the partial isomerization of the allyl double bond. This diradical could then ring close to give, as the major isomer, the Δ^2-triazoline intermediate **15** having the ring substituents in the more stable trans orientation. Such a trans stereochemical consequence would, of course, be expected to be independent of the stereochemistry of the starting diene. Thermal cleavage of the triazoline to the diazonium betaine **16** has precedence[11] and such a species could then undergo back-side displacement of nitrogen as indicated to give the *cis*-2,3-dihydroindoles (**17**) as the major products.[12] Not only does the diradical **14** account for 2-propenyl isomerization but it also rationalizes the regiospecificity of the reaction. That is, one would certainly predict that **14**, which ultimately leads to the 2-propenyl substitution pattern, is also the most stable possible diradical (or zwitterion) intermediate. In addition, the photolytic cycloaddition of an azide (π_4) to an alkene double bond (π_2) would be expected to be a nonconcerted process on the basis of orbital symmetry and thus involve a two-step sequence.

It is possible that the diradical **14** maintains the stereochemical integrity of the allyl radical and that the observed 2-propenyl isomerization results from secondary photochemical processes. That is, this isomerization may come from photochemical excitation of the alkene double bond in the product indoles **17**. The facts that allylic radicals, generated by other routes, have been shown to be stereochemically stable[13] and that intramolecular triplet energy transfer between a carbonyl and an alkene chromophore can result in alkene isomerization[14] are in agreement with this possibility.

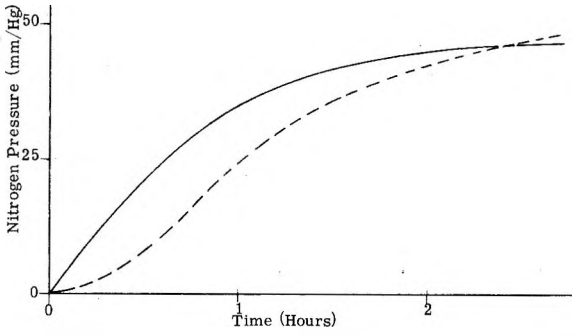


Figure 1. Rate of nitrogen evolution for the photolytic conversion of 2-azido-5-*tert*-butyl-1,4-benzoquinone and 1,3-pentadiene to 5-*tert*-butyl-2,3-dihydro-2-propenylindole-4,7-dione: (——) quinone in neat diene, (- - - -) 1% solution of quinone and diene in benzene.

The formation of the indoles **17** is indeed initiated by an unsensitized photochemical process. This was established by the observation that 2-azido-5-*tert*-butyl-1,4-benzoquinone did not react with 1,3-pentadiene under thermal conditions (ambient temperature) in the dark. However, photolysis of these components in either benzene or cyclohexane with 3600 Å light or with light greater than 4000 Å (sun lamp through a glass filter) readily resulted in 2,3-dihydroindole-4,7-dione formation. These latter experiments unambiguously rule out the possibility that light is initially being absorbed by either the diene or the benzene solvent since neither absorb light of such energy.

A nitrene intermediate in this reaction has been ruled out. Not only would such a species be inconsistent with the observed stereospecificity, it is also eliminated on the basis of kinetic studies. When 2-azido-5-*tert*-butyl-1,4-benzoquinone was photolyzed in neat 1,3-pentadiene the rate of nitrogen evolution was observed to initially follow first-order kinetics. However, when the rate of nitrogen evolution was determined for a 1% solution of the same azidoquinone in benzene, in the presence of an equimolar amount of 1,3-pentadiene, it deviated markedly from first order giving an "s" shaped curve when nitrogen pressure was plotted against time (Figure 1). *The important conclusion derived from this study is that the diene concentration affects the rate of nitrogen evolution.* The diene must therefore interact, before the step which involves the loss of nitrogen. The mechanism outlined in Scheme I illustrates such a possible interaction, *i.e.*, excited quinone reacting with ground state diene. Other possibilities exist. For example, excited quinone could conceivably sensitize the diene to its triplet state which could then react with ground-state quinone. In either event, the Δ^2-triazoline (**15**) would be generated as the penultimate precursor to the indolequinones (**17**).

All attempts to spectroscopically detect the intermediate triazoline **15** failed. However, this is not surprising in view of the fact that such Δ^2-triazolines carrying a strong electron-withdrawing substituent at the 1 position are quite unstable, even at room temperature and below, and readily cleave to the diazonium betaines analogous to **16** which then proceed to products. For example, the triazo-

line formed by reaction of benzoyl azide with norbornene decomposes at 40° and the analogous triazoline formed when benzenesulfoyl azide reacts with norbornene has yet to be detected.[15] The triazoline from 2,4-dinitrophenyl azide and norbornene could just be isolated while that from picryl azide could not be seen but its formation was established on kinetic grounds.[16-18]

These data are all in agreement with the mechanistic sequence outlined in Scheme II. One novel feature of this transformation is the photolytic cycloaddition of an organic azide to a carbon–carbon double bond. Such a reaction is certainly well known in the thermal chemistry of azides but appears to be without precedent under photolytic conditions.

Experimental Section

5-*tert*-Butyl-2,3-dihydro-2-*trans*-(1-propenyl)indole-4,7-dione (3a). A solution of 1.0 g (0.005 mol) of 2-azido-5-*tert*-butyl-1,4-benzoquinone and 5.0 ml (0.05 mol) of *trans*-1,3-pentadiene in 50 ml of benzene was deoxygenated by bubbling nitrogen through it for 15 min. Nitrogen was continuously passed through the reaction solution as it was irradiated for 3 hr with a 3600-Å light source.[19] Petroleum ether (10 ml, bp 30–60) was then added and the deep purple solution was chromatographed on 120 g of silica gel using benzene–petroleum ether (5:1) as the eluent. The first yellow band off the column was the starting azidoquinone (0.45 g, 45% recovery). The next was a light purple compound, 0.01 g, which was not identified. Finally 0.63 g (53% yield) of 5-*tert*-butyl-2,3-dihydro-2-*trans*-(1-propenyl)indole-4,7-dione (**3a**) was obtained as a dark purple crystalline solid, mp 72–73°. This was followed by 0.01 g of 2-amino-5-*tert*-butyl-1,4-benzoquinone.[20] Taking the recovered starting azidoquinone into account, the yield of 5-*tert*-butyl-2,3-dihydro-2-(*trans*-1-propenyl)indole-4,7-dione (**3a**) was 96%.

Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.47; H, 7.76; N, 5.71. Found: C, 73.23; H, 7.81, N, 5.62.

Characteristic spectral properties of **3a** follow: ir (Nujol, cm^{-1}) 3300, 1670; nmr ($CDCl_3$, δ) 1.23 s (9), 1.65 broad d (3) J = 5 Hz, 4.18–4.62 m (1), 4.70–4.98 b (1), 5.54–5.78 m (2), 6.30 s (1); uv ($CHCl_3$, nm) 281.5 (11.5×10^3).

5-*tert*-Butyl-2,3-dihydro-2-(*cis*- and -*trans*-1-propenyl)indole-4,7-diones. Reaction of 2-Azido-5-*tert*-butyl-1,4-benzoquinone with *cis*-1,3-Pentadiene. A deoxygenated solution of 0.2014 g (0.001 mol) of the azidoquinone and 1.0 ml (0.01 mol) of *cis*-1,3-pentadiene in 20 ml of benzene was irradiated with 3600 Å light for 105 min. To this solution was added 2 ml of petroleum ether and then it was chromatographed on 130 g of silica gel using benzene–petroleum ether as the eluent. This gave 0.1006 g (50%) recovery of the azidoquinone and 0.0881 g (37%) of the mixture of 5-*tert*-butyl-2,3-dihydro-2-(*cis*- and -*trans*-1-propenyl)indole-4,7-dione, mp 78–79°. The stereochemistry of the 2-propenyl group was shown by nmr to be 44% trans and 56% cis. Attempted separation of these geometric isomers by thin-layer and gas chromatography, recrystallization, or sublimation were unsuccessful. Taking into account the amount of recovered starting azidoquinone, the yield of this isomeric mixture of indole-4,7-diones was 73%.

Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.47; H, 7.76; N, 5.71. Found: C, 73.23; H, 8.03; N, 5.61.

Characteristic spectral properties follow: ir (Nujol) 3200, 1670; nmr ($CDCl_3$, δ) 1.30 s (9), 1.80 and 1.83 two sets of doublets (3) J = 5 Hz, 2.36–3.43 m (2), 4.65–4.80 m (1), 4.81–4.92 b (1), 5.43–5.65 m (2); 6.32 s (1); uv ($CHCl_3$, nm) 281.0 (10.3×10^3).

2,3-Dihydro-5-methyl-2-(*trans*-1-propenyl)indole-4,7-dione (3e). A deoxygenated solution of 0.3157 g (0.002 mol) of 2-azido-5-methyl-1,4-benzoquinone and 2.0 ml (0.02 mol) of *trans*-1,3-pentadiene in 30 ml of anhydrous benzene was irradiated for 4.25 hr with 3600-Å light. Chromatography of the reaction solution on 130 g of silica gel as described above gave 0.0344 g (11%) starting azidoquinone and 0.1387 g (35%) of the blue 2,3-dihydro-5-methyl-2-(*trans*-1-propenyl)indole-4,7-dione (**3e**), mp 86–87°. Taking into account the amount of recovered starting azidoquinone the yield of **3e** was 40%.

Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.94; H, 6.40; N, 6.90. Found: C, 71.33; H, 6.70; N, 6.94.

Characteristic spectral properties for **3e** follow: ir (Nujol, cm^{-1}) 3300, 1655, 1635; nmr ($CDCl_3$, δ) 1.69 d (3) J = 5 Hz, 2.03 d (3) J = 1.5 Hz, 2.44–3.38 m (2), 4.23–4.62 m (1), 4.65–5.69 b (1), 5.46–5.67 m (2), 6.25 q (1) J = 1.5 Hz; uv ($CHCl_3$, nm) 273.5 (7.6×10^3).

2,3-Dihydro-2-(*trans*-1-propenyl)benzo[*f*]indole-4,9-dione (3g). A deoxygenated solution of 0.2090 g (0.001 mol) of 2-azido-1,4-naphthoquinone and 1.0 ml (0.01 mol) of *trans*-1,3-pentadiene in 20 ml of anhydrous benzene was irradiated with 3600 Å light for 2 hr. The deep purple reaction solution was worked up chromatographically as described above to give 0.1015 g (49%) of recovered starting azidoquinone and 0.0936 g (37%) of deep purple crystalline 2,3-dihydro-2-(*trans*-1-propenyl)benzo[*f*]indole-4,9-dione (**3g**), mp 143–144°. Taking into account the recovered starting azidoquinone, the yield of **3g** was 72%.

Anal. Calcd for $C_{15}H_{13}NO_2$: C, 75.31; H, 5.44; N, 5.86. Found: C, 75.42; H, 5.42; N, 5.73.

Characteristic spectral properties of **3g** follow: ir (Nujol, cm^{-1}) 3280, 1670; nmr ($CDCl_3$, δ) 1.69 d (3) J = 4.0 Hz, 2.57–3.52 m (2), 4.24–4.80 m (1), 5.03–5.32 b (1), 5.47–5.77 m (2), 7.42–8.10 m (4); uv ($CHCl_3$, nm) 278.5 (23.7×10^3).

5-*tert*-Butyl-2,3-dihydro-2,3-(1,3-pentadieno)indole-4,7-dione (5). A deoxygenated solution of 0.2091 g (0.001 mol) of 2-azido-5-*tert*-butyl-1,4-benzoquinone and 2.0 ml of cycloheptatriene in 20 ml of anhydrous benzene was irradiated with 3600-Å light for 6 hr. Chromatography of the resulting purple reaction solution on 120 g of silica gel using benzene–petroleum ether (5:1) as the eluent gave 0.0523 g (25%) of recovered azidoquinone and 0.0594 g (22%) of the indole-4,7-dione derivative **5**, mp 60–62°. Taking into account the amount of recovered starting azidoquinone, the yield of **5** was 29%.

Characteristic spectral properties of **5** follow: ir (Nujol, cm^{-1}) 3400, 1670; nmr ($CDCl_3$, δ) 1.27 s (9), 2.04–2.07 m (2), 3.06–3.37 m (1), 3.43–3.83 m (1), 4.08–4.50 b (1), 5.62–5.95 m (4), 6.30 s (1); uv ($CHCl_3$, nm) 284.0 (9.99×10^3).

6-Methyl-3,4,4a,9a-tetrahydrocarbazole-5,8-dione (6). A solution of 0.2984 g (0.0018 mol) of 2-azido-5-*tert*-butyl-1,4-benzoquinone and 3.0 ml of 1,3-cyclohexadiene in 30 ml of anhydrous benzene was irradiated for 4 hr with 3600-Å light. Chromatography of the reaction solution on 130 g of silica gel using benzene–petroleum ether (5:1) gave 0.0366 g (12%) of recovered starting azidoquinone and 0.1263 (24%) of the carbazole derivative **6**, mp 116–117°. Taking into account the amount of recovered starting azidoquinone, the yield of 6-methyl-3,4,4a,9a-tetrahydrocarbazole-5,8-dione (**6**) was 37%.

Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.56; H, 6.05, N, 6.51. Found: C, 72.62; H, 6.23; N, 6.38.

Characteristic spectral properties of **6** follow: ir (Nujol, cm^{-1}) 3250, 1670, 1630; nmr ($CDCl_3$, δ) 1.81–2.14 m (4), 2.03 d (3) J = 1.5 Hz, 3.19–3.63 m (1), 4.10–4.40 m (1), 4.73–5.17 b (1), 5.49–6.08 m (2) 6.28 q (1) J = 1.5 Hz; uv ($CHCl_3$, nm) 2805 (11.5×10^3).

3,4,4a,11a-Tetrahydrobenzo[*g*]carbazole-5,10-dione (7). A deoxygenated solution of 0.2017 g (0.001 mol) of 2-azido-1,4-naphthoquinone and 1.0 ml of 1.3-cyclohexadiene in 20 ml of anhydrous benzene was irradiated with 3600-Å light for 3 hr. Chromatography of the resulting deep purple solution on 120 g of silica gel using benzene–petroleum ether (5:1) gave 0.0995 g (49%) of recovered starting azidoquinone and 0.0955 g (88%) of the carbazole derivative **7**, mp 164–165°. Taking into account the amount of recovered starting material, the yield of 3,4,4a,11a-tetrahydrobenzo[*g*]carbazole-5,10-dione (**7**) was 74%.

Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.49; H, 5.18; N, 5.58. Found: C, 76.39; H, 5.39; N, 5.47.

Characteristic spectral properties for **7** follow: ir (Nujol, cm^{-1}) 3250, 1675; nmr ($CDCl_3$, δ) 1.83–2.27 m (4), 3.34–3.75 m (1), 4.17–4.52 m (1), 5.00–5.52 b (1), 5.53–6.33 m (2), 7.48–8.25 m (4); uv ($CHCl_3$, nm) 279.5 (18.8×10^3).

5-*tert*-Butyl-2,3-dihydro-3-methyl-2-(1-propenyl)indole-4,7-dione. Isomeric Mixture of 8 and 9 from *trans,trans*-2,4-Hexadiene. A deoxygenated solution of 0.2049 g (0.001 mol) of 2-azido-5-*tert*-butyl-1,4-benzoquinone and 1.0 ml (0.009 mol) of *trans,trans*-2,4-hexadiene in 20 ml of anhydrous benzene was irradiated for 125 min with 3600-Å light. Chromatography of the resulting deep purple solution on 120 g of silica gel using benzene–petroleum ether (5:1) gave 0.0400 g (20%) of recovered azidoquinone and 0.1339 g (52%) of the 5-*tert*-butyl-2,3-dihydro-3-methyl-2-(1-propenyl)indole-4,7-dione as a mixture of isomers. The nmr spectra of this purple oil showed it to be composed of two types of isomers, those differing in stereochemistry of the 2-propenyl group (39% cis and 61% trans 1.0:1.6) and those differing in stereochemistry of the 2,3-dihydroindole ring (22% trans and 78% cis). Separation of these four isomers could not be accomplished. Taking into account the amount of recovered starting azidoquinone,

the yield of the isomeric mixture of indole-4,7-dione derivatives was 81%.

Characteristic spectral properties of this **8** and **9** mixture follow: ir (Nujol, cm^{-1}) 3400, 1670; nmr (DMSO-d_6, δ) 1.24 broad s (9), 1.03 and 1.24 two sets of doublets in ratio of 1.6:1.0, respectively, (3) J = 6.5 Hz, 1.69 and 1.73 two sets of doublets in ratio of 1.0:3,5, respectively, (3) J = 5 Hz, 2.65–3.14 m (1), 3.67–4.01 m (1), 5.47–7.79 m (2), 6.18 s (1); uv ($CHCl_3$, nm) 281.5 (10.3 × 10^3).

5-*tert*-Butyl-2,3-dihydro-3-methyl-2-(1-propenyl)indole-4,7-dione. Isomeric Mixture of 8 and 9 from *cis,cis*-2-4-Hexadiene. A deoxygenated solution of 0.2221 g (0.001 mol) of 2-azido-5-*tert*-butyl-1,4-benzoquinone and 1.0 ml (0.009 mol) of *cis,cis*-2,4-hexadiene in 20 ml of anhydrous benzene was irradiated for 2 hr with 3600-Å light. Chromatography of the resulting deep purple solution in 120 g of silica gel using benzene–petroleum ether (5:1) as the eluent gave only a trace amount of starting azidoquinone and 0.1618 g (66%) of the 5-*tert*-butyl-2,3-dihydro-3-methyl-2-(1-propenyl)indole-4,7-dione as a mixture of isomers, mp 71–73°. The nmr spectrum of this mixture showed it to be composed of two types of isomers, those differing in stereochemistry of the 2-propenyl group (86% cis, 14% trans; 1.0:0.16) and those differing in stereochemistry of the 2,3-dihydroindole ring (13% trans, 87% cis; 0.16:1.0).

Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.13; H, 8.11; N, 5.41. Found: C, 74.06; H, 8.11; N, 5.14.

Characteristic spectral properties for this **8** and **9** mixture follow: ir (Nujol, cm^{-1}) 3300, 1670; nmr (DMSO-d_6, δ) 1.24 s (9), 1.03 and 1.24 two sets of doublets in a ratio of 1.0:0.16, respectively, (3) J = 6.5 Hz, 1.69 and 1.73 two sets of doublets in a ratio of 6.7:1.0, respectively, (3) J = 5 Hz, 2.68–3.14 m (1), 4.09–4.40 m (1), 5.20–5.88 m (2), 6.18 s (1); uv ($CHCl_3$, nm) 282.5 (11.8 × 10^3).

2,3-Dihydro-3,5-dimethyl-2-(1-propenyl)indole-4,7-dione. Isomeric Mixture of 10 and 11 from *cis,cis*-2,4-Hexadiene. A deoxygenated solution of 0.2058 g (0.0013 mol) of 2-azido-5-methyl-1,4-benzoquinone and 2.0 ml (0.018 mol) of *cis,cis*-2,4-hexadiene in 30 ml of anhydrous benzene was irradiated with 3600-Å light for 4 hr. Chromatography of the resulting purple solution on 130 g of silica gel using benzene–petroleum ether (5:1) as the eluent gave 0.0188 g (9%) of recovered azidoquinone and 0.2218 g (81%) of the 2,3-dihydro-3,5-dimethyl-2-(1-propenyl)indole-4,7-dione as a mixture of isomers **10** and **11**, mp 98–99°. The nmr spectrum of this product showed it to consist of two types of isomers, those differing in the stereochemistry of the 2-propenyl group (67% cis, 33% trans; 1.0:0.48) and those differing in stereochemistry of the 2,3-dihydroindole ring (18% trans, 82% cis; 1.0:4.5). These four isomers, *i.e.*, trans–trans, trans–cis, cis–cis, cis–trans, could not be separated. Taking into account the amount of recovered starting azidoquinone the yield of the **10** and **11** mixture was 84%.

Characteristic spectral properties of this **10** and **11** isomeric mixture follow: ir (Nujol, cm^{-1}) 3300, 1660; nmr ($CDCl_3$, δ) 1.11 and 1.32 two sets of doublets in a ratio 4.5:1.0, respectively, (3) J = 7 Hz, 1.67 and 1.71 two sets of doublets in a ratio of 3.4:1.0, respectively, (3) J = 5 Hz, 2.02 d (3) J = 1.5 Hz, 2.88–3.33 m (1), 4.12–4.45 m (1), 4.72–5.03 b (1), 5.39–5.87 m (2), 6.27 g (1) J = 1.5 Hz; uv ($CHCl_3$, nm) 280.0 (11.9 × 10^3).

2,3-Dihydro-3-methyl-2-(1-propenyl)benzo[*f*]indole-4,9-dione. Isomeric Mixture of 12 and 13 from *cis,cis*-2,4-Hexadiene. A deoxygenated solution of 0.2065 g (0.001 mol) of 2-azido-1,4-naphthoquinone and 1.0 ml (0.009) of *cis,cis*-2,4-hexadiene in 20 ml of anhydrous benzene was irradiated with 3600-Å light for 3 hr. Chromatography of the resulting red solution on 120 g of silica gel using benzene–petroleum ether (5:1) as the eluent gave 0.0972 g (47%) of recovered azidoquinone and 0.114 g (44%) of the red 2,3-dihydro-3-methyl-2-(1-propenyl)benzo[*f*]indole-4,9-dione as an isomeric mixture, mp 106–108°. The nmr spectrum of this product showed it to be composed of two types of isomers, those differing in stereochemistry at the 2-propenyl group (55% cis, 45% trans; 1.0:0.81) and those differing in stereochemistry at the 2,3-indole ring positions (41% trans, 59% cis; 1.0:1.4). Attempts to separate these four isomers failed. Taking into account the amount of recovered starting azidoquinone the yield of 2,3-dihydro-3-methyl-2-(1-propenyl)benzo[*f*]indole-4,9-dione was 82%.

Characteristic spectral properties of this **12** and **13** mixture follow: ir (Nujol, cm^{-1}) 3400, 1675, 1630; nmr ($CDCl_3$, δ) 1.17 and 1.42 two sets of doublets in ratio of 1.0:1.4, respectively, (3) J = 7 Hz, 1.71 and 1.75 two sets of doublets in ratio of 1.2:1.0, respectively, (3) J = 5 Hz, 2.97–3.64 m (1), 4.19–5.50 m (1), 4.92–5.13 b (1), 5.45–5.76 m (2), 7.47–8.13 m (4); uv ($CHCl_3$, nm) 279.0 (21.9 × 10^3).

Photolysis of 2-Azido-5-*tert*-butyl-1,4-benzoquinone in the Presence of 1,3-Pentadiene Using Cyclohexane as Solvent. A deoxygenated solution of 2-azido-5-*tert*-butyl-1,4-benzoquinone (0.1 g, 0.0005 mol) in 10 ml of anhydrous cyclohexane was irradiated with 3600-Å light. The product 2,3-dihydro-5-*tert*-butyl-2-(1-propenyl)indole-4,7-dione was detected by thin-layer chromatography. After a few hours, the thin-layer chromatograms were identical in appearance with those obtained from the same reaction when benzene was employed as the solvent.

Photolysis of 2-Azido-5-*tert*-butyl-1,4-benzoquinone in the Presence of 1,3-Pentadiene Using Benzene as the Solvent and Light of >4000 Å. A deoxygenated solution of 0.1 g (0.0005 mol) of 2-azido-5-*tert*-butyl-1,4-benzoquinone and 0.5 ml of 1,3-pentadiene in 10 ml of anhydrous benzene was irradiated with a sunlamp (Sylvania, 250 W) through a Corning 3-73 glass filter which cuts off light below 4000 Å. After a few hours the thin-layer chromatograms showed appreciable buildup of the 2,3-dihydro-5-*tert*-butyl-2-(1-propenyl)indole-4,7-dione.

Kinetics. The apparatus used was a modified version of that reported by Weyler.[21] Rather than a reaction vessel which was suspended in a constant temperature bath, a water jacketed sample tube was used in which 31.50° water was circulated during the kinetic run. The 2-azido-5-*tert*-butyl-1,4-benzoquinone (0.05 g, 0.25 mmol) was dissolved in 7 ml of dry benzene and injected into the sample tube. An equal molar amount of 1,3-pentadiene was then added. The sample was deoxygenated by bubbling nitrogen through it for 15 min and then the system was closed. The cover over the ultraviolet lamps was removed and the rate of increasing pressure was recorded. In order to obtain a P infinity value the reaction was allowed to go to completion. All the samples used were pure as determined by their melting points. In addition to the above, two runs were done in which the 2-azido-5-*tert*-butyl-1,4-benzoquinone was dissolved in 7 ml of the neat 1,3-pentadiene rather than the benzene.

Registry No.—**1a**, 27977-24-8; **1e**, 27977-26-0; **1g**, 15707-29-6; *cis*-**2a**, 1574-41-0; *trans*-**2a**, 2004-70-8; *cis,cis*-**2c**, 6108-61-8; *trans,trans*-**2c**, 5194-51-4; *cis*-**3a**, 49827-80-7; *trans*-**3a**, 49827-83-0; **3e**, 49827-84-1; **3g**, 49827-85-2; **5**, 49827-86-3; **6**, 49827-87-4; **7**, 49827-88-5; **8–9**, 49827-89-6; **10–11**, 49827-90-9; **12–13**, 49827-91-0; cycloheptatriene, 544-25-2; 1,3-cyclohexadiene, 592-57-4.

References and Notes

(1) This work is taken primarily from the Ph.D. thesis of P. G.
(2) The authors are grateful to the National Cancer Institute of the National Institute of Health for Grant CA 11890 which provided financial support of this project.
(3) P. Germearaad and H. W. Moore, *J. Org. Chem.*, **39**, 774 (1974).
(4) Yields are based on consumed starting azidoquinone and correspond to isolated products.
(5) Laocoon III program written by A. A. Bothner-By and S. M. Castellano (Mellon Institute) and developed by T. Gerig and R. Faust (University of California, Santa Barbara).
(6) J. R. Dyer, "Applications of Absorption Spectroscopy of Organic Compounds," Prentice-Hall, Englewood Cliffs, N. J., 1965, p 99.
(7) (a) Product ratio from the reaction of 2-azido-5-*tert*-butyl-1,4-benzoquinone with *trans,trans*-2,4-hexadiene. (b) Product ratio from the reaction of 2-azido-5-*tert*-butyl-1,4-benzoquinone with *cis,cis*-2,4-hexadiene.
(8) J. R. Dyer, ref 6, p 99.
(9) D. S. Pearce, M. S. Lee, and H. W. Moore, unpublished data.
(10) W. Weyler, Jr., D. S. Pearce, and H. W. Moore, *J. Amer. Chem. Soc.*, **95**, 2603 (1973).
(11) R. Huisgen, R. Grashey, and J. Sauer in "The Chemistry of Alkenes," S. Patai, Ed., Interscience, London, 1964; R. S. McDaniel and A. C. Oehlschlager, *Tetrahedron*, **25**, 1381 (1969); R. L. Hale and L. H. Zalkow, *ibid.*, **25**, 1393 (1969).
(12) Normally these diazonium betaines collapse to aziridines and anils: G. L'abbé, *Chem. Rev.*, **69**, 345 (1969). However, here the quinoid double bond is presumably sufficiently electron rich to allow carbon–carbon bond formation.
(13) J. K. Kochi and P. J. Krusic, *J. Amer. Chem. Soc.*, **90**, 7157 (1968).
(14) D. O. Cowan and A. A. Baum, *J. Amer. Chem. Soc.*, **92**, 2153 (1970).
(15) R. Huisgan, L. Möbius, G. Müller, H. Stangl, G. Szeimies, and J. M. Vernon, *Chem. Ber.*, **98**, 3992 (1965).
(16) A. S. Bailey, J. J. Merer, and J. E. White, *Chem. Commun.*, 4 (1965).
(17) A. S. Bailey and J. E. White, *Chem. Ind (London)*, 1628 (1965).
(18) A. S. Bailey and J. J. Wedgwood, *J. Chem. Soc. C*, 692 (1968).
(19) Coated low-pressure mercury resonance lamps (four) No. 50053 from Ultraviolet Products, Inc., Model PCQ-X!.
(20) H. W. Moore and R. J. Wikholm, *Chem. Commun.*, 1073 (1971).
(21) Walter W. Weyler, Ph.D. Thesis, University of California, Irvine, Calif., 1972.

1,1′-Azobisformamide. II. Thermal Decomposition. Kinetics, Products, and Decomposition Mechanism

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Received November 15, 1973

The thermal decomposition of 1,1′-azobisformamide (ABFA) has been investigated in DMSO solution over the temperature range 86–115°. The decomposition products at 115° are N_2 (0.886 mol/mol of ABFA), CO (0.376), biurea (0.132), biuret (0.228), urea (0.386), and cyanuric acid (0.008). The decomposition follows first-order kinetics for any given experiment, although a threefold increase in the calculated rate constant was found over the range of initial concentrations from 0.005 to 0.50 *M*. Activation parameters were calculated as follows: $\Delta H^* = 27.4 \pm 0.5$ kcal/mol; $\Delta S^* = 8.3$ eu. The results are consistent with a decomposition mechanism involving thermal isomerization of ABFA to *cis*-ABFA. *cis*-ABFA primarily undergoes cyclization to 1,2,4-triazoline-3,5-dione and, in addition, competitively, undergoes homolysis to produce nitrogen and a pair of formamoyl radicals. Formamoyl radicals add readily to ABFA to produce trisformamoylhydrazine (TFH) as an unstable intermediate which decomposes to biurea and isocyanic acid. 1,2,4-Triazoline-3,5-dione is also unstable, yielding nitrogen, carbon monoxide, and urea.

The thermal decomposition of aliphatic azo compounds occurs by a generally predictable course to yield molecular nitrogen and a pair of free radicals.[1] For most azo compounds, induced decomposition in solution is not a significant pathway; however, cage reactions can be important in reducing the efficiency of free-radical production.[2] Diarylazo compounds, on the other hand, are remarkably stable to both thermal and photochemical decomposition and are not generally considered useful sources of free radicals.[1a]

The initial step in the decomposition of α-carbonylazo compounds is frequently formulated as a homolysis with loss of nitrogen.[1,3] However, secondary reactions of free-radical intermediates play a significant role in the reaction course. In the case of dibenzoyldiimide, homolytic decomposition accounts for about 50% of the starting material. The remaining diimide is consumed by secondary reactions with the intermediate benzoyl radicals.[4]

In another case, dimethyl azodicarboxylate decomposes in dodecane at 120–170° to yield only 7% nitrogen.[3a] Despite the low yield of nitrogen, the results are consistent with a radical mechanism, since it was shown that the major reaction is polymerization, initiated by radicals.

Prior to the current study, only a single example of an azoformamide decomposing in solution had been reported.[3c] 2-Cyano-2-propylazoformamide had been used as a radical initiator at about 100°. The nitrogen yield was quantitative and the efficiency of radical production was 60%. Traces of carbon monoxide were found, suggesting a slight amount of decarbonylation of the formamoyl radical.

$$Me_2C(CN)N{=}NC(O)NH_2 \longrightarrow Me_2\dot{C}CN + N_2 + \cdot C(O)NH_2$$

Published work on the thermal decomposition of 1,1′-azobisformamide (ABFA) is limited to its high-temperature decomposition in the solid state or in heterogeneous systems.[5] Its decomposition mechanism has not been examined in detail nor have any studies been conducted in solution. The absence of published information concerning the decomposition of ABFA in solution at moderate temperatures makes it difficult to establish a detailed mechanism. By analogy with the known thermal decomposition pathways for α-carbonylazo compounds, it is possible to suggest an initial step involving homolysis with loss of nitrogen and the formation of a pair of formamoyl radicals. Reaction products should then be determined by subsequent reactions of these radicals. However, information on the chemistry of formamoyl radicals is quite sparse,[6,7] thereby leaving little basis for judging their ultimate fate. In view of this, our primary objective was to determine the mechanism of thermal decomposition of ABFA in solution by product analysis, reaction kinetics, and various complementary studies and, in doing so, also provide information concerning the behavior of formamoyl radicals.

Results

Kinetic Studies by Spectrophotometry. The rate of decomposition of ABFA was studied primarily in dimethyl sulfoxide (DMSO) and to some extent in dimethylformamide (DMF), hexamethylphosphoryltriamide (HMPT), and formamide. The rate of disappearance of ABFA was determined spectrophotometrically by following the decrease in intensity of the azo-group absorption at 423 nm (Table I). In all these cases, first-order kinetics were found through 2–3 half-lives. The first-order rate constant increases slightly with increasing initial concentration; a threefold increase in rate results from a hundredfold increase in initial concentration. The rate data for 0.016–0.018 *M* solutions of ABFA in DMSO at 86.0, 100.3, and 115.3° were used to calculate activation parameters (Table I).

A less comprehensive study of ABFA decomposition kinetics in other solvents was made, the results of which are also included in Table I. In this series, considerably wider variations are evident. At comparable concentrations, the rate of disappearance of ABFA is faster in DMF and substantially faster in formamide compared with DMSO. Nonlinear first-order plots were obtained in these solvents. Product studies indicated that a reaction occurs between ABFA and DMF, and presumably with formamide as well. Dilution of the DMSO with *o*-dichlorobenzene (40:60), however, results in a rate decrease relative to the rate in DMSO. This is reasonably attributed to a decrease in solvent polarity. In HMPT, the rate of decomposition of ABFA is roughly one-third that in DMSO.

Kinetic Studies by Nitrogen Evolution. The second approach to kinetic information was through gas-evolution studies, usually done in conjunction with reaction-product studies. Rate data were obtained from the volume of nitrogen collected as a function of time (see Experimental Section). The rate constants are listed in Table II.

The trend found with gas-evolution kinetics generally follows that obtained from spectrophotometric data, the rate constant increasing slightly with increasing initial concentration. *N,N,N′,N′*-Tetramethylazobisformamide (TMABFA) was used as a free-radical trap in one kinetic

Table I
Spectrophotometric Rate Data for the Thermal Decomposition of ABFA in DMSO and Various Other Solvents[a]

Temp, °C	Solvent	Initial concn, *M*	First-order rate constant, $min^{-1} \times 10^3$
86.0	DMSO	0.018	0.329 ± 0.008[b] (3)[c]
	DMF	0.018	0.939 ± 0.03[d,e]
	Formamide	0.018	5.55 ± 0.06
	DMSO	0.34	0.54 ± 0.004
100.3	DMSO	0.016	1.63 ± 0.06 (3)
	DMF	0.014	3.44[e]
	DMSO	0.38	2.50 ± 0.01
115.3	DMSO	0.005	4.01 ± 0.66 (2)
	DMSO	0.018	6.06 ± 0.28 (6)
	HMPT	0.017	2.30 ± 0.03
	DMF	0.018	6.82 ± 0.11[e]
	DMSO	0.17	8.88 ± 0.13 (2)
	DMSO + ODCB[f] (40:60)	0.018	4.82 ± 0.06
	Formamide	0.018	121 ± 45[g]
	DMSO	0.34	10.57 ± 0.9 (2)
	DMSO	0.50	11.35 ± 0.30 (2)

[a] Activation parameters for 0.018 *M* ABFA in DMSO: E_A = 27.4 ± 0.5 kcal/mol; ΔS^* = −8.3 eu. [b] Average deviation from the mean. [c] Number of individual experiments. [d] Standard deviation; reported for single runs. [e] Nonlinear plot. [f] ODCB = *o*-dichlorobenzene. [g] Very rapid reaction, approximate rate constant; plot is not linear.

experiment, since it is structurally similar to ABFA and was found to be relatively stable under the reaction conditions. When TMABFA was added to ABFA in equimolar amount, the rate of nitrogen evolution in DMSO was reduced by half. When HMPT was used as the solvent, the rate of nitrogen evolution was also half that found in DMSO.

Reaction Products from Thermolysis of ABFA. Thermolysis of ABFA in DMSO yields the following products: nitrogen, carbon monoxide, biurea, biuret, urea, and cyanuric acid and carbon dioxide in minor amounts. The ratio of nitrogen to carbon monoxide is 2.0 ± 0.5:1.0 in all cases. Product analyses were carried out for all the decompositions in which rate data by gas evolution were obtained. These results are summarized in Table III. No ammonia or other basic volatiles were detected.

At 86° some trisformamoylhydrazine (TFH), $(H_2NCO)_2NNHCONH_2$, was detected. The yield of biuret was relatively constant throughout. At 115°, the yield of urea increased with increasing initial concentration of ABFA. The yield of biurea appears to be slightly influenced by changes in both temperature and initial ABFA concentration. To obtain some indication of the sequence of product formation, a reaction was run to 50% completion. The nitrogen to carbon monoxide ratio was 2:1, and the amounts of biurea and biuret, when extrapolated, approached values obtained at 100% decomposition. The level of urea, however, was quite low, indicating that its formation may be a major process in the latter stages of the thermolysis or that it is being consumed initially. Small amounts of TFH were also found.

These results were supported by nmr analysis of ABFA–DMSO reaction mixtures quenched from 115° at different time intervals. The nmr analysis also indicated a relatively rapid buildup of biurea and biuret during the first half-life (*ca.* 77 min). Urea was also present. However, its formation was relatively slow until the latter stages of the thermolysis.

In DMF, nitrogen and carbon monoxide values were higher than in DMSO. However, the nitrogen to carbon monoxide ratio was essentially unchanged (Table III, Run No. 8). Of further interest was the isolation of *N,N*-dimethylurea, which indicated solvent participation in the thermolysis process and suggested the possible involvement of radical species. In HMPT as a reaction solvent, the yields of carbon monoxide and biuret were higher and that of biurea lower than in DMSO under comparable conditions (Table III, Run No. 9). The higher carbon monoxide values obtained in HMPT and in DMF lend some support to a suspected interaction of carbon monoxide with DMSO. This matter will be considered presently.

Table II
Gas-Evolution Rate Data for the Decomposition of ABFA in DMSO and Various Other Solvents

Temp, °C	Initial concn, *M*	Solvent and conditions	First-order rate constant, $min^{-1} \times 10^3$
86.0	0.34	DMSO–formamide	2.26 ± 0.16[a]
86.0	0.52	DMSO	0.79 ± 0.01
100.3	0.34	DMSO	2.63 ± 0.06
100.1	0.52	DMSO	2.25 ± 0.18
115.3	0.17	DMSO	6.38 ± 0.16[b] (2)[c]
	0.17	DMF	4.86 ± 0.03
	0.34	DMSO	8.32 ± 0.15 (4)
115.5	0.34	DMSO, 0.34 *M* TMABFA	4.26
115.2	0.34	HMPT	4.33 ± 0.10
115.3	0.52	DMSO	8.55 ± 0.64 (3)

[a] Standard deviation, reported for single experiments. [b] Average deviation from the mean. [c] Number of experiments.

Thermolysis of ABFA in the Presence of TMABFA. TMABFA was added as a probe for free radicals (Table III, Run No. 10). It has been demonstrated that formamoyl radicals, expected reaction intermediates, will add readily to TMABFA to yield 1-formamoyl-1,2-bis(*N,N′*-dimethylcarbamoyl)hydrazine (1).[7] Furthermore, TMABFA

$$Me_2NCON{=}NCONMe_2 + \cdot CONH_2 \longrightarrow \underset{\text{TMABFA}}{}$$

$$Me_2NCON(CONH_2)\dot{N}CONMe_2 \xrightarrow{RH} Me_2NCON(CONH_2)NHCONMe_2$$
1

is relatively stable under the conditions imposed (see Experimental Section). The addition of TMABFA resulted in a nitrogen to carbon monoxide ratio well within the range observed in its absence; however, the amounts of nitrogen and carbon monoxide were high. A portion of the increased nitrogen is attributed to some decomposition of TMABFA. The urea value was low, and the biurea was virtually eliminated. Furthermore, 1,2-bis(*N,N*-dimethylcarbamoyl)hydrazine (2) was found as a major product.

Chemistry of the Formamoyl Radical. We have recently reported the facile addition of formamoyl radicals to α-carbonylazo compounds by a simple radical-chain process.[7] In the case of ABFA, using excess formamide and benzoyl peroxide (BPO) initiator at 80°, the major product was trisformamoylhydrazine (TFH, 86% yield). In the absence of BPO, 83% of the ABFA was recovered. When this latter reaction was repeated at 114 ± 2°, the major reaction products were biurea (40.5%), isocyanic acid (56.1% isolated as cyanuric acid), urea (23%), and biuret (12.5%).

By way of obtaining additional evidence for the participation of formamoyl radicals in the thermolysis, ABFA was decomposed in DMSO in the present of formamide. Kinetic data indicated an appreciable rate enhancement of ABFA decomposition in formamide compared with that in DMSO (Table I). In the present case, a mixed solvent

Table III
Reaction Products from Thermolysis of ABFA

Run no.	Temp, °C	[ABFA], mmol	Solvent	Concn, M	Decomposition products, mol/mol of ABFA: Volatiles[a] N_2	Volatiles[a] CO[a]	Volatiles[a] CO_2	Nonvolatiles: Biurea	Nonvolatiles: Biuret	Nonvolatiles: Urea	Nonvolatiles: Cyanuric acid
1	86	129.4	DMSO	0.52	0.672	0.320		0.195[b]	0.189	0.260	0.056
2	100.3	77.5	DMSO	0.35	*k*	*k*	*k*	0.168	0.232	0.387	0.065
3	100.1	129.2	DMSO	0.52	0.765	0.421	0.026	0.192	0.200	0.252	0.049
4	115.3	43.0	DMSO	0.17	0.872	0.495	0.007	0.072	0.226	0.300	0.021
5[c]	115.3	83.4	DMSO	0.34	0.886 (±0.007)	0.376 (±0.003)	0.019 (±0.003)	0.132 (±0.003)	0.228 (±0.010)	0.386 (±0.017)	0.008
6	115.3	129.6	DMSO	0.52	0.900	0.463	0.008	0.115	0.252	0.453	0.037
7[d]	115.4	129.2	DMSO	0.52	0.666	0.383		0.110[e]	0.194	0.162	0.025
8	115.2	43.5	DMF	0.17	0.919	0.623	0.025	0.055[f]	0.207	0.391	
9	115.2	86.2	HMPT	0.34	0.867	0.510	0.002	0.055	0.412	0.354	
10	115.5	86.4	DMSO[g]	0.34	1.081	0.634		0.006[h]	0.237	0.293	0.052
11	86.0	86.4	DMSO[i]	0.35[j]	0.492	0.212		0.301[j]	0.217	0.119	0.036

[a] CO values are *ca.* 10% low; see ref 14. [b] TFH (0.021 mol) and ABFA (0.077 mol) were other products isolated. [c] Values for all reaction products are averages obtained from three identical reactions; average deviation of mean is noted. [d] Decomposition carried to 50% completion; values reported for reaction products result from extrapolation of actual yields to 100% dec. [e] TFH (0.054 mol) was also identified among the decomposition products. [f] *N,N*-Dimethylurea (0.041 mol) also present. [g] TMABFA present (86.4 mmol). [h] 1,2-Bis(*N,N*-dimethylcarbamoyl)hydrazine (**2**, 0.223 mol) and TMABFA (0.616 mol) were among the decomposition products. [i] Formamide present (86.2 mmol). [j] ABFA (0.070 mol) present. [k] Not determined.

(DMSO-formamide) system was used in order to enhance the solubility of ABFA. The nitrogen and carbon monoxide yields were significantly lower than those obtained in the absence of formamide under comparable conditions (Table III, Run No. 11). By the same token, the amount of biurea formed was quite high.

Control Reactions. The following reactions were carried out to determine the stability of various reaction products and postulated intermediates.

After heating urea in DMSO at 115° for 17 hr, >90% was recovered. A maximum of *ca.* 0.5% biuret was found, indicative of a low degree of dissociation.

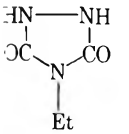
Heating a solution of biuret in DMSO at 115° resulted in a recovery of 47% of the starting material. Of the remaining biuret (53%), approximately 29% was accounted for as urea; undetermined amounts of cyanuric acid were also present. Since the dissociation of biuret to urea and isocyanic acid is reversible, in the current case the trimerization of isocyanic acid causes the process to shift away from biuret.

Upon heating at 115°, biurea was essentially unaffected, 88.3% being recovered. Small amounts of urea and biuret were found, accounting for at least 6% of the starting material.

On heating TFH in DMSO (115°), it dissociated to give biurea (78%) and isocyanic acid (94%) along with small amounts of urea (15%) and biuret (5%).

In an attempt to trap isocyanic acid formed from the thermolysis of TFH, equimolar amounts of urea and TFH were heated under thermolysis conditions. Isocyanic acid was formed, as evidenced by the presence of cyanuric acid. However, reaction with urea occurred only to a relatively minor extent; 88% of the isocyanic acid trimerized.

Thermolysis of Substituted Azobisformamides. *N,N,N′,N′*-Tetramethylazobisformamide (TMABFA). The decomposition of TMABFA in DMSO at 115.6° was extremely slow, as judged by the rate of nitrogen evolution. After prolonged heating (8 days), only 30.1% of the available azo nitrogen was accounted for as molecular nitrogen. The amount of carbon monoxide formed during this time was negligible (*ca.* 1.1%). Analysis of the nonvolatile decomposition products by nmr indicated the presence of TMABFA (*ca.* 60% starting TMABFA) and a second component, accounting for *ca.* 10% of the TMABFA, that has tentatively been identified as tris(*N,N*-dimethylcarbamoyl)hydrazine (**3**, see Experimental Section).



$Me_2NCONHN(CONMe_2)_2$ (**3**) $EtNHCONHN(CONHEt)_2$ (**5**)

4

***N,N*-Diethylazobisformamide (DEABFA).** Thermolysis of DEABFA at 115.6° in DMSO followed first-order kinetics ($k = 2.22 \pm 0.03 \times 10^{-3}$ min^{-1}, $t_{0.5} = 311.3$ min) as determined by rate of nitrogen evolution. Nitrogen (29.8%) was the only volatile decomposition product found. The major nonvolatile decomposition product, accounting for 45% of the DEABFA, was 4-ethylurazole (**4**), identified by comparison with authentic material. Nmr spectral analysis of the remaining tar-like thermolysis product suggested the presence of tris(*N*-ethylcarbamoyl)hydrazine (**5**) as a major component (see Experimental Section).

Discussion

To a first approximation, the thermal decomposition of ABFA was expected to follow a simple, homolytic pathway to yield molecular nitrogen and a pair of formamoyl radicals.

$$H_2NCON{=}NCONH_2 \longrightarrow H_2N\dot{C}O + N_2 + H_2N\dot{C}O$$

In practice, only 70-90% (86-115°) of the calculated amount of nitrogen was accounted for. The deficiency in azo nitrogen is generally accounted for by the yield of the reduced azo compounds, biurea (Table III). Carbon monoxide was a significant decomposition product (0.32–0.46 mol/mol of ABFA) which, within the framework of a free-radical decomposition mechanism, might arise from decarbonylation of the formamoyl radicals. Ammonia, a possible by-product of the decarbonylation, was not detected.

In DMSO, the decomposition of ABFA exhibits straight-line, first-order kinetic plots and only at relatively high initial concentrations was any slight curvature noted. The calculated rate constant increased with increasing initial concentration. However, this change was quite small; a hundredfold increase in ABFA concentration resulted in less than a threefold increase in the calculated rate constant (Table I). We will return to this point

below. It is noteworthy that for a given concentration of ABFA, the rate constant determined spectrophotometrically (disappearance of the azo group) was consistently larger than that calculated from nitrogen-evolution data. These results, and the less than quantitative nitrogen yields, indicate that other processes are consuming ABFA by pathways which do not yield nitrogen.

A free-radical mechanism for the decomposition of ABFA requires that reactions of formamoyl radicals be considered. Except for their addition to certain olefins,[6] little has been reported regarding their reactivity. Radical–radical coupling to produce oxamide does not occur under our conditions, since oxamide was not found. Hydrogen abstraction from solvent, or other source, by formamoyl radicals to yield formamide is considered of minor importance. While small amounts of formamide could have been lost during our work-up procedures, significant yields of formamide are clearly excluded by the material balance, which renders good accounting for all but 10–15% of the formamoyl moieties.

The question of induced decomposition bears consideration despite the fact that it is not normally considered a major factor in the homolysis of azo compounds.[2] Our kinetic data suggest the contribution of a process resembling induced decomposition. Specifically, a slight decomposition-rate enhancement occurs at higher initial concentrations in DMSO. However, in DMF and formamide, the results suggest that decomposition induced by solvent radicals may play a more significant role. The first-order kinetic plots in DMF were not linear and, although the decomposition products were not significantly altered compared with DMSO, a new product, *N,N*-dimethylurea, was found in small amounts.[8] Very large rate accelerations were observed in formamide (Table I). The low solubility of ABFA in this solvent precluded detailed product analysis. Thus, the decomposition in formamide must be regarded as incompletely characterized at this time. In DMSO with formamide added, the decomposition was also enhanced (compare the first two entries in Table II), and the product distribution was altered compared with decomposition in DMSO alone (see Table III).

The experimental data which suggest the occurrence of induced decomposition of ABFA in DMSO might also be attributed to a simple addition of formamoyl radicals to the azo bond of ABFA. Indeed, the rate accelerations observed are evident primarily in the spectrophotometric data rather than in nitrogen-evolution data. It has been shown that both ABFA and TMABFA undergo formamoylation by a free-radical chain reaction in formamide, initiated by benzoyl peroxide at 80°.[7] With ABFA, TFH was obtained in 86.4% yield. In the present study, consider-

$$H_2\dot{N}CO + ABFA \longrightarrow (H_2NCO)_2N{\cdot}NCONH_2 \xrightarrow{RH} THF$$

able evidence was obtained for the addition of formamoyl radicals to ABFA. In two experiments, one at 86° and the other at 115° (after 50% decomposition), TFH was identified among the products (Table III, Runs No. 1 and 7). A control reaction indicated that TFH is not stable at *ca.* 115°, and decomposes to biurea and isocyanic acid (which trimerizes to cyanuric acid). Both biurea and cyanuric

$$\underset{TFH}{(H_2NCO)_2NNHCONH_2} \xrightarrow[DMSO]{} H_2NCONHNHCONH_2 + HNCO$$

acid are ABFA decomposition products (Table III), whose presence is attributed to the breakdown of TFH. This is further supported by the results obtained in the presence of added formamide (Table III, Run No. 11). In this case, the yield of biurea increased significantly, indicating, by inference, an increase in the amount of TFH formed as an intermediate.

Finally, the addition of TMABFA provided further support for this scheme. The results (Table III, Run No. 10 to be compared with Run No. 5) show that biurea is virtually eliminated as a product and the corresponding reduced TMABFA, 1,2-bis(*N,N*-dimethylcarbamoyl)hydrazine (2), is obtained, from which we conclude that TMABFA successfully scavenges formamoyl radicals by the reaction below.

$$H_2\dot{N}CO + TMABFA \xrightarrow{RH} Me_2NCONH(CONH_2)CONMe_2 \xrightarrow[DMSO]{} Me_2NCONHNHCONMe_2 + HNCO$$

The thermal decomposition of TMABFA and DEABFA in DMSO was examined only briefly. In both cases, evidence was obtained for an analogous addition of the corresponding substituted carbamoyl radical to the azo compounds. TMABFA yields a minor product tentatively identified as the expected addition product, tris(*N,N*-dimethylcarbamoyl)hydrazine (3), whose formation may be rationalized by the reactions below. Similarly, DEABFA

$$TMABFA \xrightarrow[DMSO]{} Me_2\dot{N}CO + N_2 + Me_2\dot{N}CO$$

$$Me_2\dot{N}CO + TMABFA \xrightarrow{RH} \underset{3}{(Me_2NCO)_2NNHCONMe_2}$$

yielded a component whose nmr spectrum was consistent with the analogous addition product, tris(*N*-ethylcarbamoyl)hydrazine (5).

Thus, we conclude from these results that the addition of formamoyl radicals (or substituted carbamoyl radicals) to azobisformamides is a relatively important process under the reaction conditions imposed in our work. To gain further insight into the chemistry of formamoyl radicals, we examined the decomposition of ABFA in the presence of added cumene and styrene. Cumene had essentially no effect on either the decomposition rate or reaction products. In addition, no evidence was found for bicumyl, suggesting that hydrogen-atom abstraction from cumene is not an important reaction of formamoyl radicals.

Styrene was introduced into the ABFA–DMSO system, since formamoyl radicals are known to add to olefins.[6] The styrene was introduced at two levels, 50 mol % and in a tenfold excess relative to ABFA. In neither case could an adduct comprising styrene and formamoyl fragments be isolated. The azodicarboxylates are known to react with styrene to furnish cycloaddition products,[9] but no such products were identified in the case of ABFA. The decomposition products were the same as those obtained in the absence of styrene. The presence of styrene caused no significant change in reaction kinetics. The rate constant at both levels of styrene was only slightly higher than those obtained for comparable runs in the absence of styrene.

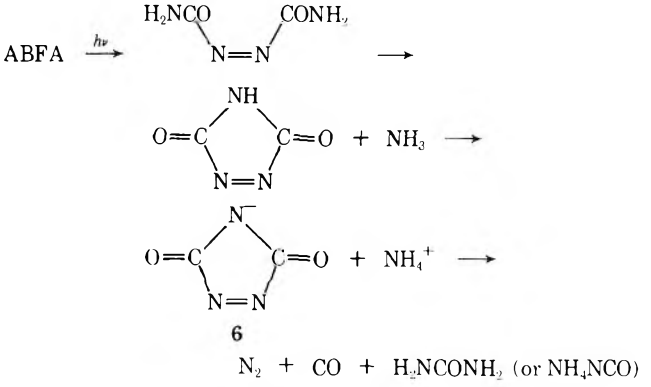
To examine the formamoyl radical further, ABFA was decomposed in the presence of several polymerizable vinyl monomers, selected on the basis of their recognized ease of polymerization by free-radicals initiators. In general, the results were inconclusive. Styrene was not polymerized; rather, its thermal polymerization appeared to be inhibited by ABFA. Methyl methacrylate was converted to a low molecular weight polymer both in the presence of ABFA and in the control reaction without ABFA. Acrylonitrile was polymerized to a very low conversion only, while styrene–methylmethacrylate (1:1 mol ratio) failed to yield polymer. These results do not preclude the existence

of formamoyl-radical intermediates. However, they indicate that formamoyl radicals may not be effective polymerization initiators under these conditions.

The formation of two major decomposition products from ABFA, carbon monoxide and urea, is difficult to rationalize from a free-radical decomposition mechanism. If formamoyl radicals and nitrogen are the only primary decomposition products, then carbon monoxide must result from decarbonylation of the formamoyl radicals. However, by analogy with the reported behavior of acyl radicals, decarbonylation is not expected to be a major pathway at 115°.[10] Moreover, 2-cyano-2-propylazoformamide yields only traces of carbon monoxide in solution at 100°, indicating very minor decarbonylation.[3c] We note further that neither TMABFA nor DEABFA yields more than traces of carbon monoxide at 115° in DMSO, although the decomposition products as noted above indicated that substituted carbamoyl radicals were produced. If neither ethylcarbamoyl nor dimethylcarbamoyl radicals exhibit any tendency to lose carbon monoxide at 115°, then, reasonably, formamoyl radicals would also be expected to be stable with respect to decarbonylation under the same conditions.[11] Finally, we note that, if decarbonylation were a significant process, the by-product would be amino radicals. Assuming that these energetic species were produced, they would be expected to abstract protons vigorously from almost any available source, to yield ammonia. We have found no evidence of ammonia among our reaction products.

Urea, the other major decomposition product, is likewise very difficult to rationalize by a free-radical mechanism.[12] Furthermore, only minor amounts of urea were obtained from control reactions. This serves to indicate that the quantities of urea found cannot be explained as arising solely from other decomposition products. Therefore, it became evident that other reaction pathways would have to be considered to rationalize our results. We subsequently directed our attention to the results obtained from the photolysis of ABFA, which have been reported earlier.[13]

These results could not be accommodated by a free-radical process, but rather were shown to involve cis–trans isomerization of ABFA. Decomposition was the result of thermal reactions of *cis*-ABFA, specifically cyclization to the unstable 1,2,4-triazoline-3,5-dione (as its ammonium salt **6**) followed by its thermal decomposition to nitrogen, carbon monoxide, and urea.



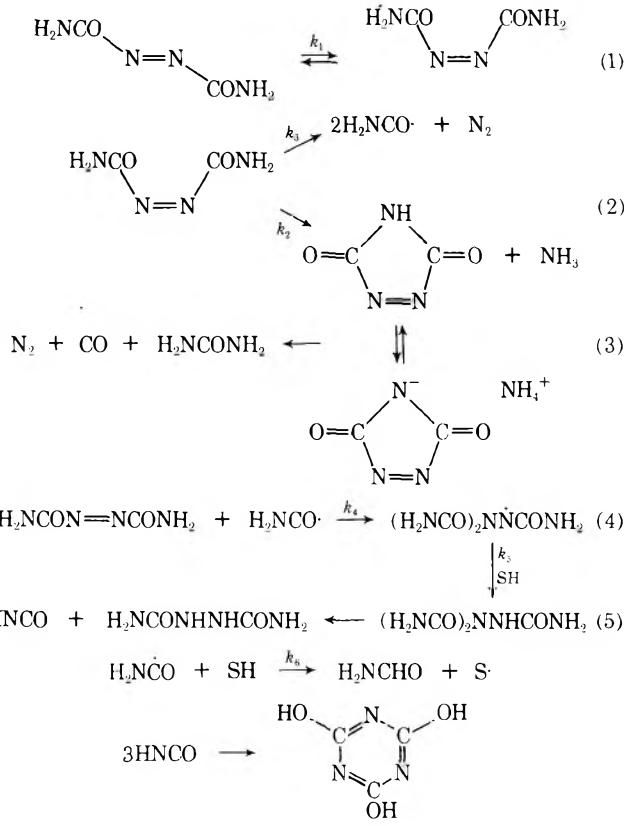
6

N_2 + CO + H_2NCONH_2 (or NH_4NCO)

The photochemical decomposition of ABFA provides a completely rational pathway to urea, carbon monoxide, and nitrogen. Since the key reaction in photolysis is isomerization of ABFA, there is expected to be a parallel thermal isomerization with the same consequences, namely cyclization followed by decomposition to nitrogen, carbon monoxide, and urea. This pathway accounts for those products which are not accommodated by a simple, free-radical mechanism. Moreover, the contribution of this decomposition route may be measured by the yield of carbon monoxide.[14] This analysis leads to the conclusion that the nonradical pathway is the predominant route in the thermal decomposition of ABFA. However, this reaction course does not exclude, but rather complements, the homolysis pathway as described above. In addition to the arguments presented in support of a free-radical addition to ABFA, and the case against decarbonylation of the formamoyl radical, the yield of nitrogen in all experiments exceeds that of carbon monoxide by an amount greater than can be explained through loss of carbon monoxide by reaction with DMSO.[14] The route which produces carbon monoxide yields an equivalent amount of nitrogen. The excess nitrogen must arise from another pathway, namely, homolysis of *cis*-ABFA.

The decomposition mechanism consistent with these results is presented in Scheme I. The primary step involves thermal isomerization to *cis*-ABFA (eq 1), which then undergoes cyclization to 1,2,4-triazoline-3,5-dione or its ammonium salt (**6**). This reaction has been shown to occur exclusively at room temperature and below.[15] Under the reaction conditions imposed in this study, however, *cis*-ABFA may decompose homolytically in competition with the cyclization reaction (eq 2). Recent reports by Porter[16] have provided specific examples of thermally unstable cis azo compounds, and our results are readily accommodated by this pathway.[17] The subsequent decomposition of 1,2,4-triazoline-3,5-dione to nitrogen, carbon monoxide, and urea (eq 3) has already been documented.[13] Therefore, the remaining reaction products must be accounted for by reactions of formamoyl radicals, or by secondary reactions of products.

Scheme I



The facile addition of formamoyl radicals to ABFA constitutes a major reaction of these radicals (eq 4). This leads to the unstable intermediate trisformamoylhydrazine,

which decomposes to biurea and isocyanic acid (eq 5). This sequence has also been studied independently and has been reported elsewhere by us.[7]

An analysis of this mechanism in terms of the decomposition kinetics provides further supporting evidence. Based on our prior studies we can reasonably conclude that both the cyclization of *cis*-ABFA and the subsequent decomposition of the cyclic intermediate are fast with respect to $-d[ABFA]/dt$, the overall rate of disappearance of ABFA. Furthermore, the homolysis of *cis*-ABFA must also be relatively fast to be competitive with the cyclization. Therefore, the rate of decomposition should be largely determined by the rate of isomerization. The entropy of activation was calculated to be −8.3 eu (Table I), consistent with the notion of a more highly ordered transition state. Considering the decomposition mechanism (Scheme I), the rate of disappearance of ABFA is given by

$$\frac{-d[ABFA]}{dt} = k_1[ABFA] + k_4[ABFA][H_2\dot{N}CO]$$

Steady-state approximations are made for $[H_2\dot{N}CO]$ and [*cis*-ABFA], *i.e.*, $d[H_2\dot{N}CO]/dt = 0$ and $d[cis\text{-ABFA}]/dt = 0$.[18] This yields the following rate expression.

$$\frac{-d[ABFA]}{dt} = k_1[ABFA] + \frac{\frac{2k_1}{(k_2/k_3) + 1}[ABFA]^2}{[ABFA] + \frac{k_6}{k_4}[SH]}$$

Qualitatively, this rate equation may be interpreted as representing a first-order process with a perturbation that is between first order and second order in ABFA. Our rate data indicated a first-order process within any given experiment, although the calculated rate constant becomes slightly larger at higher initial concentrations. Product data indicate that $k_2/k_3 \simeq 2$; *i.e.*, the cyclization reaction contributes twice as much to the decomposition of *cis*-ABFA as the homolysis. This simplifies the rate equation to that below.

$$\frac{-d[ABFA]}{dt} \approx k_1[ABFA] + \frac{\frac{2}{3}k_1[ABFA]^2}{[ABFA] + \frac{k_6}{k_4}[SH]}$$

Using a combination of numeric integration and nonlinear regression, this equation was found to be consistent with all the kinetic data obtained at 115.3° in DMSO over the range of initial ABFA concentrations of 0.005–0.50 *M* for values of $k_1 = 8.26 \times 10^{-3}$ and $(k_6/k_4) \times [SH] = 12.1$. The term [SH], the concentration of DMSO, is assumed to be a constant and equal to 12.8. This gives the result $k_6/k_4 = 0.9$.

The calculated value of k_1 compares favorably with the values reported in Table I. Of greater interest is the ratio k_6/k_4, which is close to unity and indicates, qualitatively, that the addition of formamoyl radicals to ABFA (k_4) is competitive with their reaction with solvent (k_6). Unfortunately, absolute rate constants are not available for either of these reactions.

The decomposition mechanism proposed (Scheme I) adequately accounts for all the products except biuret. Since our accounting for the azo nitrogen as molecular nitrogen and biurea is consistently good, it follows that biuret cannot be a primary decomposition product but rather must be the result of secondary reactions. One reasonable source is the reaction between urea and isocyanic acid. The latter product was shown to result from the decomposition of TFH.

$$H_2NCONH_2 + HNCO \longrightarrow H_2NCONHCONH_2$$

The control reactions also showed that biuret is produced in small amounts from urea, TFH, and biurea. We must conclude that there is no unique pathway to biuret.

As a concluding result we note the findings of our work on the substituted azobisformamides, TMABFA, and DEABFA. The proposed two-pathway decomposition mechanism led us to conclude that carbon monoxide results only from the cyclic route. TMABFA is not capable of undergoing cyclization, while with DEABFA a stable, cyclic product was isolated. Carbon monoxide was not a significant product in either case.

Experimental Section

General. Ultraviolet spectra were recorded on a Beckman DK-2A spectrophotometer. Infrared spectra were recorded on a Perkin-Elmer 451 infrared spectrophotometer. Nmr spectra were recorded on a Jeolco Model JNM-4H-100 (using TMS as an internal standard). Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Melting points were determined in open capillary tubes on a Mel-Temp apparatus and are uncorrected.

Materials. The source and any purification of ABFA, urea, and biuret, as well as preparations of *N,N,N′,N′*-tetramethylazobisformamide (TMABFA), *N,N*-diethylazobisformamide (DEABFA), and 4-ethylurazole (**4**), were previously described.[13] Biurea (Eastman Organic Chemicals), cyanuric acid, and urazole (from Aldrich Chemical Co.) were dried *in vacuo* (in the presence of P_2O_5) prior to use.

Solvents. Reagent-grade solvents were dried by appropriate means and were purified by distillation prior to use.

Miscellaneous Reagents. Styrene, methyl methacrylate (MMA), and acrylonitrile (AN) were freshly distilled just prior to use. Cumene was purified by the methods of Bartlett and coworkers.[19]

Typical Thermolysis Reaction (Table III, Run No. 6). ABFA (15.0407 g, 129.6 mmol) was placed in a 250-ml volumetric flask and DMSO was added to bring the liquid level to the calibration mark. Solution of the ABFA was achieved by heating the mixture to 40–50°. The solution was added to the reactor mounted in a constant-temperature bath,[20] and a slight nitrogen pressure was maintained until the bath temperature was reached.[21] The nitrogen flow was terminated and the system was opened to the gas train.[22] The volume of nitrogen evolved was taken from the gas buret at definite time intervals until no further volume change occurred. A total of 2650 ml (118.0 mmol)[23,24] of nitrogen was evolved.

The reactor and gas train were purged with nitrogen for several minutes, after which time the reactor was disconnected from the gas train and removed from the bath. Examination of the gas-train components indicated that no basic volatiles (*e.g.*, ammonia) were evolved. In addition, the carbon dioxide produced from thermolysis and that formed *via* oxidation of the carbon monoxide were determined as 1.0 and 60.0 mmol, respectively.

The essentially colorless reaction mixture, after cooling to room temperature, contained some white, crystalline solid that was filtered. The filter cake was washed consecutively with fresh DMSO and ether. The dried filter cake (0.699 g) was identified as biurea (6.0 mmol) by melting point (251–254° dec) and its ir spectrum. The combined DMSO filtrate and washings were flash distilled *in vacuo* (0.5 mm, pot <95°), yielding a gummy white solid residue (10.33 g). The solid residue was triturated with portions of hot methanol.[25] The soluble fraction (7.41 g) consisted of urea (3.08 g, 51.3 mmol), biuret (2.7 g, 26.2 mmol), and DMSO as determined by nmr.[26]

The methanol insolubles (3.37 g) were triturated with hot water and filtered. The dried filter cake (0.79 g) was identified as biurea (8.2 mmol). The aqueous filtrate was evaporated to dryness and dried *in vacuo* (P_2O_5) to give (as determined by nmr[26]) 2.48 g of a solid consisting of urea (0.44 g, 7.3 mmol), biurea (0.1 g, 0.85 mmol), biuret (0.66 g, 6.4 mmol), and cyanuric acid (0.62 g, 4.8 mmol).

The results of other reactions conducted in DMSO, DMF, HMPT, formamide, and added TMABFA are summarized in Table III.

Kinetics by Ultraviolet Spectrophotometry. The rate of disappearance in ABFA in DMSO was followed by the decrease in the absorbance of the azo group at its maximum (425 nm in DMSO). Beer's law was followed over the concentration range of

the measurements (5×10^{-4} to 2×10^{-2} M); a plot of absorbance *vs.* concentration yielded a straight line with a slope of 51.1 l. mol^{-1}. This value was taken as the extinction coefficient for ABFA in DMSO.

For kinetic experiments, a stock solution of the appropriate concentration was prepared. The solution was immersed in the oil bath and allowed to equilibrate for 10 min. A sample was removed and immediately quenched in ice. This sample was defined as zero on the time scale. Subsequent samples were removed periodically and treated in like manner and all samples were stored in ice, protected from light. In general, samples were removed at the rate of four or five per half-life for the first two half-lives, then less frequently afterwards. The final sample at the completion of the reaction ("infinity sample") was removed after 8 half-lives or longer.

When all the samples from a given experiment were obtained, they were removed from the ice and allowed to warm to room temperature, protected from light. The absorbance of each sample was then determined in the following way. For experiments in which the initial ABFA concentration was 0.01–0.02 M, the samples were transferred directly to 1.0-cm quartz spectrophotometer cells and their spectra were recorded in the region of the ABFA maximum at 423 nm. For initial concentrations less than 0.01 M, 2.0-cm cells were used, while for solutions more concentrated than 0.02 M, the samples were either uniformly diluted to the range where 1.0-cm cells could be used or 0.1-cm cells were employed.

The absorbance at the maximum was determined for each sample, measured against pure DMSO as the reference, and appropriate corrections for solvent interference applied. This typically amounted to less than 0.003 absorbance unit. The converted "infinity"-sample absorbance was generally indistinguishable from zero.

The absorbance data at each time interval for each complete run were then used to calculate a rate constant. The first-order rate constant was calculated from the slope of a plot of ln ($A_t - A\infty$) *vs.* time, where A_t = absorbance of the solution at any given time and $A\infty$ = absorbance after approximately 8 half-lives or more.

Kinetics from Gas-Evolution Data. The nitrogen evolved during the decomposition of ABFA was collected over water in a *ca.* 2.5-l. gas buret. The raw data consisted of buret readings as a function of time and the final (infinity) buret reading. Each volume reading was corrected to standard conditions by the ideal gas equation.

The first-order rate constant was calculated from the slope of a plot of ln $[V_\infty/(V_\infty - V_t)]$ *vs.* time, where V is the final buret reading corrected to STP and V_t is the corrected volume at any given time. The method of least squares was used to calculate the slope.[27]

Activation Parameters. The activation energy is calculated from the slope of a plot of ln k *vs.* $1/T$ and the preexponential is determined by the intercept.

The entropy of activation (ΔS^*) is calculated from the equation[28]

$$\Delta S^* = 4.576 \log(A/T) - 49.203$$

This was calculated for each temperature and an average value taken.

Thermolysis of *N,N'*-Diethylazobisformamide (DEABFA). DEABFA (10.0 g, 0.058 mol) in 150 ml of DMSO was heated at 115.6° in a thermostated bath; gas evolution was monitored as described previously for ABFA. After 22 hr, gas evolution had ceased. The only volatile product was nitrogen (0.017 mol, 29.8%).

The dark amber colored reaction mixture was flash distilled (<0.1 mm, pot <80°), leaving a viscous amber residue. Triturating this residue with chloroform (total volume 75 ml) left 3.3 g (0.026 mol) of 4-ethylurazole (**4**), identified by melting point (190–195°), mixture melting point with authentic **4**, and its nmr spectrum: nmr (DMSO-d_6) δ 1.08 (t, 3 H), 3.35 (q, 2 H), 10.0 ppm (s, broad, 1 H).

The chloroform filtrate was concentrated to dryness, yielding an organe-red tar (6.17 g). An nmr spectrum of the chloroform-soluble fraction (6.17 g) indicated traces of 4-ethylurazole (**4**) and/or DEABFA. The spectrum suggested that tris(*N*-ethylcarbamoyl)hydrazine (**5**) was the major component: nmr (DMSO-d_6) δ 0.96 (t), 1.03 (t), 2.94 (q), 3.01 (q), 8.14 (s, broad). The addition of *N,N'*-diethylurea or sparingly soluble *N,N'*-diethylhydrazobisformamide failed to enhance the signals due to the major component.

Thermolysis of *N,N,N',N'*-Tetramethylazobisformamide (TMABFA). TMABFA (14.8 g, 0.086 mol) in 250 mol of DMSO was heated at 115.6° in a manner similar to that described above. After 8 days, the reaction was terminated. The volatile products were nitrogen (0.026 mol, 30.1%) and carbon monoxide (0.001 mol, 1.1%). The dark red to amber reaction mixture was flash distilled (0.1 mm, pot temperature <80°) and left a dark amber oil that solidified on cooling to room temperature. An nmr spectrum (DMSO-d_6) of the residual semisolid (15.08 g) indicated the presence of TMABFA (*ca.* 9.0 g, 0.050 mol) and what has been tentatively identified as tris(*N,N*-dimethylcarbamoyl)hydrazine (**3**, *ca.* 2.5 g, 0.010 mol).[29]

Acknowledgment. We would like to thank Dr. A. C. Poshkus for stimulating discussions involving the proposed decomposition path for ABFA, particularly those associated with the cyclic intermediate. Our appreciation is also extended to Professor D. Swern, Temple University, for helpful suggestions in preparing the manuscript and to Messrs. W. Y. Whitmore and A. G. Geigley for recording the nmr spectra.

Registry No.—ABFA, 123-77-3; TMABFA, 10465-78-8; DEABFA, 18880-20-1.

References and Notes

(1) (a) H. Zollinger, "Diazo and Azo Chemistry: Aliphatic and Aromatic Compounds," Interscience, New York, N. Y., 1961, p 267; (b) C. G. Overberger, J.-P. Anselme, and J. G. Lombardino, "Organic Compounds with Nitrogen–Nitrogen Bonds," Ronald Press, New York, N. Y., 1966, p 32.
(2) W. A. Pryor, "Free Radicals," McGraw-Hill, New York, N. Y., 1966, p 129.
(3) (a) A. Jones, E. R. Morris, and J. C. J. Thynne, *J. Phys. Chem.*, **72**, 2677 (1968); (b) R. Cramer, *J. Amer. Chem. Soc.*, **79**, 6215 (1957); (c) J. C. Bevington and A. Wabid, *Polymer*, **4**, 129 (1963).
(4) (a) J. E. Leffler and W. B. Bond, *J. Amer. Chem. Soc.*, **78**, 335 (1956); (b) J. C. Bevington and D. J. Stamper, *Trans. Faraday Soc.*, **66**, 688 (1970); (c) D. Mackay, U. F. Marx, and W. A. Waters, *J. Chem. Soc.*, 4795 (1964).
(5) (a) R. A. Reed, "Plastics Progress (1955)," Fliffe, London, pp 51–80; (b) R. A. Reed, *Brit. Plastics*, **33** (10), 469 (1960); (c) K. Waki and T. Yamashita, *Nippon Kagaku Kaishi*, 2359 (1972).
(6) H. H. Vogel, *Synthesis*, **3**, 99 (1970).
(7) R. M. Fantazier and J. E. Herweh, *J. Org. Chem.*, **38**, 2560 (1973).
(8) *N,N*-Dimethylurea, Me_2NCONH_2, could conceivably arise from attack of solvent-derived *N,N*-dimethylcarbamoyl radicals on ABFA, in what is formally a radical displacement on nitrogen.

$$Me_2\dot{N}CO + H_2NCON{=}NCONH_2 \longrightarrow Me_2NCONH_2 + CO + N_2 + \dot{C}ONH_2$$

(9) J. Hamer, Ed., "1,4-Cycloaddition Reactions," Academic Press, New York, N. Y., 1967, p 143. Alternatively, a radical–radical coupling reaction, such as shown below, might explain this product, but would not explain the observed nonlinearity in the kinetic plots.

$$Me_2\dot{N}CO \longrightarrow Me_2\dot{N} + CO$$
$$Me_2\dot{N} + H_2\dot{N}CO \longrightarrow Me_2NCONH_2$$

(10) C. Walling, "Free Radicals in Solution," Wiley, New York, N. Y., 1957, pp 278–279.
(11) Several attempts were made to assess the extent of formamoyl radical decarbonylation. Di-*tert*-butyl peroxide was decomposed in the presence of formamide in an o-dichlorobenzene solution at 150°. Under these conditions, the extent of decarbonylation was less than 5%.
(12) If amino radicals are intermediates, a route to urea might be visualized as involving hydrogen abstraction by amino radicals to yield ammonia followed by reaction of ammonia with isocyanic acid produced in the decomposition of TFH. On the other hand, an induced decomposition requiring the attack of formamoyl radicals on ABFA might be visualized as shown below.

$$H_2\dot{N}CO + ABFA \longrightarrow H_2NCONH_2 + N_2 + \dot{C}ONH_2$$

While we cannot exclude such a process and, in fact, our results in DMF and formamide solvents may be interpreted this way in part, it seems highly unlikely that this process could be the course for the formation of major amounts of urea. Our kinetic results do not accommodate a major induced decomposition. Furthermore, the radical scavengers we employed were not effective in altering the yield of urea to a significant extent.
(13) R. M. Fantazier and J. E. Herweh, *J. Amer. Chem. Soc.*, in press.
(14) The yields of carbon monoxide are approximately 10% or more *too* low. In separate control reactions known mixtures of nitrogen and carbon monoxide, of composition approximating that typically produced in the decomposition of ABFA, were bubbled through 250 ml

of DMSO at 115° and thence through the gas train. For a mixture of 55 mmol of N_2 and 47.1 mmol of CO, 53.2 mmol (97%) of N_2 and 42.2 mmol (89.6%) were recovered. In all cases, the DMSO was an orange-brown color upon terminating the experiment. Attempts to isolate possible reaction products from the mixture were unsuccessful.

(15) J. E. Herweh and R. M. Fantazier, *Tetrahedron Lett.*, 2101 (1973).

(16) (a) N. A. Porter, M. E. Landis, and L. J. Marnett, *J. Amer. Chem. Soc.*, **93**, 795 (1971); (b) N. A. Porter, L. J. Marnett, C. H. Lochmuller, G. L. Closs, and M. Shobataki, *ibid.*, **94**, 3664 (1972); (c) N. A. Porter and L. J. Marnett, *ibid.*, 95, 4361 (1973).

(17) The results of some preliminary studies involving the photolysis of ABFA suspended in cumene provide additional support for homolysis as a decomposition path for *cis*-ABFA. When a stirred suspension of ABFA in cumene was irradiated in an immersion-type reactor with a 200-W mercury arc using a Pyrex filter for 6 days at room temperature, TFH and N_2 were the major decomposition products. TFH accounted for >30% of the starting ABFA while N_2 accounted for most of the remaining azo nitrogen of ABFA. Carbon monoxide, biurea, urea, biuret, and bicumyl were minor reaction products.

(18) The justification for the latter assumption is found in our photolysis study,[13] in which we found the half-life of *cis*-ABFA to be approximately 5 min at 25°. At 115°, ABFA has a half-life of 100 min. The lifetime of *cis*-ABFA is estimated to be at least three orders of magnitude shorter at this temperature.

(19) P. D. Bartlett, E. P. Benzig, and R. E. Pincock, *J. Amer. Chem. Soc.*, **82**, 1762 (1960).

(20) Over the course of a given experiment at 115°, the maximum temperature variation was 0.05°, while 0.02° was typical.

(21) In practice, reaction temperatures were reached after *ca.* 15 min.

(22) The gas train is of the standard type and was assembled to detect and measure, in the following order, basic volatiles, carbon dioxide, carbon monoxide, and nitrogen.

(23) Final nitrogen volume was corrected for hydrostatic pressure, vapor pressure of water, and STP.

(24) The amount of nitrogen and all other reaction products as entered in Table III have been normalized for 1 mol of ABFA.

(25) Relatively slight modifications in the work-up procedure were employed in several cases where solvents other than DMSO and/or additives were present.

(26) The composition of the dried residues was determined by nmr from a comparison with spectra of authentic samples. The amounts (per cent by weight) of the various components were subsequently calculated from the integrated area.

(27) W. Y. Youden, "Statistical Methods for Chemists," Wiley, New York, N. Y., 1951.

(28) A. Streitweiser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill, New York, N. Y., 1962, p 8.

(29) The amounts of TMABFA and **3** were determined from the integrated area of each component. Chemical shifts attributed to **3** at δ 2.84 (d, 18 H) and 8.67 (s, 1 H).

Photochemical Alkylation of s-Triazolo[4,3-*b*]pyridazine and Imidazo[1,2-*b*]pyridazine

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Received July 31, 1973

s-Triazolo[4,3-*b*]pyridazine (I), when irradiated in methanol and the reaction mixture was heated to 250°, gave nearly a 50:50 mixture of 7-methyl- and 8-methyl-*s*-triazolo[4,3-*b*]pyridazines (Va and VIa). There was no reaction when I was irradiated in tetradeuteriomethanol. Similar products were isolated in ethanol. The intermediate mixture when I reacted with isopropyl alcohol decomposed on heating to 7-isopropyl- and 8-isopropyl-*s*-triazolo[4,3-*f*]pyridazines (Vc and VIc) and 7,8-dihydro-*s*-triazolo[4,3-*b*]pyridazine (VII). Product VII resulted from a reverse aldol-type condensation reaction. Imidazo[1,2-*b*]pyridazine (II) did not react when irradiated in methanol. In acidified methanol and in the presence of benzophenone, II reacted to give 8-hydroxymethylimidazo[1,2-*b*]pyridazine (X) and a trace of the 8-methyl product (XI).

There have been numerous studies of the photochemical alkylation reactions of N-heterocyclic aromatic compounds. Stermitz and coworkers[2] first reported that, when N-heterocyclic aromatic compounds were photolyzed in acidified ethanol, ethyl-substituted compounds were formed. They showed that the reaction proceeded through an n,π^* triplet state much like the photoreduction of benzophenone.[3] The ethyl group was attached to carbon 2 (next to nitrogen) or carbon 4.[2] In the absence of acid, the corresponding hydroxyethyl products formed.[4] Other workers have shown that photoalkylation also takes place in ethers[5] and amines.[6,7]

We have irradiated *s*-triazolo[4,3-*b*]pyridazine (I) in methanol and have found that the reaction mixture yielded 7-methyl- and 8-methyl-*s*-triazolo[4,3-*b*]pyridazines (Va and VIa) in nearly equal amounts upon heating to 250°. No reaction took place when I was irradiated in tetradeuteriomethanol. When I was irradiated in ethanol and the reaction mixture heated, 7-ethyl- and 8-ethyl-*s*-triazolo[4,3-*b*]pyridazines (Vb and VIb) were isolated with a ratio of 1:2. The reaction mixture of the irradiation of I in isopropyl alcohol gave 7-isopropyl- and 8-isopropyl-*s*-triazolo[4,3-*b*]pyridazines (Vc and VIc) and 7,8-dihydro-*s*-triazolo[4,3-*b*]pyridazine (VII) in a ratio of 2:3:5, respectively, when heated. In each of these reactions, analysis of the crude reaction mixture indicated that the corresponding 7- and 8-hydroxyalkyl-7,8-dihydro-*s*-triazolo[4,3-*b*]pyridazines (IIIa–c and IVa–c) were the initial products (see Scheme I). 7,8-Dimethyl-*s*-triazolo[4,3-*b*]pyridazine (VIII) was the only product when the reaction mixture from the irradiation of Va in methanol was heated to 250°.

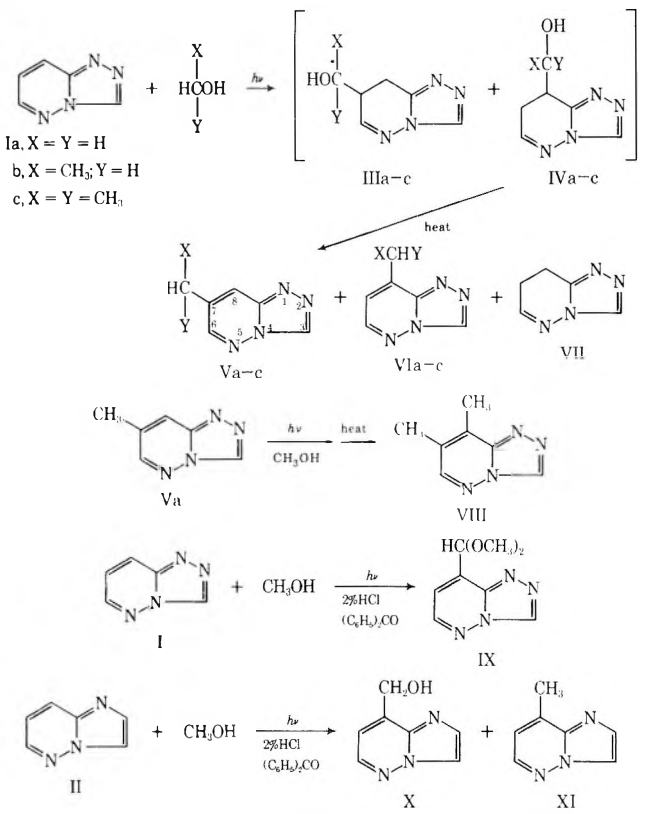
When irradiated in acidified methanol and in the presence of benzophenone, I did not give Va or VIa but gave the dimethyl acetal of 8-formyl-*s*-triazolo[4,3-*b*]pyridazine (IX). Imidazo[1,2-*b*]pyridazine (II) reacted with methanol in the presence of acid and benzophenone to give a good yield of 8-hydroxymethylimidazo[1,2-*b*]pyridazine (X) and a trace of the 8-methyl product (XI). In the absence of acid and benzophenone, II did not react.

Results and Discussion

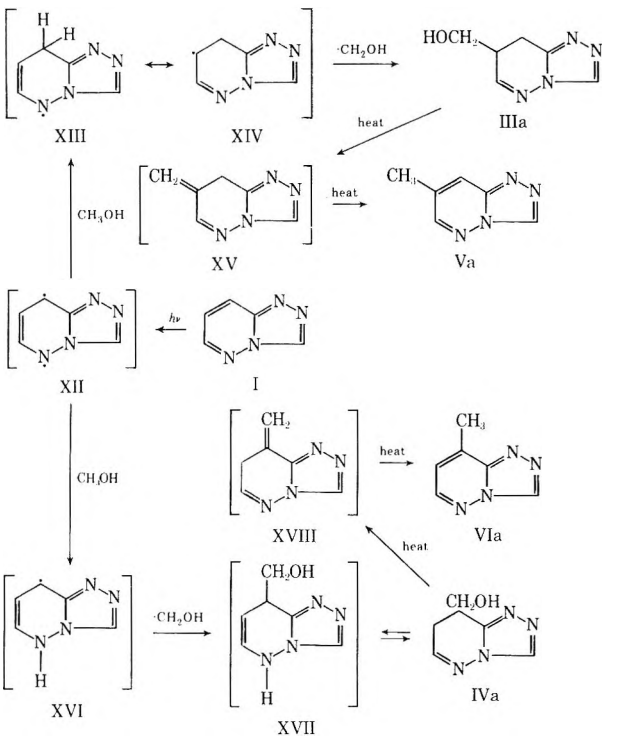
The starting material was dissolved in the appropriate solvent and irradiated until no starting material was left in solution. The solvent was then removed and the gummy material was analyzed by nuclear magnetic resonance (nmr) spectroscopy and separated by vpc (250° inlet temperature) or thin layer chromatography (tlc). The products were compared with authentic samples where possible or analyzed by nmr, infrared (ir), and mass spectrometry. The reactions are shown in Scheme I.

The structures of the products were consistent with their spectra. The nmr spectra for compounds I and II and their derivatives are very distinctive.[8-10] The doubled doublet at δ 7.17 observed for the hydrogen at position 7 in the nmr spectrum of I[8] was not observed in the spectra of compounds Va–c. The nmr spectra of compounds X and XI also did not show the octet at δ 7.95 which was attributed to the hydrogen at position 8 in compound II.[9]

Scheme I

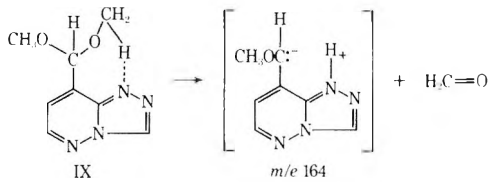


Scheme II



Compound VII was soluble in water and exhibited an nmr spectrum which was the same as that for authentic 7,8-dihydro-*s*-triazolo[4,3-*b*]pyridazine, which we prepared by a different process.

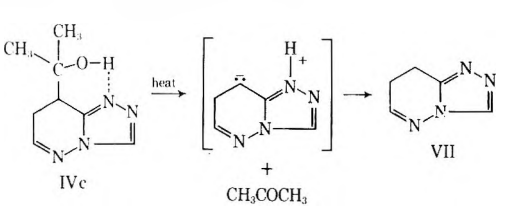
Compound IX exhibited a small parent peak at *m/e* 194 in the mass spectrum. Acetals usually have small parent peaks.[11] A large metastable (M − CH_2O) peak was observed. Generally, dimethyl acetals have large (M − CH_3O)$^+$ peaks.[11] Methyl ethers, on the other hand, have large (M − CH_2O) peaks which have been attributed to the loss of formaldehyde.[12] 8-Dimethylaminoimidazo[1,2-*b*]pyridazine, a structurally similar compound, has been observed to have a large (M − NCH_3)$^+$ peak but no [M − $N(CH_3)_2$]$^+$ peak in the mass spectrum.[13] The second methyl group probably migrated to the nitrogen in position 1. This same type of phenomenon could be taking place with compound IX wherein a hydrogen migrates from a methyl to nitrogen and a neutral formaldehyde molecule is lost.



The initial photochemical reaction of I led to mixtures of what we believe are the 7- and 8-hydroxyalkyl-7,8-dihydro products III and IV. These products were not isolated; however, the nmr spectra of the crude mixtures were very characteristic. Peaks at δ 8.6 and 7.7 are indicative of hydrogens at positions 3 and 6, respectively. The peaks at δ 3.5–2.7 can be attributed to the hydrogens in the 7 and 8 positions and the peak area always equated to three hydrogens. The hydroxy hydrogen peak in the case of the mixture of IIIc and IVc appeared at δ 4.75 and was exchangeable in deuterated water. The remaining alkyl group was also observed in each spectra. The relative amounts of III and IV changed from 50:50 in the methanol reaction to 20:80 in the isopropyl reaction. The two methyls in compound IVc were not equivalent. The separation of the two peaks in hexadeuteriodimethyl sulfoxide was 0.32 Hz at room temperature but decreased to 0.22 Hz at 150°. The nonequivalence of the methyls can be attributed to hindrance in rotation about the alkyl carbon–carbon 8 bond due to hydrogen bonding between the hydroxy group and the nitrogen in position 1. Also at 150° a new peak at δ 2.12 appeared and increased with increasing time. The addition of a trace of acetone increased the size of this peak.

When the above-mentioned reaction mixtures were heated at 250°, the 7- and 8-alkyl products were formed. In the case of the 2-propanol reaction, compound VII was also formed as the major product. This product had to be formed from IVc, which was the major intermediate. Acetone was also a product of the thermal reaction, as shown by its presence in the hot dimethyl sulfoxide solution.

The photoreaction probably involves an excited state wherein the 5 and 8 positions of I are activated toward radical reactions (may be like XII in Scheme II). The excited intermediate then abstracts a hydrogen atom from the alcohol either in position 8 to give XIII or in position 5 to give XVI. Resonance form XIV reacts with the hydroxy methyl radical to give IIIa, while XVI leads to IVa. Each of these hydroxyalkyl intermediates dehydrates and rearomatizes in heat to give the observed alkyl products Va and VIa. When the hydroxyalkyl compound IVc is heated, a reverse aldol-type condensation reaction competes with dehydration to give VII and acetone. The reverse aldo-type condensation reaction is most pronounced in the case of IVc (a trace of VII may have formed from IVb) because tertiary alcohols undergo this reaction more readily than do secondary or primary alcohols.[14]



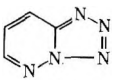
The change in the ratio of III to IV as the alcohol is changed from methanol (50:50 ratio) to 2-propanol (20:80 ratio) is interesting. The reactive intermediate (XII) should not be different in the two cases. Since the first step is probably hydrogen abstraction by XII, this could indicate that the pair of electrons on nitrogen 1 create more steric hindrance than the hydrogen on carbon 3.

Failure of compound I to react in tetradeuteriomethanol is surprising. To the best of our knowledge, this is the first example of an isotope effect in a photoalkylation reaction.

The reactions in acidified methanol were expected to yield methyl-substituted products as previously observed for this reaction with other N-heterocyclic compounds.[2] The dimethyl acetal (product IX) probably derived from the corresponding hydroxymethyl compound. The aldehyde could have formed by oxidation of the hydroxymethyl compound. Formation of the acetal would then be expected in acidified methanol.

We expected at least some 6-substituted products. None was detected. These results closely parallel radical addition to these compounds. Both I and II reacted with radicals to give mainly 8-substituted products with some in position 7 but very little in position 6.[8-10]

The fact that neither II nor the structurally similar tetrazolo[1,5-*b*]pyridazine XIX reacted with methanol in the absence of sensitizer is consistent with other studies of these compounds. We have previously reported that I reacted readily with cyclohexene to form photocycloaddition products wherein the alkene added to the 1,8 positions of I with a concurrent opening of the N_4–N_5 bond.[15,16] Neither II nor XIX reacted to form those products.[15,16] It is also known that II and XIX are not as reactive toward radical reactions as I.[10]



XIX

Experimental Section

Materials and Apparatus. All starting materials, compounds I,[8] II,[17] and VIa,[8] were prepared in this laboratory. All infrared (ir) spectra were obtained on a Perkin-Elmer Model 137 spectrophotometer. A JOEL JNM C60-HL spectrometer was used to obtain the nuclear magnetic resonance (nmr) spectra. A Varian Model 1800 temperature-programming vapor phase chromatograph (vpc) using a 5 ft × 0.25 in. stainless steel column packed with 10% SE-30 on 80/100 mesh Chromosorb G/AW was employed for all separations. The mass spectra were obtained on a CEC-20-110 C high-resolution mass spectrometer. A Rayonet photochemical reactor with 3600-Å lamps was used for all irradiations.

7,8-Dihydro-s-triazolo[4,3-*b*]pyridazine (VII). A solution of 6-chloro-s-triazolo[4,3-*b*]pyridazine[8] (1.56 g) in 70 ml of methanol was treated with 1 ml of concentrated ammonia and 0.15 g of 10% palladium on charcoal. The mixture was stirred in an atmosphere of hydrogen under normal pressure for 6 days. The catalyst was filtered and the filtrate was evaporated under vacuum almost to dryness. The residue was treated with a solution of 20 ml of 5% aqueous sodium hydroxide and extracted five times with chloroform. The combined extracts were washed with water and dried over anhydrous magnesium sulfate. Upon evaporation of the solvent, the residue (0.92 g) was found by nmr analysis to consist of 7,8-dihydro-s-triazolo[4,3-*b*]pyridazine (VII, 75%) and s-triazolo[4,3-*b*]pyridazine (I, 25%). Several recrystallizations from ethanol gave pure VII: mp 132°; nmr δ 8.60 (s, H_3), 7.70 (t, H_6), 3.20 (m, 8-CH_2), and 2.80 (m, 7-CH_2).

Anal. Calcd for $C_5H_6N_4$: C, 49.17; H, 4.95; N, 45.81. Found: C, 49.30; H, 5.18; N, 45.89.

Irradiation of I in Methanol. Compound I (0.20 g, 1.7 mmol) in 15 ml of methanol was irradiated in a Pyrex tube for 40 hr. Thin layer chromatography (tlc) showed that no starting material remained in the solution. The solvent was removed under vacuum, leaving a yellow gum (0.25 g). The nmr spectrum of this material exhibited peaks at δ 8.65 (s, 1), 7.65 (s, 1), 3.85 (d, 2, J = 5 Hz), and 3.5–2.7 (m, 3). This material could not be further purified. When the material was heated to 250° for 10 min and then sublimed at 250° (1 mm), a mixture (40% overall yield) of 7- and 8-methyl-s-triazolo[4,3-*b*]pyridazine (Va and VIa) resulted. The products were isolated by vpc, yielding Va (18%) and VIa (22%). The products exhibited ir and nmr spectra which were identical with those of authentic samples.[8]

Irradiation of I in Ethanol. A mixture of I and 100% ethanol was irradiated as above, yielding 0.27 g of a yellow gum. The nmr of this material contained peaks at δ 8.4 (d, 1), 7.6 (s, 1), 4.3 (m, 1–2), 3.5–2.7 (m, 3), and 1.5–1.0 (m, 4). Peak areas were imprecise. When heated to 250° for 10 min and sublimed at 250° (1 mm), a white semisolid formed (35% overall yield). Three peaks were isolated on the vpc. Peak 1 (9%) proved to be starting material, compound I. Peak 2 (18%, compound VIb) exhibited the following spectra: nmr δ 9.11 (s, 1, H_3), 8.27 (d, 1, J = 7 ± 1 Hz, H_6), 6.90 (d, 1, J = 8 ± 1 Hz, H_7), 3.18 (q, 2, CH_2), 1.47 (t, 3, CH_3); mass spectrum m/e (rel intensity) 148 (M^+, 86), 147 (100), 120 (25), 93 (14), 65 (7); mol wt calcd for $C_7H_8N_4$, 148.07489; found, 148.07588.

Peak 3 (8%) (compound Vb) exhibited the following spectra: nmr δ 9.07 (s, 1, H_3), 8.27 (d, 1, J = 2.5 ± 0.5 Hz, H_6), 7.85 (d, 1, J = 1.5 ± 0.5 Hz, H_8), 3.2 (m, impurity), 2.80 (q, 2, CH_2), 1.38 (t, 3, CH_3); mass spectrum m/e (rel intensity) 148 (M^+, 100), 147 (12), 133 (10), 120 (5); mol wt calcd for $C_7H_8N_4$, 148.07489; found, 148.07559.

Irradiation of I in 2-Propanol. A solution of I in 2-propanol was irradiated as above, yielding 0.21 g of a yellow gum. The gum exhibited nmr peaks ($CDCl_3$) at δ 8.58 (s, 1), 7.80 (m, 1), 4.75 (s, 1, exchanged with D_2O), 3.5–2.8 (m, 3), 1.41 (s, 3), and 1.26 (s, 3). The latter two peaks appeared at δ 1.32 and 1.00 in hexadeuteriodimethyl sulfoxide and changed to 1.34 and 1.12 at 150°. Also at 150°, a new peak appeared in the nmr spectrum at δ 2.12. This peak was increased when a trace of acetone was added. The gum, when heated to 280° for 10 min and sublimed at 250° (1 mm), yielded a white semisolid (29%). The semisolid gave three peaks in the vpc with a ratio of 14:12:74. Peak 1 proved to be starting material, compound I. Peak 2 (compound VIc) exhibited the following spectra: nmr δ 9.01 (s, 1, H_3), 8.19 (d, 1, J = 8 Hz, H_6), 6.82 (d, 1, J = 7 Hz, H_7), 3.63 (m, 1, CH), 1.51 (d, 6, J = 6 Hz, CH_3); mass spectrum m/e (rel intensity) 163 (33), 162 (M^+, 84), 148 (24), 147 (100), 138 (33), 136 (36), 120 (66); mol wt calcd for $C_8H_{10}N_4$, 162.09054; found, 162.09051.

Peak 3 (compounds Vc and VII) exhibited an nmr spectrum as follows: δ 9.21 (s, 1), 8.60 (s, compound VII), 8.42 (d, 1, J = 4 Hz), 7.97 (d, 1, J = 3 Hz), 7.70 (m, compound VII), 3.30–2.80 (m, compound VII), 1.42 (d, 6, J = 6 Hz). The ratio of Vc to VII was 1:3. When the solution was extracted with water, the nmr peaks at δ 8.60 and 7.70 and most of the multiplet at δ 3.30–2.80 were removed from the spectrum. Those peaks were the same as those exhibited by authentic VII as shown above. The new spectrum showed peaks at δ 9.21 (s, 1, H_3), 8.42 (d, 1, J = 4 Hz, H_6), 7.97 (d, 1, J = 3 Hz, H_8), 3.12 (m, 1, CH), 1.42 (d, 6, J = 7 Hz, CH_3). The mass spectrum of purified Vc exhibited peaks at m/e (rel intensity) 162 (M^+, 10), 149 (33), 148 (33), 147 (100); mol wt calcd for $C_8H_{10}N_4$, 162.09054; found, 162.09051.

Irradiation of Va in Methanol. A solution of Va in methanol was irradiated as above. A white solid separated, 0.04 g, mp 200–204°. The solid was insoluble in all normal nmr solvents. Sublimation of the solid at 250° (1 mm) gave a white solid which proved to be compound VIII[8] and some impurity. This material gave only compound VIII when subject to separation on the vpc.

Irradiation of I and Benzophenone in Acidified Methanol. Compound I (0.72 g, 6 mmol), 1.09 g (6 mmol) of benzophenone, and 300 ml of 2% hydrochloric acid in methanol were saturated with nitrogen and irradiated for 65 hr. Nitrogen was sparged through the solution throughout the irradiation. The solvent was then removed under vacuum, 50 ml of water was added, and the resulting aqueous solution was extracted three times with 50-ml portions of ether to yield the neutral fraction. This fraction was found to contain benzophenone and methyl benzoate.[18] The remaining aqueous phase was made basic by adding solid sodium hydroxide and extracted continuously for 24 hr. The ether extract was dried over anhydrous sodium sulfate and evaporated to give 0.35 g of a gummy material. The gummy material was dissolved in methylene chloride and separated on a preparative silica gel thin layer plate using chloroform–methanol (9:1) for development. Two fractions were isolated. Fraction 1 (100 mg) proved to be starting compound I. Fraction 2, 36 mg (5%) (compound IX), was sublimed at 160° (20 mm): nmr δ 9.10 (s, 1, H_3), 8.30 (d, 1, J = 4 Hz, H_6), 7.68 (d, 1, J = 4 Hz, H_7), 5.88 (s, 1, CH), 3.50 (s, 6,

OCH_3); mass spectrum *m/e* (rel intensity) 164 ($M^+ - 30$, 67), 163 (22), 149 (100); mol wt calcd for $C_8H_{10}N_4O_2$ ($M^+ - 30$), 164.06780; found, 164.06882.

Irradiation of II and Benzophenone in Acidified Methanol. A mixture of II, benzophenone, and acidified methanol was irradiated as in the preceding experiment. The neutral fraction yielded benzophenone and methyl benzoate[18] as above. The basic fraction yielded 0.55 g of a gummy solid. Most of this dissolved in 5 ml of methylene chloride, leaving 110 mg of a white solid. The solid was sublimed at 170° (20 mm) to give compound X: ir 3200 cm^{-1} (OH); nmr δ 8.22 (d, 1, J = 6 Hz, H_6), 7.88 (s, 1, H_3), 7.62 (s, 1, H_2), 6.98 (d, 1, J = 5 Hz, H_7), 5.09 (s, 2, CH_2OH), 3.05 (s, 1, exchanged with D_2O, OH).

Anal. Calcd for $C_7H_7N_3O$: N, 28.17. Found: N, 27.91.

The remaining gummy material, which was soluble in methylene chloride, was chromatographed on 50 g of alumina using increasing amounts of chloroform in petroleum ether (bp 30–60°) as eluent. Fractions 19–22 contained 95 mg of starting II and 10 mg (>1%) of XI (ir and nmr were the same as those of an authentic sample[10]). Fractions 51–60 were further separated on a preparative silica gel tlc plate to yield 60 mg of X. This gave a total yield of 170 mg (22%) of X.

Miscellaneous Irradiations. No reaction was observed when II or tetrazolo[1,5-*a*]pyridazine (XIX) were irradiated in methanol. No reaction was observed when I was irradiated in tetradeuteriomethanol for over 40 hr or in *tert*-butyl alcohol.

Acknowledgment. The authors wish to thank Dr. V. Kramer and Mr. M. Medved of the Jozef Stefan Institut for obtaining the mass spectrometric analysis and to Dr. J. Kobe for his many helpful discussions of this work.

Registry No.—I, 274-83-9; II, 766-55-2; Vb, 50357-91-0; Vc, 50357-92-1; VIb, 50357-93-2; VIc, 50357-94-3; VII, 50357-95-4; IX, 50357-96-5; X, 50357-97-6; 6-chloro-*s*-triazolo[4,3-*b*]pyridazine, 28593-24-0.

References and Notes

(1) U. S. National Academy of Sciences Exchange Professor, 1972–1973, on leave from the Brigham Young University, Provo, Utah 84602.
(2) F. R. Stermitz, R. P. Seiber, and D. E. Nicoderm, *J. Org. Chem.*, **33**, 1136 (1968).
(3) G. S. Hammond, W. P. Baker, and W. M. Moore, *J. Amer. Chem. Soc.*, **83**, 2795 (1961).
(4) F. R. Stermitz, C. C. Wei, and C. M. O'Donnell, *J. Amer. Chem. Soc.*, **92**, 2745 (1970).
(5) See M. Natsume and M. Wada, *Tetrahedron Lett.*, 4503 (1971), for additional references.
(6) A. Stankunas, I. Rosenthal, and J. N. Pitts, Jr., *Tetrahedron Lett.*, 4770 (1971).
(7) D. Elad and J. Solomon, *Tetrahedron Lett.*, 4783 (1971).
(8) M. Japelj, B. Stanovnik, and M. Tišler, *Monatsh. Chem.*, **100**, 671 (1969).
(9) J. Kobe, B. Stanovnik, and M. Tišler, *Tetrahedron*, **24**, 239 (1968).
(10) A. Pollak, B. Stanovnik, and M. Tišler, *Tetrahedron*, **24**, 2623 (1968).
(11) W. A. McFadden, J. Wasserman, J. Corse, R. E. Lundin, and R. Texanishi, *Anal. Chem.*, **36**, 1031 (1964).
(12) Z. Pelah, J. M. Wilson, M. Ohashi, M. Budzikiewicz, and D. Djerassi, *Tetrahedron*, **19**, 2233 (1963).
(13) B. Stanovnik, M. Tišler, V. Kramer, and M. Medved, unpublished observations.
(14) See, for example, D. J. Cram, F. Hauck, K. R. Kopecky, and W. D. Nielsen, *J. Amer. Chem. Soc.*, **81**, 5767 (1959).
(15) J. S. Bradshaw, B. Stanovnik, and M. Tišler, *Tetrahedron Lett.*, 2199 (1973).
(16) J. S. Bradshaw, B. Stanovnik, and M. Tišler, *J. Heterocycl. Chem.*, **10**, 801 (1973).
(17) B. Stanovnik and M. Tišler, *Tetrahedron*, **23**, 387 (1967).
(18) The photolysis of benzophenone in acidified methanol yielded methyl benzoate as the major product: J. S. Bradshaw, *J. Chem. Soc., Chem. Commun.*, 504 (1973).

3-Aryl-1,3,5,5-tetramethylcyclohexanols. Preparation and Stereochemical Characterization by Proton Nuclear Magnetic Resonance[1]

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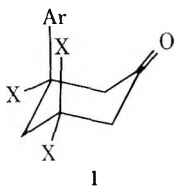
Received August 27, 1973

A series of cis and trans isomers of 3-aryl-1,3,5,5-tetramethylcyclohexanols (the 3-aryl substituent being phenyl, *o*-, *m*- or *p*-methoxyphenyl, *p*-chlorophenyl, or α-naththyl) was prepared; the separated isomers were characterized by detailed proton nmr studies. These studies included an extensive characterization of stereochemistry by means of lanthanide-induced shifts (LIS), primarily using $Eu(FOD)_3$, and by temperature variation. The results of these studies are consistent with the existence of biased mobile equilibria between two chair-like conformers. The extent of biasing is much greater in the cis alcohols than in the trans, with the biasing being toward an axial disposition of the hydroxyl group (with the cis aryl substituent also enjoying an axial oientation). LIS data are used to examine the possible mechanisms involved in aryl ring bond rotation processes in these highly hindered systems. The varying steric requirements and resulting LIS variations (including the observation of numerous *upfield* europium-induced LIS) are investigated using ortho, meta, or para substituents; these studies also provide structurally similar cases for probing shift reagent complexation of two sites of greatly differing basicities. An additional conformational biasing, caused by $Eu(FOD)_3$, was observed in the cis o-anisyl alcohol derivative.

For some time now, we have studied a number of 3,3,5,5-tetrasubstituted (and other) cyclohexanones,[3] of the type of structure 1, where X is a substituent other



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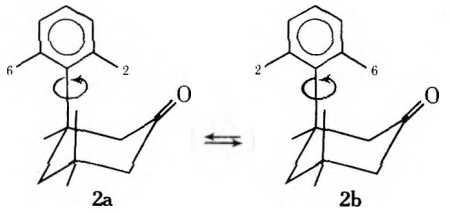
than hydrogen and Ar is an aryl moiety. Also, we have studied various alcohols as well as other compounds[4] derived in turn from these ketones. It was found for the cyclohexanones that, when one of the four substituents is an aryl group, this substituent uniformly exhibits a strong tendency to adopt an axial orientation in preference to a methyl group being in the analogous disposition.[3a] Previous reports have dealt with several consequences of this structural preference, the chemistry, the special nmr spectroscopic observations, and the LIS (lanthanide-induced shifts) in these systems.[3b] In addition to findings previously described, we have noted that, in ketones containing an axial phenyl or axial para-substituted phenyl substituent, the two ortho and the two meta hydrogens appear equivalent on the nmr time scale. It is of interest, then, to obtain an understanding of the process(es) that permits the observed equilibration of these energetically

identical conformers, shown for example by structures **2a** and **2b**.



It is also relevant to see whether a similar time-averaged equivalencing of aryl rotamers such as **2a** and **2b** occurs for the more hindered axial cyclohexan*ols*, and it will be shown that such averaging is indeed the case. For instance, *cis*-3-(*p*-anisyl)-1,3,5,5-tetramethylcyclohexanol (*vide infra*) shows an aryl hydrogen nmr spectrum of the AA′BB′ type (rather than the ABCD type which could arise from an aromatic ring in a fixed orientation), not only at room temperature, but even down to −75°. Even more striking is the observation that the AA′BB′ nature of this spectrum is retained even when the chemical shift difference for these aryl protons is increased by addition of $Eu(FOD)_3$ (*vide infra*) to ten times the undoped-spectrum shift difference; this corresponds to complete rotational averaging of shifts even at an hypothetical 1000-MHz spectrometer frequency, at which processes of one-tenth the rate, *i.e.*, ~1.5 kcal/mol lower energy, would be detectable.

There were, in addition, several other reasons for preparing and studying this series of compounds. The first reason was to investigate any possible aromatic substituent effects on the observed high-field methyl chemical shift of the syn C-5 methyl group of the cis isomers relative to the shift induced by an unsubstituted phenyl. Although ring current induced shifts have been investigated quite extensively for protons lying in or near the aromatic ring plane, few data are available for out-of-plane, diamagnetic shifts (however, see ref 4a). An accurate knowledge of these ring current effects for a wide variety of aromatic substituents is potentially of great use in structural analysis, and such findings have important implications for the spectral studies of biologically interesting systems.[5] The second reason was to make an exploratory study of the LIS observed in cases where there are two binding sites of markedly different basicity in the molecule—a strongly binding alcohol function and a much more weakly binding aryloxy group. The third reason was to study the effects of 3-aryl substituents with different electronic and steric natures on flattened, chair-like cyclohexane rings and on the axial *vs.* equatorial preference of an aromatic substituent. Finally, these methoxyphenyl compounds provide valuable synthetic intermediates for conversion to a variety of benzobicyclic hydrocarbons analogous to previously reported compounds of synthetic and theoretical interest because of their very high-field methyl resonances (δ −0.15 to −0.38).[4a]

This report, then, will be concerned with the detailed analysis of the aromatic and aliphatic parts of the proton nmr spectra of these compounds, with special emphasis placed on the variety of stereochemical information contained therein.

Compound Identification and Nomenclature. To facilitate a clear and simple discussion of these compounds we have adopted the use of abbreviations for compound names[6] rather than constant referral to Roman numerals. The cis or trans naming of these compounds refers to whether the *aryl* group at C-3 is cis or trans to the hydroxyl group at C-1. As shown in Figure 1, the designation of the protons in both the cis and trans isomers is as follows: (1) in the *major* conformer, protons a, c, and e are equatorial and cis to the hydroxyl group whereas protons b, d, and f are axial and trans to the hydroxyl; (2) methyl groups are labeled with respect to their disposition relative to the aromatic ring, such that Me_{5c} is always cis and Me_{5t} is always trans to the aryl moiety. This is consistent with our previous reports on these compounds and is a useful designation, since Me_{5c} is always the group most influenced by the anisotropy of the aromatic ring.

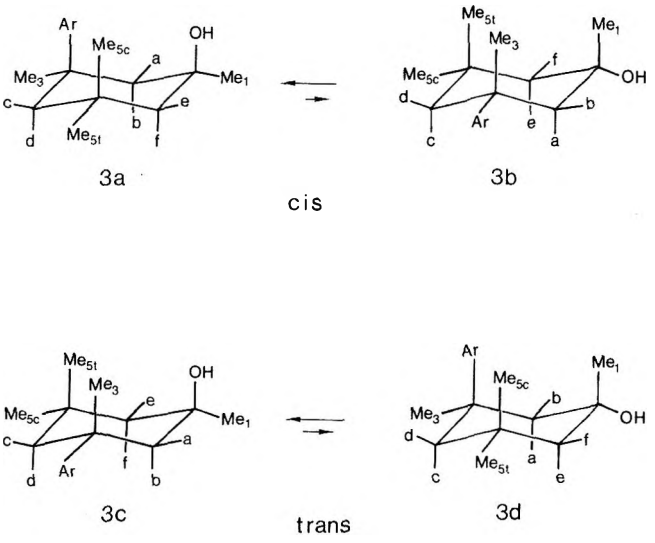


Figure 1. Proton designations for the cis (**3a** and **3b**) and trans (**3c** and **3d**) alcohol isomers where the aryl moiety (Ar) is C_6H_5, *p*-ClC_6H_4, *p*-$OMeC_6H_4$, *m*-$OMeC_6H_4$, *o*-$OMeC_6H_4$, or α-$C_{10}H_7$.

Preparation and Characterization of Compounds. In all cases, the individual cis and trans isomers were readily separated by chromatography from the mixture of alcohols obtained by the addition of methylmagnesium bromide to the corresponding cyclohexanone.[3b] The expected tertiary alcohol nature of these compounds was confirmed in the usual fashion, as well as by the extensive proton nmr studies to be described. The cis and trans identification of the isomeric tertiary alcohols so obtained was readily accomplished by means of proton nmr spectroscopy. In the cis alcohols, the most immediate evidence of an axially disposed aromatic ring (as the sole or highly predominant conformer) is the observation of a methyl chemical shift (Me_{5c}) at markedly high field,[3a] resulting from the perpendicular ring current shielding effect suffered by the methyl in a conformation like **3a**. Although these methyl (Me_{5c}) shifts occur at sufficiently high field to permit ready identification of isomers, they are in fact at significantly lower fields than those in their precursor ketones. This fact is readily consistent only with the axial disposition of the hydroxyl function, such that the electric field effect deshielding caused by the oxygen is felt at a syn-axial methyl group, Me_{5c}. The axial-hydroxyl, equatorial-aryl nature of the trans isomers was deduced in an analogous fashion. These structural assignments are consistent with expectations based on the principles of conformational analysis.

LIS Methodology. A considerable amount of work has appeared on the mechanism involved in lanthanide shift reagent (LSR)–substrate binding.[7,8] As in most cases of chemical interest, it is clear that we are dealing here with time-averaged spectra of the "fast-exchange" type, where the observed shift, δ_{obsd}, of a given proton is a concentration-weighted average of the shifts of the individual species in solution (S, LS, LS_2, *vide infra*).

It has been shown that the observed concentration dependence of the LIS for compounds of these types requires at least a two-step equilibrium model[8] with four parame-

Table I
δ_0 Values Observed and Slope Values[a] Derived for Methyl Protons, from LIS Data Using Eu(FOD)$_3$ at 30°, CCl_4 Solution

		Cis alcohols (3a ⇄ 3b)						Trans alcohols (3c ⇄ 3d)					
		PhOH (50361-38-1)[b]	PCOH (50361-40-5)	PAOH (50361-42-7)	MAOH (50361-44-9)	OAOH (50361-46-1)	αNOH (33875-98-8)	PhOH (50361-39-2)	PCOH (50361-41-6)	PAOH (50361-43-8)	MAOH (50361-45-0)	OAOH (50361-47-2)	αNOH (33875-97-7)
δ_0	Me_{3c}	0.66	0.66	0.67	0.70	0.67	0.48	1.29	1.29	1.25	1.27	1.24	1.38
	Me_3	1.08	1.06	1.04	1.08	1.16	1.59	1.51	1.49	1.44	1.48	1.54	1.91
	Me_{3t}	0.90	0.90	0.88	0.90	0.87	0.90	0.90	0.90	0.88	0.90	0.87	0.92
	Me_1	1.18	1.21	1.16	1.18	1.16	1.24	1.25	1.22	1.19	1.22	1.17	1.24
λ	Me_{3c}	6.56	6.36	5.78	5.70	5.74	5.79	4.40	4.54	4.48	4.42	5.13	6.16
	Me_3	3.62	3.38	3.20	3.64	4.66	3.47	4.32	4.42	4.40	4.38	5.25	6.60
	Me_{3t}	3.99	3.98	3.44	3.54	3.42	3.84	4.01	3.96	4.22	4.02	3.99	4.12
	Me_1	16.68	16.28	14.92	15.40	10.10	16.28	12.59	12.06	13.18	12.44	13.14	13.29

[a] In parts per million. [b] Registry no.

Table II
δ_0 Values Observed and Slope Values[a] Derived for Methylene Protons, from LIS Data Using Eu(FOD)$_3$ at 30°, CCl_4 Solution

		Cis alcohols (3a ⇄ 3b)						Trans alcohols (3c ⇄ 3d)					
		PhOH	PCOH	PAOH	MAOH	OAOH	αNOH	PhOH	PCOH	PAOH	MAOH	OAOH	αNOH
δ_0	a	2.62	2.62	2.62	2.64	2.90	2.92	1.95	1.90	1.89	1.92	2.05	2.25
	e	1.37	1.38	1.42	1.45	1.43	1.42	1.54	1.52	1.55	1.53	1.50	1.62
	b	1.21	1.22	1.28	1.27	1.17	1.48	1.72	1.64	1.66	1.68	1.80	1.92
	f	1.25	1.25	1.19	1.19	1.19	1.24	1.21	1.21	1.21	1.19	1.21	1.32
	c	2.39	2.33	2.34	2.39	2.90	2.80	1.78	1.78	1.74	1.79	1.89	2.16
	d	1.18	1.27	1.20	1.22	1.03	1.36	1.57	1.49	1.52	1.52	1.64	1.80
λ	a	14.43	14.40	12.86	13.98	15.80	13.45	15.63	15.68	16.70	15.62	15.73	16.73
	e	15.81	15.78	14.24	14.90	13.06	15.85	16.02	15.48	16.76	15.90	16.90	17.25
	b	9.24	8.76	8.00	8.52	8.44	9.17	12.83	12.56	13.66	12.64	12.61	11.62
	f	9.10	9.02	8.06	8.70	7.06	9.25	12.25	11.60	12.96	11.96	12.24	11.07
	c	5.18	4.98	4.66	4.92	5.90	5.14	5.14	5.06	5.40	5.04	5.38	6.28
	d	6.37	6.10	5.56	5.92	6.18	5.94	5.05	5.14	5.36	5.14	5.88	6.28

[a] In parts per million.

ters being necessary to describe fully the observed shifts, as shown in eq 1, where K_1 and K_2 are the equilibrium

$$\begin{aligned} L + S &\rightleftharpoons LS \quad (K_1, \Delta_1) \\ LS + S &\rightleftharpoons LS_2 \quad (K_2, \Delta_2) \end{aligned} \tag{1}$$

constants for association and Δ_1 and Δ_2 are the incremental shifts of the pure LS and LS_2 species, respectively. Both Δ_1 and Δ_2 are intrinsic functions of the LS and LS_2 species, and have been shown[8] to be related directly to the observed initial slope (λ) of a δ_{obsd} *vs.* ρ (= L_0/S_0 where L_0 = the total molar LSR *concentration and* S_0 = the total substrate molarity) plot, by

$$\lambda = \frac{\partial(\Delta\delta)}{\partial\rho} \approx \frac{\Delta_1}{S_0 K_2} + 2\Delta_2 \tag{2}$$

In the incremental dilution, constant S_0 method employed in this work, the slope observed up to $\rho \leq ca.$ 0.4 is a linear combination of Δ_1 and Δ_2. If K_2 be very small, both terms in the equation are required. However, when K_2 is large, λ is simply $2\Delta_2$ to an excellent degree of approximation. We have found that the term containing Δ_1 is dominant for tertiary alcohols; these findings will be presented elsewhere. Although sufficient "contamination" of the slope by Δ_2 enters in so as to preclude the slopes as being suitable numbers for a rigorous structure calculation, the λ values are more than adequate for the present purposes. Even though two binding sites are available in each molecule, the two-step mechanism is still valid owing to LSR binding at the hydroxyl being much greater than the binding to (aryl) methoxy. The LSR interaction with the methoxy group will be discussed later.

Thus in the discussion which follows, we will be using λ values for incorporation into the pseudo-contact shift equation,[9] which may then be conveniently expressed as

$$\lambda_i = k(3\cos^2\theta_i - 1)(R_i^{-3}) \tag{3}$$

where k is a collection of constants, θ_i is the angle describing the position of the proton i relative to the principle magnetic axis of the LSR, and R_i is taken as a proton-lanthanide ion distance. Parenthetically, one should note that the constant, k, has different values depending upon which parameter is being fitted [*i.e.*, λ_i, observed shifts, $(\Delta_1)_i$, $(\Delta_2)_i$, etc.]. The λ_i values, then, may be used for assessments of molecular geometry, *viz.*, to distinguish between the relative importance of two or more specific geometric possibilities. Rather than attempting to fit the structures in a fully rigorous parametric fit to eq 3, we shall simply compare the magnitudes of λ for protons symmetrically disposed to the alcohol oxygen, and therefore to the metal of the LSR.

It may be pointed out that, by the incremental dilution, constant-S_0 method employed here, the λ_i values are determined experimentally to very high precision: for doping levels expressed by $\rho \leq ca.$ 0.4, a linear least-squares regression analysis yields a correlation coefficient always greater than 0.99 for any acceptable set of data (usually >0.999) and it is useful in obtaining δ_0 values (the chemical shifts in the absence of LSR) of partially obscured or strongly coupled protons.[3b,10] Values of this coefficient less than *ca.* 0.98 are most often caused by "scavenging" (*i.e.*, binding by strongly basic impurities),[10] and are cause for rejection of the data of a particular experiment.

Results and Discussion

In Tables I–III are presented the δ_0 values (either observed or obtained by extrapolation) and λ values for the methyl, methylene, and aromatic protons, respectively, for the alcohol isomers. The λ values refer to 0.15 *M* sub-

Table III
δ_0 Values Observed and Slope Values[a] Derived for Aromatic Protons, from LIS Data Using Eu(FOD)$_3$ at 30°, CCl_4 Solution

		Cis alcohols (3a ⇄ 3b)						Trans alcohols (3c ⇄ 3d)					
		PhOH	PCOH	PAOH	MAOH	OAOH	αNOH	PhOH	PCOH	PAOH	MAOH	OAOH	αNOH
δ_0	2	7.45	7.42	7.35	7.09	7.59	7.88	7.32	7.18	7.22	6.88	7.18	*b*
	3	7.22	7.14	6.70	7.10	6.80	7.27	7.21	7.21	6.72	7.11	7.05	*b*
	4	7.05			6.58	7.07	7.56	7.05			6.57	*b*	*b*
	5	7.22	7.14			6.80	7.72	7.21	7.21	6.72		*b*	*b*
	6	7.45	7.42		7.16			7.32	7.18	7.22	6.83		
	OMe			3.71	3.74	3.84				3.72	3.75	3.82	
λ	2	3.99	3.28	3.50	4.14	5.74	6.69	3.59	3.51	3.82	3.68	4.19	4.45
	3	−3.52	−4.30	−3.10	−3.94	−3.46	−7.76	1.20	1.36	1.72	1.42	1.48	
	4	−2.56			−1.26	−1.14	−1.98	1.40			1.22		
	5	−3.52	−4.30	−3.10		0.76	−0.45	1.20	1.36	1.72			
	6	3.93	3.28	3.50	5.30			3.59	3.51	3.82	3.76		
	OMe			−1.70	−1.54	1.40				1.02	0.96	1.50	

[a] In parts per million. [b] Resonances obscured owing to complex multiplets.

strate solutions in CCl_4, at 30° and, except where noted, doped with Eu(FOD)$_3$. Coupling constants ($^2J_{HH}$ and $^4J_{HH}$) were typical in magnitude for a cyclohexane chair structure, but were not measured precisely, for they are of little utility for the present purposes. It should be noted that the specific assignments given do not rest on any interpretation of the relative LIS *magnitudes*, but are of course consistent with these. Rather, the assignments follow unambiguously from the undoped shifts (*cf.* ref 3b) and the multiplicity and relative widths of the individual signals seen in the LIS-dispersed spectra. The methylene assignments were confirmed by the appropriate spin-decoupling experiments.

Cis Alcohols. Aliphatic Protons. Inspection of the δ_0 values of Table I immediately permits the conclusion that the structures of the various cis alcohols do not vary appreciably, at least for the substituted phenyl alcohols, from one to the other. For example, one may note the constancy of the chemical shift of a given type of methyl. The exceptions of Me_3 and Me_{5c} in *cis*-αNOH clearly arise from the additional ring-current and anisotropy effects associated with ring B of the α-naphthyl system. A similar trend is observed on a qualitative examination of the *methylene* δ_0 values (Table II). It is also of some theoretical interest here that the Me_{5c} chemical shift cannot be used to distinguish between the various substituted phenyl groups on C-3. The correlations observed for the aryl anisotropy and alterations in it caused by various substituent groups have also been of interest in other types of compounds studied in our work. For instance, in a closely related system where all the aromatic hydrogen atoms are replaced by chlorine, no substantial difference in the upfield shifts experienced by Me_{5c} was observed.[11]

This similarity of structure is also evident from the observed λ values. An important aspect of these values is the consistent pairing of proton types equivalently disposed about a pseudo-symmetry plane (*i.e.*, a plane passing through the hydroxyl group, C-1, and C-4), *viz.*, a and e, b and f, as well as Me_3 and Me_{5t}. This complementary pairing of the methylene protons and equatorial methyl protons is consistent with the results obtained on the ketone precursors of these alcohols and is most readily rationalized in terms of a flattened cyclohexanoid ring system which possesses chair-like symmetry and shape. (The complementary pairing of the LIS would be unlikely for otherwise plausible twist-boat conformations, without numerous fortuitous shift averagings.)

This view is supported both by the similarity of the slopes obtained for proton d and for Me_{5c}, and by four-bond couplings of proton a (and proton e) to proton c without analogous proton b–d and proton f–d couplings.

The observed flattening distortion to this ring is caused by a syn-axial compression ("reflex effect") between the two large axial substituents at C-3 and C-5. This deformation appears to have only lateral, rather than longitudinal, twisting components; that is, the axial C-3 and C-5 substituents move away from each other along the normal of the O–C_1–C_4 plane. In the case of 3-(*p*-chlorophenyl)-3,5,5-trimethylcyclohexanone (PCK), LIS-based conclusions about such a structural feature in the liquid state are found precisely mirrored in the carefully determined solid-state structure.[12] The present LIS data suggest strongly that similar considerations should apply to the cyclohexanols.

We turn now to a more detailed examination of the λ values obtained for the cis alcohols. Looking first at the methyls at the C-3 and C-5 cyclohexyl ring positions, it is clear that Me_{5c} consistently has larger λ values than do the equatorial Me_3 and Me_{5t}. The reverse behavior is noticed for the methylene protons at C-2 and C-6 (Table II), with the equatorial protons havig the larger LIS. In addition, as previously observed for the ketones,[3b] proton d has a similar λ value to Me_{5c}. This presumably results from the flattening of the chair due to the reflex effect.

In *cis*-OAOH there is somewhat of a departure from the similarity of the LIS experienced for complementary proton pairs. An example of this deviation can be observed on examination of the λ values for Me_3 and Me_{5t}. A reasonable explanation of this difference involves the orientation of the aryl substituent. From the δ_0 values in Table II, it is readily observed that the proton c resonance for *cis*-OAOH is abnormally downfield in comparison with the other phenyl-type compounds, but displays a similar shift to the analogous proton of *cis*-αNOH. For *cis*-αNOH this downfield shift has been explained[3a] by ring B of the α-naphthyl system spending a considerable amount of time near proton c, its edge effect (and associated paramagnetic anisotropy) causing the observed downfield displacement. A similar orientation of the o-anisyl ring would place the oxygen of the methoxy group near proton c, causing deshielding resulting from the electric field effect of the oxygen.[13] Proton d is probably placed in the shielding region of the oxygen anisotropy and/or the aromatic ring, and the resonance shifted upfield. The LIS results for *cis*-OAOH can then most readily be accommodated by a biased rotation of the aromatic ring, upon addition of Eu(FOD)$_3$, to a conformer in which the methoxy group is oriented toward the hydroxy group. In such an orientation, a bidentate chelate species could be formed with the LSR, as depicted in Figure 2.

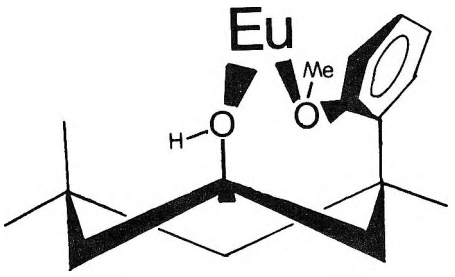
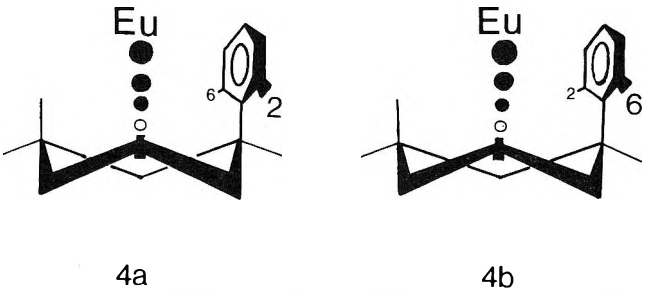


Figure 2. Bidentate chelate complex for *cis*-OAOH.



4a 4b

Figure 3. Orientations of the two low-energy rotamers in the case of phenyl or para- or meta-substituted phenyl aryl substituents.

Inspection of molecular models serves to confirm the steric reasonableness of this proposal. Such binding probably causes the LSR to move slightly away from the O–C_1–C_4 pseudo-symmetry plane closer to protons a and b than to protons e and f, and similarly closer to Me_3 than to Me_{5t}. The observed λ values are consistent with this notion, as is the absence of this effect in the other cis alcohols. (These arguments require only a reasonable similarity in the O–Eu–H angles, so that the observed differences are sensitive primarily only to the R_i^{-3} distance term of eq 3.) Although this effect of bidentate chelation appears to be small, it becomes more important to the observed LIS of *cis*-OAOH at lower temperatures, as discussed later.

It is interesting that the above-described rotation of *cis*-OAOH and subsequent chelation is not observable when $Eu(DPM)_3$ is used as the LSR, as indicated by the λ values of the complementary proton pairs (Table IV). A possible explanation lies in the fact that $Eu(DPM)_3$ is a weaker Lewis acid than $Eu(FOD)_3$ with, therefore, far smaller binding to the weakly basic methoxy oxygen. The larger magnitude for the LIS produced by $Eu(DPM)_3$ is consistent with our previous findings.[14]

Aromatic Protons. The aromatic resonances show LIS behavior much different from that observed for the other protons discussed above. The observation of *upfield* shifts is noteworthy owing to the important stereochemical implications associated with them.[4b,15] Such shifts are predicted by the pseudo-contact equation, the direction of the shift change being a consequence of the molecular geometry of the system studied, as required by the angle-dependent term of eq 3. These LIS to high field were first observed in *cis*-αNOH[4b] and serve to further confirm the axial disposition and the rotational preference of such an aromatic moiety. The similar structures of *cis*-αNOH and the other cis alcohols here suggest that upfield LIS might be observed. In fact, it was found that the λ values for protons at the phenyl ring positions 3 and 4 have negative (upfield) shifts (see Table III). (Analogous *downfield* shifts induced by $Pr(DPM)_3$ for protons 3 and 4 in *cis*-PAOH were observed.) As previously mentioned, protons 2 and 6 are nmr equivalent, as are protons 3 and 5. Examination of Dreiding models and the precise X-ray crystallographic structure of PCK indicate that it may be difficult for the aryl protons, such as 2 and 6, in the phenyl or para-substituted aromatic rings to become equivalent simply by rotation of the aromatic ring in a single aryl-axial conformer such as indicated in **2a**.

A method for estimating the rotational orientation of the aryl substituent was developed for the analogous ketones and is also applicable here. The model assumes that the energy minima for aryl rotation occur when the aromatic ring is parallel (or nearly so) to the C_2–C_3 cyclohexane ring bond, and that, if this be so, one may be able to neglect other orientations to a fair degree of approximation. Thus for phenyl or para-substituted phenyl, there is an equal population of rotamers **2a** and **2b**. Now in ortho- or meta-substituted compounds, if protons 2 and 3 have LIS similar to those of protons 6 and 5, respectively, it is assumed that the aromatic moiety does not show substantial biasing toward one rotamer or another as indicated by structures **2a** and **2b**. Since, for steric reasons, *cis*-αNOH is capable of only one low-energy orientation (that which places ring B of the naphthyl system near proton c), it serves as a good model. In a system in which there is no single preferred aryl orientation, the LIS experienced by protons 2 and 3 should be about one-half those observed for the *cis*-αNOH, since they are in an analogous position, for one-half the time. Actually, considering protons 2 and 6, this is due to an averaging of a large downfield LIS occurring from an orientation of the aromatic ring such as in **4a** with a small downfield shift occurring in **4b** (see Figure 3).

Thus these LIS's for protons 2 and 6 are mainly due to the R_i^{-3} term of eq 3, since the variation in $\cos^2\theta$ is not substantial between these two rotamers. Similarly, for proton 3 and 5, a large *upfield* shift is averaged with a small downfield shift; hence the observed results. Previously it was shown that *cis*-OAOH is capable of existing in two descrete orientations with the minor one facilitated by the methoxy interaction with the LSR. Judging from the LIS of proton 2, the aryl group behaves so as to be hindered in rotation more like the α-naphthyl group in *cis*-αNOH.

The molecular dynamics by which protons 2 and 6 (as well as 3 and 5) are made equivalent is worthy of comment. For reasons previously mentioned the simple rotation of an unsubstituted (or para-substituted) phenyl ring might be energetically prohibitive even for the reflex effect flattened cyclohexanone or cyclohexane rings. Such a view would seem to require that aryl rotation occur in the cyclohexane ring inverted conformer **3b** which, of course, need not be present to a major extent if the aryl rotation barrier in **3b** be markedly less than that for the **3a** ⇄ **3b** interconversion, as is reasonable.

Table IV
λ Values[a] Observed for *cis*-OAOH Using $Eu(DPM)_3$ [$Eu(FOD)_3$ Values in Parentheses for Comparison]

Me_1	Me_3	Me_{5c}	Me_{5t}	a	e	b	f	c	d	H_2	H_3	H_4	H_5	OMe
20.20	5.66	8.66	5.48	21.34	21.85	13.94	14.28	8.24	8.74	13.14	−8.04	−2.26	~0	0.39
(10.10)	(4.66)	(5.74)	(3.42)	(15.80)	(13.06)	(8.44)	(7.06)	(5.90)	(6.18)	(5.74)	(−3.46)	(−1.14)	(0.76)	(1.40)

[a] In parts per million.

An alternative mechanism involving a "gearing" of aryl rotation with some cyclohexane ring flexing process remains to be considered, for such a process seems consistent with both the experimental evidence now available and with the known lowered ring inversion barriers in 1,1,3,3-polysubstituted cyclohexane rings.[16]

LSR–Methoxy Interaction. Although a relatively minor effect overall, methoxy binding is important in order to understand more completely the LIS observed for the aromatic proton types. Since an excellent comparison exists between *cis*-PAOH and *cis*-PCOH, the only difference in these being chlorine *vs.* methoxy, any interactions resulting from methoxy binding should be directly observable. It was found that the LIS of protons 3 and 5 in *cis*-PAOH is of significantly smaller magnitude than that for the 3,5 pair in *cis*-PCOH. This observation is in accord with the methoxy group acting as a secondary binding site in competition with complexation at the hydroxyl group. (The probability of complexation occurring at both sites simultaneously is, of course, negligible.) Even a small interaction by the methoxy should cause the LIS of the cyclohexyl proton shifts to be reduced, as observed on comparing the λ values for *cis*-PCOH *vs.* *cis*-PAOH. Additionally, when the LSR is bound to the methoxy group, only the closer ring protons 3 and 5 are afforded a substantially enhanced downfield shift. It is the above interaction which probably causes the large differences in the LIS of protons 2 and 6 in *cis*-MAOH and the downfield shift of proton 5 in *cis*-OAOH. Finally, it is noticed at high doping levels ($\rho \approx 3$) that, when a limiting shift is approached for even greatly shifted resonances ($\lambda > 12$ ppm), the methoxy resonance continues to be altered in value (now with a *downfield* LIS for *cis*-PAOH and *cis*-MAOH). The resonances of the protons adjacent to the methoxy also continue to be shifted downfield. The *direct* effect of the LSR–methoxy interaction on the cyclohexane ring proton shifts is negligible.

Trans Alcohols. All of the LIS observed for the trans alcohols are to lower field and, like their cis isomers, show similar λ values for the symmetry-paired proton types. Except for *trans*-αNOH and *trans*-OAOH, the difference between the LIS magnitude for equatorial and axial proton types is markedly smaller than was obtained for the cis isomers. Considering first only the methylene protons at C-2 and C-6, the average differences were found to be 3.28, 3.50, 3.42, and 3.54 ppm for *trans*-PhOH, -PCOH, -PAOH, and -MAOH, respectively, 4.39 ppm for the *trans*-OAOH, and 6.14 ppm for *trans*-αNOH. In comparison, the average difference observed in the cis isomers was 5.85 ppm, clearly indicating that, at least for the first four trans isomers, some additional interaction must be occurring so as to tend to equalize the λ values of the C-2 and C-6 protons.

As indicated above, in *trans*-αNOH two methyls (Me_3 and Me_{5t}) have similar λ values of considerably larger magnitude than that of Me_{5c}. This observation is in accord only with an axially disposed hydroxyl group and an equatorial aromatic ring and is similar to the results obtained in the cis isomers. In *trans*-OAOH the difference in the λ values for these methyl protons is not as large as in *trans*-αNOH. However, in the other trans alcohols, despite the similar LIS for the symmetry-paired cyclohexyl protons, all three methyls have nearly identical LIS. It is our present view that this unexpected result probably originates from the presence of a less biased equilibrium mixture of the two possible chair conformers which now both contribute significantly to the time-averaged structure.

These equilibria can be illustrated schematically by eq 4, where A is the axial-OH conformer, E is the equatorial-OH conformer (the structures of A and E are given in Figure 1, **3c** and **3d**, respectively), and AL and EL are the respective complexed species. It appears from our data that A and E *each* form their own complex with the LSR. The results cannot be explained by an alteration of the above equilibria where the formation of EL must arise from the prior formation of AL (*i.e.*, equilibration between AL and EL is much less important than equilibration between A and E). Conversely, AL and EL may not be long lived enough to undergo interconversion. It should be noted that any equatorial conformer present would bind more readily to the LSR then would the axial (OH) conformer.[17]

$$\begin{array}{ccc} A + L & \rightleftharpoons & AL \\ \updownarrow & & \updownarrow \\ E + L & \rightleftharpoons & EL \end{array} \qquad (4)$$

An alternative possibility (ref 18) which should be considered involves the *a priori* reasonable contribution from twist-boat and/or boat forms in the trans isomer. We feel that such involvements may be neglected as less probable than the above explanation, for the following reasons. The first reason is that, as with the cis isomers, there is marked symmetry pairing of the slopes observed for protons a–f. Any reasonable twist-boat or boat form would destroy the possibility of the observed symmetry pairing of the λ values, in the absence of several coincidences of shift averaging, plus the requirement that this coincidental averaging be uniform for the several cases where symmetry pairing is observed. The second reason is that, again as in the case of the cis isomers, the observation of line-width variations or actually observed long-range couplings for protons a, c, and e, but not for b, d, and f, suggest strongly that any time-averaged structure partakes very little of the nonchair conformation.

The data, then, serve to indicate that the A $\rightleftharpoons$ E and subsequently the E + L $\rightleftharpoons$ EL equilibria are not important for *trans*-αNOH, moderately important for *trans*-OAOH, and quite significant for *trans*-PhOH, -PCOH, -PAOH, and -MAOH. For instance, considering Me_3, Me_{5c}, and Me_{5t}, it was found that the Me_3 (or Me_{5c}) to Me_{5t} λ ratio (Table I) averaged to 1.61 for *trans*-αNOH, to 1.30 for -OAOH, and to only 1.09 for the other trans alcohols, *trans*-PhOH, -PCOH, -PAOH, and -MAOH. (Additionally, it may be noted that a qualitative experiment where the aryl substituent was *p*-tolyl yielded results similar to those of the latter group of compounds.) Since the normal trends still predominate in these latter compounds [LIS of equatorial protons (of **3c**) are greater than axial protons at C-2 and C-6], it is necessary that the AL complex always be predominant.

When the conformer with an equatorial hydroxyl is present to a significant amount as part of an equilibrium mixture, such as in *trans*-PAOH, its effects on the behavior of the LIS can be predicted. In a recent study of 4-*tert*-butylcyclohexanol[19] it was found that the difference between the LIS for the axial and equatorial protons on C-2 and C-6 in the trans isomer (equatorial OH) is less than for the cis isomer (axial OH). A similar result was noticed for protons in the C-3 and C-5 positions but with the axial protons of the trans isomer having a larger LIS. The relationsip of these results to our system is instructive. If an equatorially disposed hydroxyl conformer were present to any significant extent, the LIS differences in protons a, b, e, and f would become less than the LIS differences observed for the same protons in the cis alcohols, which appear to be much more conformationally pure. Similarly, the differences in Me_{5c}, Me_{5t}, and Me_3 should become smaller. Also, in the *trans-tert*-butylcyclohexanol, H_1 has a LIS less than the LIS of H_1 of the cis isomer.

Table V
Variable-Temperature LIS Data Slope Values[a] Derived for Methyl Groups [Eu(FOD)$_3$, CS_2 Solution]

	Ketones and cis alcohols							Trans alcohols			
	PAK[b]	MAK[c]	OAK[d]	PAOH	MAOH	OAOH	PCOH	PAOH	MAOH	OAOH	PCOH
Me_1				3.00	3.63	−0.51	3.60	2.78	3.07	2.45	2.76
Me_{5c}	1.33	1.12	1.30	1.07	1.00	0.91	1.53	0.44	0.38	0.42	0.49
Me_3	0.37	0.21	0.45	0.53	0.64	0.92	0.55	0.41	0.44	0.51	0.45
Me_{5t}	0.54	0.46	0.64	0.65	0.68	0.39	0.81	0.69	0.74	0.49	0.70

[a] In parts per million. [b] 3-(*p*-Anisyl)-3,5,5-trimethylcyclohexanone. [c] 3-(*m*-Anisyl)-3,5,5-trimethylcyclohexanone. [d] 3-(*o*-Anisyl)-3,5,5-trimethylcyclohexanone.

Table VI[a]
Variable-Temperature LIS Data Slope Values[b] Derived for Methylene Protons [Eu(FOD)$_3$, CS_2 Solution]

	Ketones and cis alcohols							Trans alcohols			
	PAK	MAK	OAK	PAOH	MAOH	OAOH	PCOH	PAOH	MAOH	OAOH	PCOH
a	2.60	1.93	2.79	2.45	2.45	2.77	2.74	2.26	2.52	1.98	2.48
e	2.80	2.12	3.39	2.49	2.75	0.60	3.27	2.79	3.16	2.06	2.70
b	1.60	1.20	1.85	1.63	1.86	1.21	1.75	2.35	2.56	1.78	2.34
f	1.69	1.44	1.98	1.66	1.86	0.40	1.97	2.46	2.69	2.00	2.46
c	0.81	0.78	0.94	0.84	0.90	0.90	1.02	0.65	0.72	0.57	0.72
d	0.94	0.79	1.08	1.04	1.07	1.08	1.20	0.73	0.83	0.62	0.72

[a] See footnotes to Table V. [b] In parts per million.

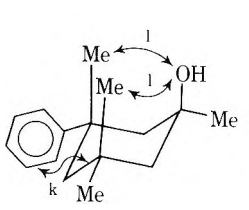
Table VII[a]
Variable-Temperature LIS Data Slope Values[b] Derived for Aromatic Protons [Eu(FOD)$_3$, CS_2 Solution]

	Ketones and cis alcohols							Trans alcohols			
	PAK	MAK	OAK	PAOH	MAOH	OAOH	PCOH	PAOH	MAOH	OAOH	PCOH
2	1.75	1.34	3.26	0.32	0.36	1.00	0.27	0.53	0.24	0.53	0.52
3	0.31	0.36	*c*	−0.98	−1.31	−0.05	−1.08	0.22	0.26	*c*	0.20
4		0.43	*c*		−0.53	0.01			0.00	*c*	
5	0.31		*c*	−0.98		0.35	−1.08	0.22	*c*	*c*	0.20
6	1.75	2.51		0.32	1.15		0.27	0.53		*c*	0.52
OMe	0.00	0.37	0.40	−0.41	−0.59	0.59		0.16	0.16	0.24	

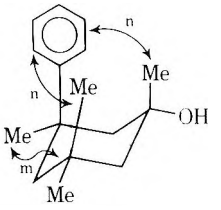
[a] See footnotes to Tables IV. [b] In parts per million. [c] Resonance obscured owing to complex multiplets.

Therefore, the LIS of Me_1 in the trans alcohols should be less than that obtained for the cis isomers. The LIS magnitudes for protons a, e, b, and f in the trans alcohols are seen to be similar to those observed in the corresponding ketones (where the average λ values for protons a, e, b, and f are 16.54, 16.18, 14.18, and 14.46 ppm, respectively). This is not surprising, since if an equilibrium mixture of A and E existed the LSR would behave, on the average, as if it were near the plane bisecting the Me_1-C-1-OH angle and in a position similar to where the LSR is believed to be for the ketones.[3b]

Substantial involvement of the equatorial-OH conformer in the trans alcohols may be rationalized by an examination of the relative energies in each conformer, as indicated in the diagram below. The major factors involved in



5a



5b

comparing the two conformers are as follows: in **5a** there are two 1,3-diaxial methyl–hydroxyl (l) interactions and one aromatic–cyclohexane ring (k) while in **5b** there are two 1,3-diaxial aromatic–methyl interactions (n) and one methyl–cyclohexane ring (m). It can be assumed that the other steric interactions in these two compounds are approximately the same. Allinger[20] recently calculated that, in 1-(phenyl)-1,3,3-trimethylcyclohexane, the conformer with an axial phenyl group is favored by 3.3 kcal/mol. It can then be calculated that the difference in energy between these two systems is approximately 1.15 kcal/mol or about 85% in favor of the conformer with the axial hydroxyl.[21] Qualitative estimates of the relative amount of each conformer present by LIS data are made difficult by the LIS not only depending on the ratio of components in solution, but on the respective association equilibrium constants of each conformer. Although **5b** may be present to a lesser degree, it would be a proportionally larger contributor to the observed LIS because of the stronger LSR binding of equatorial *vs.* axial hydroxyl groups.[17]

A possible reason for *trans*-αNOH and -OAOH preferring **5a** to a greater extent than do the other trans alcohols involves the steric nature of each of these aromatic substituents. In **5b**, the aromatic ring is axial, and, as seen from the data on the cis isomers of αNOH and OAOH, is capable of only one low-energy orientation of the aryl substituent, resulting in a loss of entropy. Owing to the similar energies of **5a** and **5b** this relatively small factor now becomes important and results in the observed trends.

Temperature Effects. To obtain a further understanding of rotational behavior of the aromatic substituent and the conformational mobility of these compounds, the nmr spectra of the LSR-doped and undoped ketones and alcohols were studied as a function of temperature. Virtually no change was observed in any of the undoped trans alcohols over the temperature range studied (43 to −75°). The ketones and cis alcohols did exhibit some relatively minor changes in their spectra on decreasing temperature; the only significant change was in the chemical shift of Me_{5c}, where on the average an *upfield* shift change of 0.1 ppm was observed. This upfield shift in the ketones and cis alcohols is consistent with an even greater

biasing of the chair-to-chair equilibrium (shown in Figure 1) such that the population of the conformer having the axially substituted aryl moiety is enhanced. The overall effect, then, would be to keep Me_{5c} in the face of the aromatic ring for a greater fraction of the time.

Although studies involving LSR have been very numerous,[22] the temperature dependence of these solutions has received comparatively little attention.[23] Investigations have shown that the magnitude of the LIS increases with decreasing temperature, and behavior opposite to this probably arises from changes in the steric requirement of the lanthanide,[23c] hence its binding position. In this study the concentrations of the substrate solutions were prepared as close as possible to the concentrations used in the incremental dilution method. The ρ value of 0.3 was chosen so that it was in the linear portion of the LIS curve, ensuring that the shifts induced by varying the temperature would be of the largest magnitude. The slopes obtained [$(\delta_{ds} - \delta_0)/\rho$ where δ_{ds} is the chemical shift of proton in the LSR doped solution] in CS_2 solutions at ambient temperature were found to be very similar to those obtained from the incremental dilution method, indicating that both the lanthanide complexation equilibria and the binding position are similar for both solvents. This finding is consistent with other recently published results.[24]

In the LSR-doped solutions (see Tables V–VII), the ketones and cis alcohols, as expected, showed trends similar in the temperature dependence of their LIS to those exhibited in the incremental dilution data. For instance, the average Me_{5c} to Me_3 λ values in *cis*-MAOH is 1.55 ppm for the incremental dilution method *vs.* 1.50 ppm for the temperature-dependence data, suggesting that the average binding position in these alcohols (except for *cis*-OAOH) is not affected very much by the variation of temperature. If any change in this binding position does occur, it is probably along the symmetry plane previously described, since symmetry-paired protons still show similar LIS (see Tables V–VII).

An interesting result was obtained from the variable-temperature study of *cis*-OAOH. Except for Me_1, all of the proton types show the usual downfield shifts with decreasing temperature. Surprisingly, Me_1 showed an *upfield* shift (Me_1 in all the other alcohols shows the *largest downfield* shifts). Again one must consider the orientation of the aromatic ring to understand this anomaly. As the temperature is lowered, the rotamer where the methoxy group points toward the hydroxy group becomes very important. This orientation and subsequent chelation could well change the binding position of the LSR, causing the Eu–O–Me_1 angle to be greater than ~55°, the angle at which the angle term in eq 3 requires an upfield LIS. Additionally, this new LSR position is responsible for the now very large differences between the LIS of protons a and e as well as b and f (see Table VI).

The temperature dependence of the LIS of the trans alcohols exhibits the normal downfield shifts for all proton types. Additionally, the observed values for the temperature-dependent LIS follow the same trends as did the LIS obtained for the incremental dilution data. Since *trans*-αNOH behaves very differently from the other trans alcohols, it will be discussed first. As previously found, Me_3 and Me_{5t} have λ values larger (by an average ratio of 1.79) than that of Me_{5c}. This is indicative of a compound having an axial OH as pictured in **3c**, and compares well with the axial to equatorial methyl λ ratios in the cis isomers.

In the incremental dilution data, *trans*-OAOH was an intermediate example of the biasing of the equilibria shown. It is seen that now Me_3, Me_{5t}, and Me_{5c} have nearly identical LIS. Finally, for *trans*-PCOH, -PAOH, and -MAOH, the LIS of Me_{5c} is 1.60 times larger than for Me_3 and Me_{5t}, and "axial" methyls of **3c**. Similar trends are observed for the methylene protons for all of the trans alcohols.

Experimental Section

***cis*- and *trans*-3-(Aryl)-1,3,5,5-tetramethylcyclohexan-1-ols.** A mixture of approximately 60:40 cis (**3a**) to trans (**3c**) cyclohexanols was obtained in quantitative yield from the reaction (at reflux, for *ca.* 2 days) of the corresponding 3-(aryl)-3,5,5-trimethylcyclohexanone[3b] with excess ethereal methylmagnesium bromide. These isomers were cleanly separated by column chromatography on silica by elution with a 5% hexane–acetone mixture, the cis isomer eluting much more rapidly. Satisfactory combustion analyses were obtained for the alcohols.

All nmr spectra were run on a Varian HA-100 nuclear magnetic resonance spectrometer in the frequency sweep mode. Shifts were measured on carefully precalibrated chart paper and are estimated to be accurate to ±0.01 ppm or better. Temperature was varied using a standard Varian Associates variable-temperature probe and controller; the temperature was determined using methanol in the standard fashion.

The LSR used (unless otherwise noted) was europium(III) tris-1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedione, denoted as $Eu(FOD)_3$. For comparison of LIS values from one compound to another, it is essential to use carefully purified LSR and to start with a very pure substrate (especially one dry and solvent free). In our experience, $Eu(FOD)_3$ supplied by Merck Sharp and Dohme is suitable. For each run, the LSR was sublimed *in vacuo* and stored for at least 24 hr over P_4O_{10} *in vacuo*. The solvent employed for all samples was molecular sieve dried CCl_4 or CS_2; the latter was used for the variable-temperature data (owing to the insolubility of the solutes in CCl_4 at lower temperatures). All substrates were stored over $CaSO_4$ or P_4O_{10} in a vacuum desiccator prior to use.

The method used in the LSR runs was the incremental dilution, constant S_0 technique described in detail by Shapiro and Johnston.[8] All regression analyses were performed on a Hewlett-Packard Model 9100B programmable calculator with ten significant figure precision. The fits were optimized in terms of maximizing the correlation coefficient, R.

Acknowledgment. The authors wish to thank The Robert A. Welch Foundation of Houston, Texas, for its generous support of this research. Helpful discussion with Professor E. L. Eliel of the University of North Carolina is also gratefully acknowledged.

References and Notes

(1) Lanthanide-Induced Shifts in Proton Nuclear Magnetic Resonance Spectra. X. For Part IX, see ref 17.
(2) (a) Postdoctoral Fellow of The Robert A. Welch Foundation; (b) Predoctoral Fellow of The Robert A. Welch Foundation.
(3) (a) B. L. Shapiro, M. J. Gattuso, N. F. Hepfinger, R. L. Shone, and W. L. White, *Tetrahedron Lett.*, 219 (1971); (b) B. L. Shapiro, M. D. Johnston, Jr. and M. J. Shapiro, *Org. Magn. Resonance*, **5**, 21 (1973); (c) B. L. Shapiro and M. M. Chrysam, III, *J. Org. Chem.*, **38**, 880 (1973).
(4) (a) B. L. Shapiro, M. J. Gattuso, and G. R. Sullivan, *Tetrahedron Lett.*, 223 (1971); (b) B. L. Shapiro, J. R. Hlubucek, G. R. Sullivan, and L. F. Johnson, *J. Amer. Chem. Soc.*, **93**, 3281 (1971); (c) B. L. Shapiro, M. D Johnston, Jr., and T. W. Proulx, *ibid.*, **95**, 520 (1973); (d) B. L. Shapiro, M. D. Johnston, Jr., J. R. Hlubucek, G. R. Sullivan, and G. Stroebel, *J. Magn. Resonance*, **9**, 411 (1973).
(5) (a) C. C. McDonald and W. D. Phillips, *J. Amer. Chem. Soc.*, **89**, 6332 (1967); (b) M. Cushman and N. Castagnoli, Jr., *J. Org. Chem.*, **38**, 440 (1973).
(6) The following abbreviations are used in this paper for the *cis*-(aryl)-1,3,5,5-tetramethylcyclohexanols: where aryl is phenyl, PhOH; *p*-anisyl, PAOH; *m*-anisyl, MAOH; o-anisyl, OAOH; *p*-chlorophenyl, PCOH; and α-naphthyl, αNOH. Similarly the trans isomers are denoted as *trans*-PhOH, -PAOH, -MAOH, -OAOH, -PCOH, and -αNOH.
(7) (a) I. Armitage, G. Dunsmore, L. D. Hall, and A. G. Marshall, *Can. J. Chem.*, **50**, 2119 (1972); (b) D. R. Kelsey, *J. Amer. Chem. Soc.*, **94**, 1764 (1972); (c) J. K. Sanders, S. W. Hansen, and D. H. Williams, *ibid.*, **94**, 5325 (1972); (d) J. W. ApSimon, H. Beierbeck, and A. Fruchier, *ibid.*, **95**, 939 (1973); (e) J. Reuben, *ibid.*, **95**, 3534 (1973).
(8) B. L. Shapiro and M. D. Johnston, Jr., *J. Amer. Chem. Soc.*, **94**, 8185 (1972).
(9) H. M. McConnell and R. E. Robertson, *J. Chem. Phys.*, **29**, 1361 (1958).
(10) B. L. Shapiro, M. J. Shapiro, A. D. Godwin, and M. D. Johnston, Jr., *J. Magn. Resonance*, **8**, 402 (1972).

(11) Unpublished results, this laboratory.
(12) R. L. R. Towns and B. L. Shapiro, *Cryst. Struct. Commun.*, **1**, 151 (1972).
(13) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, Oxford 1969, p 81, and references cited therein.
(14) B. L. Shapiro, M. D. Johnston, Jr., A. D. Godwin, T. W. Proulx, and M. J. Shapiro, *Tetrahedron Lett.*, 3233 (1972).
(15) (a) T. H. Siddall, III, *Chem. Commun.*, 452 (1971); (b) S. Farid, A. Ateya, and M. Maggio, *ibid.*, 1285 (1971); (c) P. H. Mazzocchi, H. J. Tamburin, and G. R. Miller, *Tetrahedron Lett.*, 1819 (1971); (d) S. B. Tjan and F. R. Visser, *ibid.*, 2833 (1971); (e) M. Kishi, K. Tori, and T. Komeno, *ibid.*, 3525 (1971).
(16) H. Freibolin, H. G. Schmid, S. Kabuss, and W. Faisst, *Org. Magn. Resonance*, **1**, 147 (1969), as well as others.
(17) B. L. Shapiro, M. D. Johnston, Jr., R. L. R. Towns, A. D. Godwin, H. L. Pearce, T. W. Proulx, and M. J. Shapiro, chapter in "NMR Shift Reagents," R. E. Sievers, Ed., Academic Press, New York, N. Y., 1973.
(18) We thank Professor E. L. Eliel for a helpful and full discussion of the energetic reasonablness of this alternative explanation.
(19) P. V. Demarco, T. W. Elzey, R. B. Lewis, and E. Wenkert, *J. Amer. Chem. Soc.*, **92**, 5734 (1970).
(20) N. L. Allinger and M. T. Tribble, *Tetrahedron Lett.*, 3259 (1971).
(21) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1962. In the systems studied here, **5a** has two additional Me–OH syn-axial interactions instead of two Me–H interactions. This should add 2 × 1.9 − 1.7 or 2.1 kcal/mol to the 3.3 kcal/mol calculated by Allinger.[20] Now, **5b** differs from Allinger's model by a Me–Me and a Me–phenyl syn-axial interaction taking the place of a Me–H and a phenyl–H interaction. This yields a difference of 1.35 kcal/mo plus a phenyl–Me interaction. From Allinger's work it can be assumed that the latter is less than a Me–Me syn-axial interaction, and, if we assign it a value of 3.0 kcal/mol, this would yield the 1.15 kcal/mol. In any case **5b** would appreciably contribute to the **5a** ⇌ **5b** equilibrium.
(22) For an extensive list see *Anal. Chem.*, **44**, 413R (1972).
(23) (a) S. I. Weissman, *J. Amer. Chem. Soc.*, **93**, 4928 (1971); (b) J. Armitage and L. D. Hall, *Can. J. Chem.*, **49**, 2770 (1971); (c) L. Tomic, Z. Majerski, M. Tomic, and D. E. Sunko, *Chem. Commun.*, 719 (1971); (d) N. Ahmad, N. S. Bhacca, J. Selbin, and J. D. Wander, *J. Amer. Chem. Soc.*, **93**, 2564 (1971); (e) R. D. Bennett and R. E. Schuster, *Tetrahedron Lett.*, 673 (1972); (f) N. S. Bhacca, J. Selbin, and J. D. Wander, *J. Amer. Chem. Soc.*, **4**, 8719 (1972).
(24) J. Bouquant and J. Chuche, *Tetrahedron Lett.*, 493 (1973).

Carbon-13 Nuclear Magnetic Resonance. Conformation in Some 1,3-Dioxacycloheptanes

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Received September 14, 1973

The carbon-13 nuclear magnetic resonance chemical shifts for some 1,3-dioxacycloheptanes are reported. The chemical shifts for the ring carbons are affected by the positions and conformations of the substituents. Substituent shift parameters can be transferred from 1,3-dioxanes and cycloheptanes to 1,3-dioxacycloheptanes. Bulky substituents in the 2, 4, and 7 positions of the 1,3-dioxacycloheptanes do little to reduce the number of available low-energy conformations.

Carbon-13 nuclear magnetic resonance is a potent tool for conformational analysis because carbon-13 chemical shift substituent parameters reflect both substituent and conformational effects. Appropriate substituent parameters can be obtained not only in cyclohexanes,[3] but also in cycloheptanes[4] and 1,3-dioxanes,[5] provided that the effects of oxygen substitution in the six-membered ring and of pseudo-rotation of the seven-membered ring are taken into account.

Encouraged by previous work,[3-5] we undertook a study of carbon-13 substituent effects in some 1,3-dioxacycloheptanes in an effort to extend the correlations to this ring system and to provide a basis for conformational assignment therein.

Conformational analysis of cyclohexane[6] and 1,3-dioxane[5] is facilitated by the absence of a low-energy pseudo-rotational barrier and the availability of only one low-energy conformation. The interpretation of conformational data for cyclopentanes,[7] 1,3-dioxolanes,[8] cycloheptanes,[4] and 1,3-dioxacycloheptane[1b] is made more difficult by the availability of numerous low-energy conformations and by the low-energy pseudo-rotational barriers for each of these compounds, with the result that in these systems one must think in terms of conformational arrays.

The geometry of 1,3-dioxacycloheptane has been discussed previously and comparisons were made with cyclohexanes, cycloheptanes, and 1,3-dioxanes:[1b] there are four distinct chair conformations for 1,3-dioxacycloheptane compared to one for each of the other compounds; the 1,3-COC distance is small owing to the shorter carbon–oxygen bond (compared to the CCC distance); 1,3-diaxial Me–H interactions are more severe (as in the 1,3-dioxanes)[9,10] than in cyclohexane and cycloheptane;[10] and the 4,7-diaxial Me–H interaction is more severe than that in cycloheptane. Accordingly, an additional objective of these studies was to test whether these more severe interactions could be used to advantage to produce compounds with only one or two low-energy conformations in the conformational array. Therefore the synthesis of 1,3-dioxacycloheptanes with a number of bulky substituents properly located to take advantage of the decreased 1,3-diaxial and 4,7-diaxial distances was undertaken.

The carbon-13 spectra were recorded at ambient temperatures at which the rates of interconversions of the conformations were fast. Therefore the chemical shifts are average values to which each of the conformations contributes according to its population.

The carbon-13 chemical shifts for a series of 1,3-dioxacycloheptanes are summarized in Table I. The assignments of the carbon-13 resonances were made on the basis of relative intensities, comparisons with chemical shifts for 1,3-dioxanes,[5,11] and comparison with values for 1,3-dioxacyclohept-5-ene.[1]

The chemical shift assignments are reasonably straightforward. The *tert*-butyl methyl carbons were readily distinguished from methyl groups substituted directly on the ring by signal intensity. The signal of the quaternary carbon of the *tert*-butyl group was distinguished from those for C_5 and C_6 by its reduced intensity.[12] The chemical shifts for C_5 and C_6 were readily assigned, since they were the only ones without parallel in the spectrum of 1,3-dioxacyclohept-5-ene. The signals assigned to C_2, C_4, and C_7 correspond to the chemical shifts for C_2, C_4, and C_6 in 1,3-dioxanes.

Some important generalizations may be drawn from Table I. The difference in geometry between a seven- and

Table I
Carbon-13 Chemical Shifts for Some 1,3-Dioxacycloheptanes[a]

Entry	Compd	C_2	C_4	C_7	C_5	C_6	2Cc[b]	Bu_{Me}	Me
I	1,3-Dioxacycloheptane	94.67	67.24		30.05				
		(96.77)	(68.71)		(27.95)				
II	*cis*-4,7-Dimethyl-	94.07	75.89		33.76				22.36
III	*trans*-4,7-Dimethyl	91.95	72.39		36.51				22.58
IV	*cis*-2-*t*-Butyl 4-methyl-	108.70	76.98	70.68	36.70	28.31	36.64	25.10	22.32
		(107.26)	(72.49)		(33.69)		(35.06)	(24.95)	(21.92)
V	*trans*-2-*t*-Butyl-4-methyl-	106.39	71.23	66.87	36.64	29.50	36.21	25.36	22.32
VI	*r*-2-*tert*-Butyl-*cis*-4,*cis*-7-dimethyl-	108.88	75.12		33.79		35.72	25.10	22.65
VII	*r*-2-*tert*-Butyl-*cis*-4,*trans*-7-dimethyl-	105.60	70.54	77.90	36.64		35.90	25.24	22.65
VIII	5,5-Dimethyl-	94.64	75.93	63.05	34.68	44.15			25.73
		(96.22)	(79.10)		(31.71)				(23.20)
IX	2-*tert*-Butyl-5,5-dimethyl-	110.24	78.47	64.14	36.68	43.67	35.05	24.82	25.33, 25.08
		(108.41)	(77.31)		(30.13)		(34.99)	(25.17)	(23.36, 22.18)
X	4-Methyl-	93.50	75.32	66.80	36.93	29.29			22.51
XI	5-Methyl-	94.65	72.40	64.84	34.95	38.44			17.27
XII	2-*tert*-Butyl-	109.94	68.70		29.71		36.51	25.21	
		(107.83)	(66.92)		(26.37)		(35.23)	(25.01)	

[a] All values are in parts per million downfield from internal TMS. Parenthetical values are from ref 5. [b] The quaternary carbon of the *tert*-butyl group.

six-membered ring has little effect on the chemical shifts of the ring carbons. The chemical shifts of 1,3-dioxane and 1,3-dioxacycloheptane differ by not more than 3 ppm. Those for substituent groups are within ±2 ppm.

The chemical shifts of the quarternary carbon of the *tert*-butyl group are remarkably constant and give no indication of a major contribution from an axially oriented *tert*-butyl group. The same conclusion is drawn from the narrow range of the chemical shifts for the methyl carbon of the *tert*-butyl group. A steric compression at the methyl carbon of the *tert*-butyl group must result in a paramagnetic shift for that carbon as well as for the particular ring or substituent carbon. There is no indication of any major paramagnetic shift for the *tert*-butyl carbons; thus conformations with axial *tert*-butyl groups are excluded.[5]

Contrary to the reports for the cyclohexanes and the 1,3-dioxanes, the chemical shifts for the substituent methyl groups do not indicate a conformational preference. This is certainly due to conformational averaging; for example, there are two methyl absorptions for 2-*tert*-butyl-5,5-dimethyl-1,3-dioxacycloheptane but chemical shift difference is only 0.2 ppm. The difference between the chemical shift for an axial and equatorial methyl carbon is greater than 1 ppm for the 1,3-dioxanes and 3 ppm for the cyclohexanes.

Configurational Assignments. Configurations for entries II–V have been previously established.[1b] The 2,5-hexanediol which was used for the preparation of *cis*-4,7-dimethyl-1,3-dioxacycloheptane and *trans*-4,7-dimethyl-1,3-dioxacycloheptane was shown to contain 80% of the meso iosmer and 20% racemate. The meso diol gave the cis isomer and the racemate gave the trans isomer.[1b] The meso diol also gave the *r*-2-*tert*-butyl-*cis*-4,*cis*-7-dimethyl-1,3-dioxacycloheptane in reaction with trimethylacetaldehyde while the racemic diol gave the *r*-2-*tert*-butyl-*cis*-4,*trans*-7-dimethyl-1,3-dioxacycloheptane.[13] The proton magnetic resonance spectra are consistent with this assignment. The cis-4,trans-7 isomer has absorptions at τ 6.43 and 6.04 for the protons on C_4 and C_7, consistent with nonequivalency at these positions, while the cis-4,cis-7 isomer had only one absorption at τ 6.21. In addition the C_2 proton absorption of the cis-4,trans-7 isomer is at lower field, τ 5.74, than that of the cis-4,cis-7 isomer, τ 5.92. This is consistent with the data for *cis*-2-*tert*-butyl-4-methyl-1,3-dioxacycloheptane (τ 5.89) and *trans*-2-*tert*-butyl-4-methyl-1,3-dioxacycloheptane (τ 5.83). The carbon-13 data are also consistent with these assignments. The carbon-13 chemical shift of C_2 in *r*-2-*tert*-butyl-*cis*-4,*trans*-7-dimethyl-1,3-dioxacycloheptane is 3.3 ppm upfield from the same absorption for the cis-4,cis-7 isomer. This is consistent with a 1,3-Me–H interaction at C_2 for the cis-4,trans-7 isomer. There are no conformations for the cis-4,cis-7 isomer in which the methyl groups contribute a paramagnetic[3] shift at C_2. In addition the cis-4,trans-7 isomer gives different chemical shifts for C_4 (70.54) and Ci7 (77.90), which is consistent with the proton nmr data, while the cis-4,cis-7 isomer has only one absorption for C_4 and C_7 (75.12 ppm) indicating equivalency for these positions.[15]

Conformational Assignments. Table II lists the carbon-13 chemical shift substituent effects produced by substitution on 1,3-dioxacycloheptane. Table III summarizes these same effects but lists them as to their origin, *i.e.*, α, β, γ, δ, and also lists substituent effects produced by substitution in 2-*tert*-butyl-1,3-dioxacycloheptane and 4-methyl-1,3-dioxacycloheptane. The values in brackets are from corresponding cycloheptanes and the values in parentheses are from corresponding 1,3-dioxanes.

The α and β effects are consistent with those for cyclohexane, cycloheptane, and 1,3-dioxane. The correlation in the direction (sign) of these substituent effects is excellent but the magnitude of the values shows some variation. The α effect of −8.08 ppm for a 4-methyl substituent compares favorably with −6.7 ppm for methylcycloheptane and −5.96 ppm for methylcyclohexane. The β effect of −6.88 ppm is also reasonable when compared to −9.3 ppm for methylcycloheptane and −9.03 ppm for methylcyclohexane. The values for the 5-methyl substituent agree somewhat more closely.

Substitution of a geminal dimethyl group gives α values of −4.63, −3.76, −5.1, and −3.1 ppm for 5,5-dimethyl-1,3-dioxacycloheptane, 5,5-dimethyl-1,3-dioxane, 1,1-dimethylcycloheptane, and 1,1-dimethylcyclohexane, respectively. The β effects are −8.69 (−14.10), −10.39, −14.4, and −12.7 ppm for the same sequence. The α and β effects are in remarkably good agreement. The change in geometry and substitution of two oxygen atoms in the ring does not prohibit the use of these parameters for the assignment of chemical shifts. Their utility in the assignment of conformation, however, appears questionable. No clear correlation with the degree of axial substitution is apparent. The γ and δ effects do however, appear to corre-

Table II
Carbon-13 Chemical Shift Substitutent Effects for Some 1,3-Dioxacycloheptanes[a,b]

Entry	Compd	C(2)	C(4)	C(5)	C(6)	C(7)
1	4-Methyl-	+1.17	−8.08	−6.88	+0.76	+0.44
2	5-Methyl-	+0.02	−5.16	−4.90	−8.39	+2.40
3	*cis*-4,7-Dimethyl-	+0.60 (+0.7)	−8.65 (−4.9)	−3.71 (−14.0)	−3.71	−8.65 (−4.9)
4	*trans*-4,7-Dimethyl-	+2.72 (+7.2)	−5.15 (−0.0)	−6.46 (−10.7)	−6.46	−5.15
5	5,5-Dimethyl-	+0.03	−8.69	−4.63	−14.10	+4.19
6	2-*tert*-Butyl-	−15.27	−1.46	+0.34	+0.34	−1.46
7	2-*tert*-Butyl-5,5-dimethyl-	−15.57	−11.23	−6.63	−13.62	+3.10
8	*cis*-2-*tert*-Butyl-4-methyl-	−14.03	−9.74	−6.65	+1.74	−3.44
9	*trans*-2-*tert*-Butyl-4-methyl-	−11.72	−3.99	−6.59	+0.55	+0.37
10	*r*-2-*tert*-Butyl-*cis*-4,*cis*-7-dimethyl-	−14.21	−7.88	−3.74	−3.74	−7.88
11	*r*-2-*tert*-Butyl-*cis*-4,*trans*-7-dimethyl-	−10.93	−3.30	−6.59	−6.59	−10.66

[a] All values are in parts per million calculated from 1,3-dioxacycloheptane. [b] Values in parentheses are for the corresponding 1,3-dioxanes from ref 11. A negative value indicates a signal downfield from the reference carbon.

Table III
Carbon-13 Chemical Shift Substituent Effects Produced by Substitution on 1,3-Dioxacycloheptane,[a] 4-Methyl-1,3-dioxacycloheptane,[b] and 2-*tert*-Butyl-1,3-dioxacycloheptane[c]

Compd	α	β	γ	δ
4-Methyl-[a]	−8.08 [−6.7][d]	−6.88 [−9.3]	1.17, −0.76 [1.3]	0.44 [−0.7]
5-Methyl-[a]	−4.90	−5.16, −8.39	2.40	0.02
2-*tert*-Butyl-[a]	−15.27 (−11.06)[e]		−1.46 (1.79)	0.34 (1.58)
5,5-Dimethyl-[a]	−4.63 (−3.76) [−5.1]	−8.69, −14.10 (−10.39) [−14.4]	4.19 [4.4]	0.03 (0.55) [−2.6]
cis-4,7-Dimethyl-[b]	−9.09 [−5.3]	−4.47 [−6.6, −9.5]	3.17, −0.57 [4.0, −0.1]	−2.57 [0.7, −0.9]
trans-4,7-Dimethyl-[b]	−5.59 [−6.3]	−7.22 [−9.7 or −7.9]	0.42, 1.55 [2.8, 0.9]	2.93 [0.7, −0.3]
2-*tert*-Butyl-5,5-dimethyl-[c]	−6.97 (−3.76)	−9.77, −13.96 (−10.39)	4.56	−0.30 (−0.58)
cis-2-*tert*-Butyl-4-methyl-[c]	−8.28 (−5.55)	−7.00 (−7.32)	1.40, 1.24 (0.51, 0.57)	−1.98
trans-2-*tert*-Butyl-4-methyl-[c]	−2.56	−7.14	0.21, 3.55	1.93
r-2-*tert*-Butyl-*cis*-4,*cis*-7-dimethyl	−6.42	−4.08	1.06	
r-2-*tert*-Butyl-*cis*-4,*trans*-7-dimethyl-[c]	−1.84, −9.20	−6.93	4.34	

[a] Taken from chemical shifts compared to 1,3-dioxacycloheptane. [b] Chemical shifts compared to 4-methyl-1,3-dioxacycloheptane. [c] Chemical shifts compared to 2-*tert*-butyl-1,3-dioxacycloheptane. [d] Values for cycloheptanes taken from ref 4. [e] Values for 1,3-dioxanes taken from ref 5.

late with the degree of axial character in a conformational array.

The relation of the γ effect to conformation is probably the best understood of the chemical shift substituent parameters.[3,5,7] It reflects a paramagnetic shift due to a 1,3-diaxial steric compression. The δ effects reflect the same type of interaction for the 4,7-diaxial compression found in cycloheptanes and 1,3-dioxacycloheptanes.

The γ shift substituent parameter indicates that there are more conformations with axial-like methyl groups for the cis isomer of 4,7-dimethyl-1,3-dioxacycloheptane than there are for the trans isomer. It is also evident that *trans*-2-*tert*-butyl-4-methyl- and *r*-2-*tert*-butyl-*cis*-4,*trans*-7-dimethyl-1,3-dioxacycloheptane have a higher population of methyl axial conformers than the corresponding cis isomers.

It is evident from the data that the chemical shifts and the substituent shift parameters parallel those found for other systems. As expected, the data for the substituted 1,3-dioxacycloheptanes studied here fail to indicate the presence of a single, highly populous conformation. The data are capable of signaling the presence of conformations with axial-like methyl groups and the absence of conformations with axial-like *tert*-butyl groups but do not indicate the total conformational picture.

Experimental Section

Proton nmr spectra were recovered on a Varian A-60A instrument. Samples were run as 10% solutions in carbon tetrachloride. All chemical shifts are reported in τ units. The carbon-13 nmr spectra were recorded at 25.15 MHz on a HA-100D nmr spectrometer interfaced to a Digilab NMR-FTS-3 pulse and data system. The samples were neat liquids. The number of data points was $8K$ or $16K$ as required to obtain satisfactory resolution. Spectra were recorded with broad-band decoupling. All chemical shifts were referenced to internal TMS and reported in parts per million. All m/e values were determined on a AEI MS-9 high-resolution mass spectrometer. Separations were carried out on a Hewlett-Packard F & M 5752 gas chromatograph. The infrared spectra were recorded on a Beckman IR-8 instrument and the absorption values are reported in microns.

The preparation of 1,3-dioxacycloheptane, 4,7-dimethyl-1,3-dioxacycloheptane, 2-*tert*-butyl-4-methyl-1,3-dioxacycloheptane, 4-methyl-1,3-dioxacycloheptane, and 5-methyl-1,3-dioxacycloheptane were previously described.[1]

2-*tert*-Butyl-1,3-dioxacycloheptane. The general procedure for the preparation of these compounds is that of Branncock and Lappin.[16] The preparation of 2-*tert*-butyl-1,3-dioxacycloheptane is described as a representative example. A mixture of 1.4 g (0.1 mol) of 1,4-butanediol, 8.6 g (0.1 mol) of pivaldehyde, 100 ml of benzene, and 50 mg of *p*-toluenesulfonic acid was refluxed using a Dean-Stark distillation trap. The reaction was terminated when 1.5 ml of water was evolved. The mixture was distilled under vacuum to give a 74% yield of the desired product: bp 28–30° (0.1

Torr); ir (neat) 3.23, 3.33, 6.56, 6.76, 8.22, and 9.30 μ; proton nmr (CCl_4) τ 5.96 (HC_2), 6.31 ($HC_{4,7}$), 8.51 ($HC_{5,6}$); *m/e* 101 (parent − *tert*-butyl).

2-*tert*-Butyl-4,7-dimethyl-1,3-dioxacycloheptane. The mixture of isomers distilled at 26° (0.3 Torr). The isomers were separated by glpc (8-ft 10% Apiezon-Chromosorb column) and the cis,cis isomer was the first peak: ir (neat) 3.38, 3.43, 3.50, 6.93, 8.78, 9.05 μ; proton nmr (CCl_4) τ 5.95 (HC_2), 6.21 (HC_7), 8.36 (HC_5, HC_6), 8.83 (CH_3), 9.12 (*tert*-butyl); *m/e* 130 (parent − tert-butyl). The cis,trans isomer was the second peak: proton nmr τ 5.94 (HC_2), 6.43 (HC_4), 6.04 (HC_7), 8.36 ($HC_{5,6}$), 8.86, 8.83 (CH_3), 9.12 (*tert*-butyl); *m/e* 130 (parent − *tert*-butyl).

5,5-Dimethyl-1,3-dioxacycloheptane. This compound was prepared in 75% yield from 2,2-dimethyl-1,4-butanediol and paraformaldehyde. The physical properties follow: bp 28° (0.3 Torr); proton nmr τ 5.28 (HC_2), 6.68 (HC_4), 6.31 (HC_7), 8.53 (HC_6), 9.10 (CH_3); *m/e* 130 (parent peak).

2-*tert*-Butyl-5,5-dimethyl-1,3-dioxacycloheptane. This compound was prepared in 57% yield from 2,2-dimethyl-1,4-butanediol and pivaldehyde: bp 22° (0.05 Torr); proton nmr τ 5.83 (HC_2), 6.30, 6.80 (HC_4, J = 11.5 Hz), 8.52 (HC_6), 9.02, 9.16 (CH_3), 9.12 (*tert*-butyl); *m/e* 186 (parent peak).

Acknowledgment. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

Registry No.—I, 505-65-7; II, 41887-61-0; III, 41887-62-1; IV, 41887-63-2; V, 41887-64-3; VI, 50273-53-5; VII, 50273-54-6; VIII, 50273-55-7; IX, 50458-29-2; X. 2463-48-1; XI, 41887-69-8; XII, 41887-67-6; 1,4-butanediol, 110-63-4; 2,2-dimethyl-1,4-butanediol, 32812-23-0.

References and Notes

(1) St. Michael's College. For the previous paper in this series see M. H. Gianni, J. Saavedra, and J. Savoy, *J. Org. Chem.*, **38**, 3971 (1973).
(2) New York State University at Albany.
(3) D. K. Dalling and D. M. Grant, *J. Amer. Chem. Soc.*, **94**, 5318 (1972).
(4) M. Christl and J. D. Roberts, *J. Org. Chem.*, **37**, 3443 (1972).
(5) A. J. Jones, E. L. Eliel, D. M. Grant, M. C. Knoeber, and W. F. Baily, *J. Amer. Chem. Soc.*, **93**, 4772 (1971).
(6) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965.
(7) M. Christl, H. J. Reich, and J. D. Roberts, *J. Amer. Chem. Soc.*, **93**, 3462 (1971).
(8) W. E. Willy, G. Binsch, and E. L. Eliel, *J. Amer. Chem. Soc.*, **92**, 5394 (1970).
(9) E. L. Eliel and M. C. Knoeber, *J. Amer. Chem. Soc.*, **88**, 5347 (1966).
(10) F. G. Riddell, *Quart. Rev., Chem. Soc.*, 364 (1967).
(11) F. G. Riddell, *J. Chem. Soc. B*, 331 (1970); (b) G. M. Kellie and F. G. Riddell, *ibid.*, 1030 (1971).
(12) H. G. Hertz, *Progr. Nucl. Magn. Resonance Spectrosc.*, **3**, 159 (1963).
(13) We use the Beilstein system of nomenclature (see also IUPAC Bulletin 35, June 1969) for cis-trans isomers with rings with more than two substituents whose stereochemistry must be indicated. The lowest number substituent of specified stereochemistry (equatorial 2-*tert*-butyl) is used as the reference point and given the prefix *r*. We follow Eliel[14] and use cis and trans instead of c and t for the purpose of homogeneity.
(14) E. L. Eliel and F. W. Nader, *J. Amer. Chem. Soc.*, **92**, 584 (1970).
(15) This equivalency is due to conformational averaging, since there are conformations which contain one axial and one equatorial methyl group.
(16) K. C. Branncock and G. Lappin, *J. Org. Chem.*, **21**, 1366 (1956).

Chemistry of the Sulfur–Nitrogen Bond. VII.[1] Rearrangement of Sulfenimines (*S*-Aryl Thiooximes) to β-Keto Sulfides. Attempted Synthesis of Benzo[*b*]thiophenes

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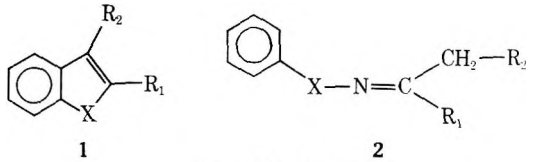
Received September 27, 1973

Attempts to rearrange sulfenimines **2** (X = S) to benzo[*b*]thiophenes are described. The major reaction is cleavage of the S–N bond. Sulfenimines in the presence of benzoyl chloride and 1,5-diazobicyclo[4.2.0]non-5-ene (DBN) rearrange to 2-benzamido-1-(arylthio)alkenes **11** and **13**. These compounds are readily hydrolyzed to β-keto sulfides. An intermolecular rearrangement involving a sulfenyl chloride is proposed to account for the formation of these products.

The synthesis of substituted indoles **1** (X = NH) involves a one-step rearrangement of the readily available phenylhydrazone **2** (X = NH). This rearrangement is known as the Fisher indole synthesis and is the primary synthetic route to these compounds.[3] Benzofurans **1** (X = O) have been prepared from the *O*-phenyl oxime ethers **2**



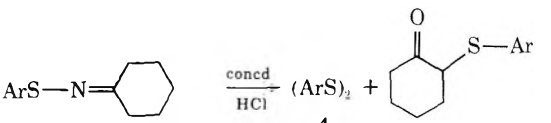
1 **2**

X = NH, O, S

(X = O).[4,5] These rearrangements are effected by heating the hydrazone or oxime ether in the presence of a Lewis acid or concentrated hydrochloric acid.[3-5] The rate-determining step is believed to involve a tautomerism of the hydrazone (or oxime ether) to the ene-hydrazine (ene-ether) followed by cyclization.[3,6]

The synthesis of substituted benzo[*b*]thiophenes **1** (X = S), however, generally involves multistep synthetic routes.[7] It would be convenient, therefore, if similar synthetic routes from the corresponding sulfenimines, **2** (X = S), were available for the synthesis of substituted benzo[*b*]thiophenes. Recently we reported a convenient one-step synthesis of sulfenimines, **2** (X = S), from silver nitrate, aromatic disulfides, ammonia and aldehydes, and ketones.[1,8]

Kaminsky, Shavel, and Meltzer reported an attempt to rearrange cyclohexanone sulfenimines **3a,b**, using concentrated hydrochloric acid, to the corresponding benzo[*b*]-



3a, Ar = 4-nitrophenyl **4** **5**
b, Ar = 2-pyridyl
c, Ar = 2-benzothiazole

Table I
Reaction of Sulfenimines and Related Compounds

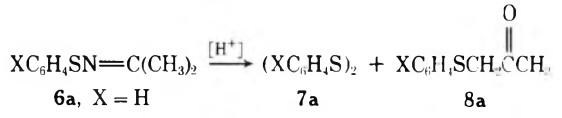
Compd	Reaction conditions	Products (yield)
6a	BF_3 ether; reflux	**7a** (~100)
	Acetic acid, reflux	**7a** (45); **8a** (~3)[a]
	HCl–alcohol, reflux	**7a** (90); **8a** (~3)[a]
	Absolute alcohol–NaOH	NR
	DBN benzene, reflux	NR
	Aqueous alcohol–NaOH; CH_3I[b]	**9** (65)
	Aqueous alcohol–NaOH; CH_3I[c]	**7a** (25); **9** (26)
	Benzoyl chloride–DBN–benzene	**11a** (21); **7a** (3)
6d	Benzoyl chloride–DBN–benzene	**11d** (22)
12a	Benzoyl chloride–DBN–benzene	**13a** (26)
12b	Benzoyl chloride–DBN–benzene	**13b** (22)
11a	Water–alcohol, reflux	**8a** (100)[a]
11d	Water–alcohol, reflux	**8d** (95)
13a	Water–alcohol, reflux	**14a** (97)[d]
13b	Water–alcohol, reflux	**14b** (93)

[a] Reference 12. [b] Reaction time 15 hr. [c] Reaction time 7 hr. [d] P. Faller and P. Cagniant, *Bull. Soc. Chim. Fr.*, 30 (1962).

thiophene.[5] The major product isolated was the disulfide, **4**, and a low yield of β-keto sulfide **5**. A mechanism for this rearrangement was not proposed.

Electron-withdrawing groups on the phenyl ring are known to slow the rate of indolization of cyclohexanone phenylhydrazone[9] and in some cases completely inhibit the reaction.[10] The sulfur–nitrogen bond in sulfenamides is cleaved by acid to give disulfides.[11] We felt, therefore, that a more detailed investigation of the use of sulfenimines to prepare benzo[*b*]thiophenes was warranted. In this paper we report the results of that investigation.

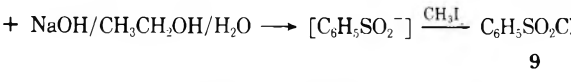
Initial attempts to effect the rearrangement of sulfenimines to benzo[*b*]thiophenes were performed with acetone benzenesulfenimine **6a**. This sulfenimine does not contain electron-withdrawing groups and the reaction products are readily identified by glc techniques.



6a, X = H **7a** **8a**

Treatment of **6a** with zinc chloride, silver nitrate, and mercuric chloride in refluxing ether produced no reaction. Boron trifluoride etherate gave a quantitative yield of disulfide **7a**. Acids such as acetic acid and concentrated hydrochloride primarily gave disulfide **7a** but also some of the β-keto sulfide **8a**[12] was detected.

Bases such as sodium hydroxide in absolute ethanol or 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) in benzene had no effect on the sulfenimine. When **6a** was treated with aqueous ethanolic sodium hydroxide followed by methyl iodide, a 65% yield of methyl phenyl sulfone (**9**) was ob-



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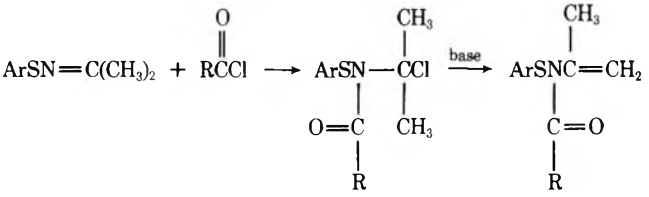
tained. The initial reaction probably involves hydrolysis of the sulfenimine to give the disulfide. Subsequent attack of hydroxide on the disulfide would give the sulfinic acid.[13] Shorter reaction times gave mixtures of disulfide and sulfone. Phenyl disulfide (**7a**), under the reaction conditions, gave a good yield of the sulfone. These results are summarized in Table I.

Acid chlorides are reported to add to the C–N double bond of imines to give addition products.[14] Consequently, if a similar reaction occurs with sulfenimines, it may be possible by treatment of the adduct with base to prepare the required ene–sulfenamide **10**.

Table II
Reaction of Sulfenimines with Benzoyl Chloride and DBN Followed by Hydrolysis

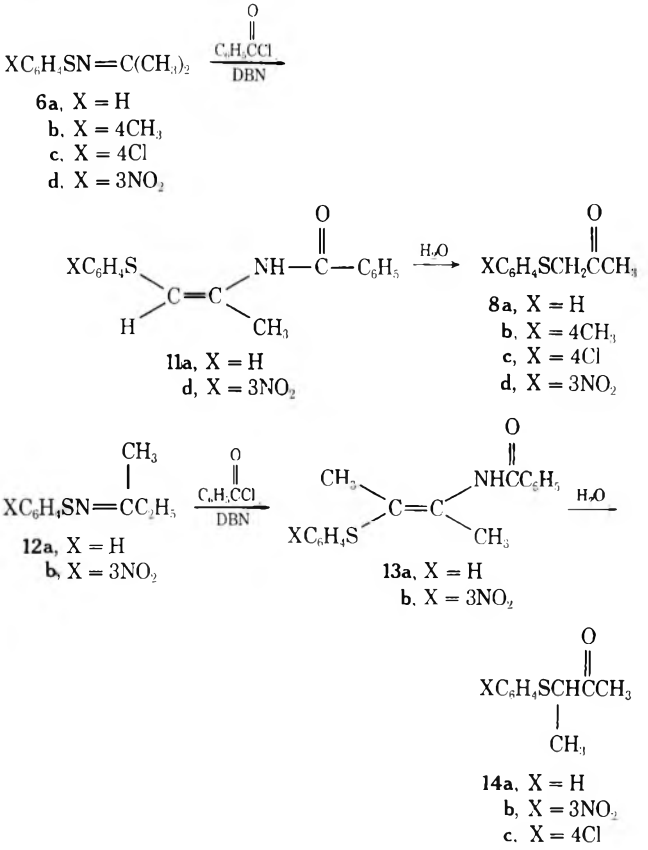
Sulfenimine	Solvent	Products (yield)
6a	Benzene	**8a** (33), **7a** (8)
6b	Benzene	**8b** (34),[a] **7b** (3)
6d	Benzene	**8d** (40)
12a	Benzene	**14a** (32), **7a** (13)
12b	Benzene	**14b** (36–45)
6c + 12b	Benzene	**8a** (19), **8c** (22),[b] **14a** (21), **14c** (23)[c]
6d	Cyclohexene	**8d** (42), **15** (13), **16** (21)

[a] Reference 12. [b] A. Boehringer, E. Boehringer, I. Liebrecht, and J. Liebrecht, British Patent 721,263 (1955); *Chem. Abstr.*, **50**, 4217 (1956). [c] P. Cagniant, P. Faller, and D. Cagniant, *Bull. Soc. Chim. Fr.*, 3055 (1966).



10

Treatment of **6a** with benzoyl chloride and DBN in refluxing benzene produced an oil from which 2-benzamido-1-(phenylthio)propene (**11a**) was obtained. A small amount of the disulfide **7a** was also isolated. Sulfenimine **6d** under these conditions gave **11d**, and sulfenimines **12a,b**, prepared from 2-butanone, gave **13a,b**, respectively (Table I).



14a, X = H
b, X = $3NO_2$
c, X = 4Cl

Enamides **11a,d**, and **13a,b** were quantitatively hydrolyzed to β-keto sulfides **8a,d**, and **14a,b**, respectively (Table I). Since the enamides decomposed in the gas chromatograph, for analytical purposes the reaction mixture was hydrolyzed and the resulting ketones analyzed by gas chromatography. These results are summarized in Table II.

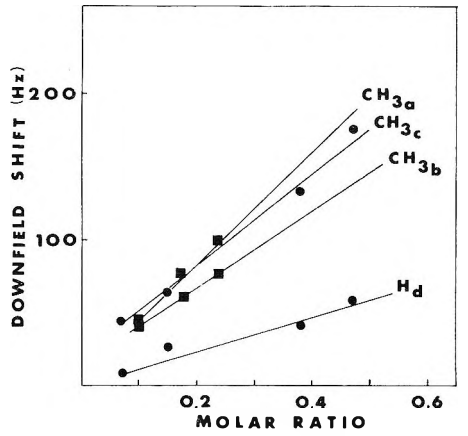


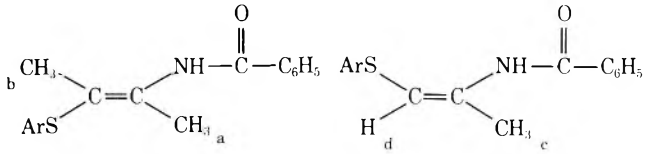
Figure 1. Variation of induced shift with molar ratio $Eu(fod)_3$–substrate for enamide **13b** and **11d**.

Structural proof of the enamides **11a**, **11d**, and **13a,b** was based on their elemental analysis and infrared and nmr spectra. The infrared spectra of the enamides showed absorption at 3260–80 cm^{-1} (NH) and 1650–40 cm^{-1} (C=O). Compounds **11a** and **13a** showed strong absorption at 1520 cm^{-1} (amide II band). This region was obscured in **11d** and **13b** as a result of the presence of the nitro group.

The proton nmr spectra of the enamides further supports the proposed structures. The methyl groups in enamides **11a** and **11b** appeared as doublets at δ 2.65 (J = 1.3 Hz). The coupling constant of 1.3 Hz does not permit an unambiguous assignment of the enamides structure to the Z configuration since the 1,3 hydrogen–methyl coupling constant in (E)- and (Z)-2-methyl-2-butenoic acid has been reported to be 1.43 and 1.28 Hz, respectively.[15] Shift reagent experiments with $Eu(fod)_3$ do, however, suggest that **11a** and **11d** have the Z configuration (*vide infra*).

The methyl groups in enamides **13a,b** also appeared as doublets at δ 2.5 and 1.9 with a coupling constant of 1.5 Hz. This coupling constant agrees with that observed for (Z)-2-methyl-2-butenoic acid[15] and suggests that **13a** and **13b** have the E configuration.

Further support for this interpretation is obtained from shift reagent experiments using $Eu(fod)_3$. Assuming that $Eu(fod)_3$ is associated with the lone pair of electrons of the carbonyl[16] group, then a large induced chemical shift is expected for the $CH_{3,a}$ in **13b** and is observed (Figure 1). A similar magnitude for the induced shift for CH_{3b} is anticipated provided **13b** has the E configuration. Figure 1



13b, E Ar = 3-nitrophenyl **11d**, Z

shows that the induced shift for CH_{3b} is nearly identical with that observed for CH_{3a}. If, however, **13b** had the Z configuration it would not be possible for the shift reagent to come into close proximity to CH_{3b} and a much smaller shift would be expected. These results along with the coupling constant support the assignment of E configuration to **13a,b.**

A similar argument may now be used to assign the Z configuration to **11a** and **11b.** As anticipated a large induced shift for CH_{3c} in **11d,** similar to the shifts obtained for CH_{3a} and CH_{3b} in **13b,** was observed. If **11d** were in the E configuration where the proton H_d would be brought into close proximity to the shift reagent, a large induced shift would be expected. Figure 1 shows only a relatively small shift was observed for H_d. These results suggest that **11a** and **11d** have the Z configuration.

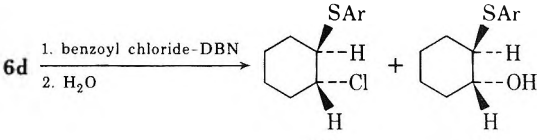
The β-keto sulfides **8a–d** and **14a–c** were identified by comparison of their properties with authentic samples prepared by procedures reported in the literature or synthesized independently.

Mechanism. An attractive mechanism for the rearrangment of sulfenimines to enamides is an intramolecular rearrangment involving the ene–sulfenamide **10.** Such a rearrangment would be analogous to the rearrangement of arenesulfenanilides to *o*- and *p*-aminodiphenyl sulfides.[17,18] Recently we have shown that this rearrangment is intramolecular.[18]

D'Amico has reported that, when 2-benzothiazolesulfenamide ($ArSNH_2$) was allowed to react with cyclohexanone and base for 1 week, **5c** was obtained in good yield.[19] If the reaction was stopped after 0.5 hr the sulfenimine **3c** was obtained. An intramolecular rearrangement involving tautomerism of the sulfenimine, **3c,** to the ene–sulfenamide was suggested.

To test for an intramolecular rearrangment under our reaction conditions, crossover experiments were performed. Sulfenimines **6c** and **12a** were refluxed together in benzene with DBN and benzoyl chloride. The reaction mixture was hydrolyzed and analyzed by glc. The four possible β-keto sulfides, **8a, 8c, 14a,** and **14c,** were formed in about equal amounts (Table II). This experiment clearly demonstrates that the rearrangment of sulfenimines to enamides cannot be intramolecular but must follow some intermolecular pathway.

When sulfenimine **6d** was reacted with DBN–benzoyl chloride in cyclohexene followed by hydrolysis, β-keto sulfide **8d** and addition products **15** and **16** were obtained (Table II). Identification of **15** and **16** was based on comparison of their spectral properties with authentic samples.



15 **16**

Ar = 3-nitrophenyl

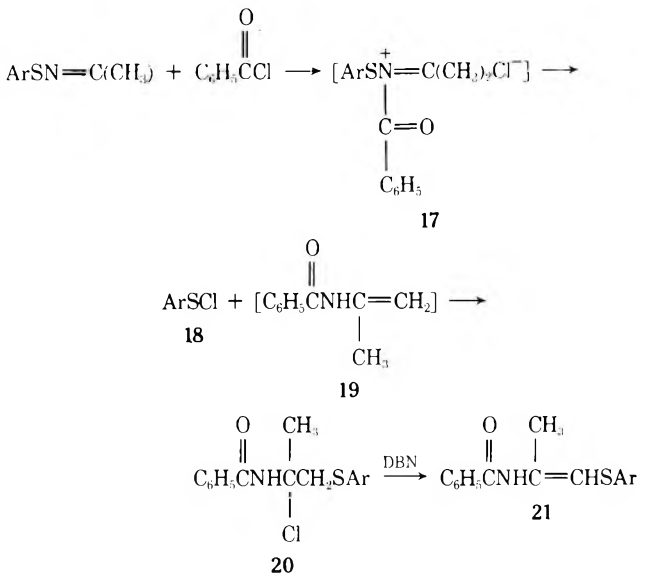
Compound **15** was prepared from 3-nitrobenzenesulfenyl chloride[20] and cyclohexene. Hydrolysis of **15** with ethanol and water gave **16** which was isolated as the phenylurethane. Sulfenyl halides are known to add exclusively trans to alkenes,[21] and anchimeric assistance to hydrolysis by the adjacent sulfur atom[22] would lead to the suggested stereochemistry in **15** and **16.**

A sulfenyl halide is a probable intermediate in the rearrangement of sulfenimines to enamides under these conditions. Consistent with these results is the mechanism proposed in Scheme I.

Benzoyl chloride reacts with the sulfenimines to give adduct **17.** The chloride ion rather than adding across the C–N double bond attacks the more reactive S–N bond to give the sulfenyl chloride, **18,** and enamide, **19.** The S–N bond in sulfenamides is known to be readily attacked by nucleophiles[8,23] and sulfenyl chlorides react with ketones to give β-keto sulfides.[12,24] Addition presumably occurs across the enolized ketone.

Enamides such as **19** have been reported and they decolorize bromine and add hydrogen.[25] Addition of the sulfenyl chloride **18** to **19** would yield **20** and subsequent reaction of the chloride with DBN results in the enamide **21.** In all reactions only one isomer was detected.[26] A sim-

Scheme I



ilar mechanism can be used to explain the rearrangement of sulfenimines **3a,b** to β-keto sulfides **5a,b.**[5]

Since our finding that the rearrangement of sulfenimines to β-keto sulfides was intermolecular and conflicted with the results obtained by D'Amico,[19] we decided to reinvestigate his results. 2-Benzothiazolesulfenamide ($ArSNH_2$) was allowed to react with base and cyclohexanone according to the experimental procedure reported by D'Amico. A good yield of the β-keto sulfide **5c** was obtained. D'Amico's mechanism, however, required the sulfenimine **3c** act as an intermediate in the rearrangement. When **3c** was subjected to the reaction conditions only starting material was obtained; the sulfide, **5c**, was not detected.

Sulfenamides have recently been shown to react with compounds containing activated methylene groups to give mono- and disulfenylated products.[8] These reactions presumably involve attack of the conjugate base of the active methylene compound on the S–N bond of the sulfenamide. 3-Nitrobenzenesulfenamide, for example, reacts with acetylacetone to give 3-(3-nitrophenyl)-2,4-pentanedione.[1] D'Amico's reaction may well be a member of this class of reactions.

The inability to effect the rearrangment of sulfenimines **2** (X = S) to benzo[*b*]thiophenes **1** (X = S) under acid and base conditions most probably reflects the lack of formation of the ene-sulfenamide required for cyclization. The major reaction of sulfenimines with acids and bases is cleavage of the sulfur–nitrogen bond. In this respect, the chemistry of the sulfur–nitrogen bond in sulfenimines parallels the chemistry of the sulfur–nitrogen bond in sulfenamides.[8]

Experimental Section

Sulfenimines **6a, 6b, 6d,** and **12b** were prepared from the corresponding disulfides as previously described.[1] Melting points were measured on a Fisher–Johns apparatus. Proton nmr spectra were measured on a Varian A-60A instrument, and infrared spectra were measured on a Perkin-Elmer 457 spectrometer. Gas chromatographic analyses were obtained on a Perkin-Elmer 900 gas chromatograph using a 6 ft 3% OV-1 or OV-17 on 80–100 mesh Chromosorb W (regular) column. The analyses were performed by comparison of peak areas with standard solutions of the reaction products.

Acetone 4-Tolylsulfenimine (6b). Sulfenimine **6b** was prepared as previously described[1] from 5.0 g (0.02 mol) of *p*-tolyl disulfide to give after crystallization from pentane–ether 2.4 g (65%) of white needles: mp 41–2°; nmr ($CDCl_3$) δ 2.1 (d, J = 4 Hz, 6 H, CH_3), 2.3 (s, 3 H, CH_3), and 7.3 (q, 4 H).

Anal. Calcd for $C_{10}H_{13}NS$: C, 67.04; H, 7.26. Found: C, 66.85; H, 6.94.

2-Butanone Benzenesulfenimine (12a). Sulfenimine **12a** was prepared from 5.0 g (0.023 mol) of phenyl disulfide as previously described[1] to give, after washing at 0° with a 5% HCl solution saturated with Na_2SO_4, an oil which was distilled giving 3.5 g (88%) of a colorless oil: bp 79–81° (0.04 mm); ir (thin film) 1615 cm^{-1} (C=N); nmr ($CDCl_3$), sample contains both the *E* and *Z* forms,[1] δ 1.1 (q, 3 H), 2.0 (d, 3 H), 2.2 (q, 2 H), 7.4 (m, 4 H); mass spectrum *m/e* (rel intensity), 179 (46) M, 109 (100) M-C_4H_8N. A satisfactory elemental analysis could not be obtained. See reference 1.

Reaction of Sulfenimine 6a with Acid and Lewis Acids. Sulfenimine **6a,** 2.0 g (0.012 mol), was allowed to react with 5 ml of boron trifluoride etherate at −78° or refluxed with 10 ml of concentrated HCl or glacial acetic acid for 20 min. Water was added and the reaction mixture extracted with ether (3 × 50 ml) and dried over $MgSO_4$. The solvent was removed and the residue dissolved in methylene chloride and analyzed by gas chromatography.

Reaction of Sulfenimine 6a with Alcoholic Sodium Hydroxide. In a 100-ml three-necked flask equipped with a magnetic stir bar and reflux condenser was placed 2.0 g (0.012 mol) of **6a** in 25 ml of 75% aqueous ethanol containing 0.74 g (0.024 mol) of sodium hydroxide. After the reaction mixture was refluxed for the specified time period (Table I), the solution was cooled, 5 ml of methyl iodide added, and the reaction mixture refluxed for 1 hr. The reaction mixture was diluted with water and extracted with ether (3 × 50 ml). After drying over $MgSO_4$ the ether solvent was removed to give an oil which was crystallized from pentane–ethanol to give 1.2 g (65%) of white plates, mp 88–9° (lit.[27] mp 88°), identified as methyl phenyl sulfone (**9**).

General Procedure for the Rearrangment of Sulfenimines to Enamides with Benzoyl Chloride and DBN. In a 100-ml three-necked flask equipped with magnetic stir bar, reflux condenser with drying tube, and dropping funnel were placed 0.03 mol of the appropriate sulfenimine and 3.7 g (0.03 mol) of DBN (Aldrich) in 30 ml of dry benzene. The reaction mixture was heated to reflux and 4.2 g (0.03 mol) of benzoyl chloride in 20 ml of benzene added rapidly. After refluxing the reaction mixture for 15 hr the solution was cooled to room temperature and washed with water (4 × 20 ml) followed by washing with 20 ml of an ice-cold 2% HCl solution saturated with Na_2SO_4. After drying over $MgSO_4$ the solvent was removed to give the enamide.

2-Benzamido-1-(phenylthio)propene (11a). Recrystallization from ethanol gave 1.7 g (21%) of white crystals: mp 108–109°; ir (KBr) 3260 (NH), 1645 cm^{-1} (C=O); nmr ($CDCl_3$) δ 2.1 (d, J = 1.3 Hz, 3 H, CH_3), 5.4 (d, J = 1.3 Hz, 1 H), 7.5 (m, 10 H).

Anal. Calcd for $C_{16}H_{15}NOS$: C, 71.35; H, 5.61. Found: C, 71.10; H, 5.35.

2-Benzamido-1-(3-nitrophenyl)propene (11d). Crystallization from ethanol gave 2.1 g (22%) of yellow needles: mp 123–124°; ir (KBr) 3260 (NH), 1650 cm^{-1} (C=O); nmr ($CDCl_3$) δ 2.2 (d, J = 1.3 Hz, 3 H, CH_3), 5.4 (d, J = 1.3 Hz, 1 H), 7.4 (m, 9 H).

Anal. Calcd for $C_{16}H_{14}N_2O_3S$: C, 61.13; H, 4.48. Found: C, 61.28; H, 4.46.

2-Benzamido-3-(phenylthio)butene (13a). Crystallization from ethanol gave 2.3 g (26%) of white crystals: mp 125–126°; ir (KBr) 3290 (NH), 1650 cm^{-1} (CO); nmr ($CDCl_2$) δ 1.9 (d, J = 1.5 Hz, 3 H, CH_3), 2.4 (d, J = 1.5 Hz, 3 H, CH_3), 7.3 (m, 10 H).

Anal. Calcd for $C_{17}H_{17}NOS$: C, 72.08; H, 6.0. Found: 71.82; H, 5.72.

2-Benzamido-3-(3-nitrophenylthio)butene (13b). The enamide was sublimed at 150° (2 mm) and crystallized from ethanol to give 2.2 g (22%) of yellow needles: mp 161–162°; ir (KBr) 3280 (NH), 1650 cm^{-1} (C=O); nmr ($CDCl_3$) δ 2.2 (d, J = 1.5 Hz, 3 H, CH_3), 2.5 (d, J = 1.5 Hz, 3 H, CH_3), 7.4 (m, 9 H).

Anal. Calcd for $C_{17}H_{16}N_2O_3S$: C, 62.2; H, 4.87. Found: C, 61.73; H, 4.77.

Hydrolysis of Enamides. In a 100-ml flask equipped with magnetic stir bar and reflux condenser was placed 0.02 mol of the appropriate enamide in 25 ml of 75% aqueous ethanol. After refluxing the reaction mixture for 5 min the solvent was removed under vacuum and the residue dissolved in ether and dried over $MgSO_4$. The solvent was removed and the residue redissolved in methylene chloride and analyzed by glc.

General Procedure for the Hydrolysis of the Sulfenimine, DBN, Benzoyl Chloride Reaction Mixture. The sulfenimine, benzoyl chloride, and DBN were reacted as described above in dry benzene or cyclohexene (Table II). After separating the sol-

vent from the DBN residue the latter was dissolved in water. After extracting the aqueous solution with benzene (3 × 50 ml) the organic solvents were combined and washed with water and the solvent removed under vacuum. The residue was dissolved in 75% aqueous ethanol and refluxed for 5 min, the solvent removed, and the residue redissolved in ether and dried over $MgSO_4$. The solvent was removed and the residue dissolved in methylene chloride and analyzed by glc.

Preparation of β-Keto Sulfides 8d and 14b. 3-Nitrophenyl disulfide, 5.0 g (0.016 mol), was placed in 250 ml of absolute ethanol in a 500 ml three-necked flask equipped with mechanical stirrer, reflux condenser with nitrogen inlet, and dropping funnel. Sodium metal, 0.7 g (0.033 mol), was added and the reaction mixture stirred under N_2 until the sodium had dissolved. The reaction mixture was then heated to reflux and an equivalent amount of 2-chloroacetone (Eastman) or 3-chlorobutanone[28] was added dropwise. The reaction mixture was refluxed for 3 hr, the precipitated salts removed by filtration, and the solvent evaporated. The resulting oil was distilled or crystallized.

2-(3-Nitrophenylthio)acetone (8d). Crystallization from ether–pentane gave 4.5 g (45%) of yellow needles: mp 61–62°; ir (KBr) 1700 cm^{-1} (C=O); nmr ($CDCl_3$) δ 2.3 (s, 3 H, CH_3), 3.8 (s, 2 H, CH_2), 7.2–8.2 (m, 4 H).

Anal. Calcd as the 2,4-DNPH (mp 138–140°) for $C_{15}H_{13}N_5O_6S$: C, 46.04. H, 3.32. Found: C, 47.79; H, 3.27.

3-(3-Nitrophenylthio)-2-butanone (14b). The oil was distilled at 180° (0.05 mm) to give 4.7 g (65%) of a yellow oil: ir (thin film) 1720 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.4 (d, J = 7 Hz, 3 H, CH_3), 2.3 (s, 3 H, CH_3), 3.9 (q, J = 7 Hz, 1 H), 7.9 (m, 4 H).

Anal. Calcd as the 2,4-DNPH (mp 132–133°) for $C_{16}H_{15}N_5O_6S$: C, 47.43. H, 3.70. Found: C, 47.70; H, 3.37.

2-(3-Nitrophenylthio)chlorocyclohexane (15). In a 250-ml three-necked flask equipped with gas inlet, addition funnel, magnetic stir bar, and reflux condenser with drying tube was placed 5.0 g (0.016 mol) of 3-nitrophenyl disulfide in 50 ml of dry methylene chloride. The reaction was cooled to 0° and dry chlorine gas was passed through the solution for 15 min followed by dry nitrogen for 30 min. Anhydrous aluminum chloride, 0.5 g (0.004 mol), was added followed by dropwise addition of 5 ml of cyclohexene in 25 ml of methylene chloride. After refluxing the reaction mixture for 4 hr water was added and the organic layer dried over $MgSO_4$. The solvent was removed and the resulting oil chromatographed on Florisil. Elution with pentane–benzene (1:3) gave 8.0 g (94%) of an oil identified as **15**: nmr ($CDCl_3$) δ 1.2–2.3 (m, 8 H, cyclohexane ring), 3.4 (m, 1 H), 4.0 (m, 1 H), 7.6 (m, 4 H).

Anal. Calcd for $C_{12}H_{14}ClNO_2S$: C, 53.03; H, 5.19. Found: C, 53.13; H, 5.46.

2-(3-Nitrophenylthio)cyclohexanol (16). In a 100-ml flask equipped with a magnetic stir bar and reflux condenser was placed 8.0 g of the crude chloride, **15**, in 75% aqueous ethanol. After refluxing for 1 hr the solvent was removed under vacuum and the residue dissolved in ether and dried over $MgSO_4$. After removal of the solvent the residue was chromatographed on Florisil. Elution with pentane–benzene (1:3) gave 2.0 g (25%) of an oil identified as **15**. Further elution with benzene gave 4.0 g (54%) of an oil: ir (thin film) 3400 cm^{-1} (broad, OH); nmr ($CDCl_3$) δ 1.1–2.3 (m, 8 H), 2.6–3.6 (broad, m, 3 H), 7.7 (m, 4 H).

Anal. Calcd for the phenylurethane (mp 94–95°) for $C_{19}H_{20}N_2O_4S$: C, 61.30; H, 5.37. Found: C, 61.11; H, 5.20.

Reaction of Cyclohexanone 2-Benzothiazolesulfenimine (3c) with Base. Sulfenimine **3c**, 0.1 g (0.0004 mol), in 0.2 ml of 0.2 *N* sodium hydroxide and 0.5 ml of water in 25 ml of ethanol, was allowed to stand for 1 week at room temperature. The reaction mixture was than diluted with water and extracted with ether (3 × 50 ml). After drying over $MgSO_4$, the solvent was evaporated to give 0.09 g (90%) of **5c**, mp 106° (lit.[19] mp 106–107°).

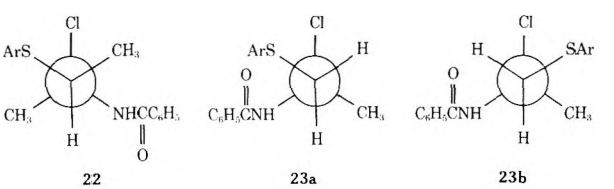
Shift Reagent Experiments. The enamides, 0.74–1.1 mmol, were dissolved in dry $CDCl_3$ to which was added an appropriate amount of tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-3,5-octanedionato)europium, $Eu(fod)_3$ (Aldrich). Induced chemical shifts were measured relative to internal TMS.

Acknowledgment. We wish to thank Mr. W. A. R. Slegeir for preparing **6b** and Mr. A. Schwartz for preparing **8d**. A National Science Foundation undergraduate fellowship to E. B. S. is gratefully acknowledged.

Registry No.—**6b**, 50314-90-4; **8d** (2,4-DNPH), 50314-91-5; **11a**, 50314-92-6; **11d**, 50314-93-7; **12a**, 50314-94-8; **13a**, 50314-95-9; **13b**, 50314-96-0; **14b** (2,4-DNPH), 50314-97-1; **15**, 50314-98-2; **16** (phenylurethane derivative), 50404-54-1; phenyl disulfide, 882-33-7; benzoyl chloride, 35913-09-8; DBN, 3001-72-7; 3-nitrophenyl disulfide, 537-91-7; 2-chloroacetone, 78-95-5; 3-chlorobutanone, 4091-39-8.

References and Notes

(1) Part VI: F. A. Davis, W. A. R. Slegeir, S. Evans, A. Schwartz, D. L. Goff, and R. Plamer, *J. Org. Chem.*, **38**, 2809 (1973).
(2) National Science Foundation Undergraduate Research Participant, 1972.
(3) For reviews on the Fisher indole synthesis, see B. Robinson, *Chem. Rev.*, **63**, 376 (1963); **68**, 227 (1968).
(4) T. Sheradsky, *Tetrahedron Lett.*, 5225 (1966).
(5) D. Kaminsky, J. Shavel, Sr., and R. I. Meltzer, *Tetrahedron Lett.*, 859 (1967).
(6) H. J. Shine, "Aromatic Rearrangements," Vol. 6, Elsevier, New York, N. Y. 1967, p 190.
(7) H. D. Hartough and S. L. Meisel, "Compounds with Condensed Thiophene Rings," Interscience, New York, N. Y., Chapter 2; B. Iddon and R. M. Scrowston, *Advan. Heterocycl. Chem.*, **11**, 178 (1970).
(8) For a recent review of the chemistry of sulfenimines, see F. A. Davis, *Int. J. Sulfur Chem., Part B*, in press.
(9) K. H. Pausacker and C. I. Schubert, *J. Chem. Soc.*, 1814 (1950).
(10) D. Desaty and D. Keglavic, *Croat. Chem. Acta*, **36**, 103 (1964).
(11) L. Zervas, D. Borovas, and E. Gazis, *J. Amer. Chem. Soc.*, **85**, 3660 (1963).
(12) J. A. Barltop and K. J. Morgan, *J. Chem. Soc.*, 4486 (1960).
(13) E. Fromm and J. Wittmann, *Chem. Ber.*, **41**, 2269 (1908); R. Schiller and R. Otto, *ibid.*, **9**, 1636 (1876); see also W. E. Truce and A. M. Murphy, *Chem. Rev.*, **48**, 69 (1950).
(14) H. Bohme and K. Hartke, *Chem. Ber.*, **96**, 600 (1963); H. Bohme, S. Ebel, and K. Hartke, *ibid.*, **98**, 1463 (1965).
(15) R. R. Fraser, *Can. J. Chem.*, **38**, 549 (1960).
(16) M. R. Peterson, Jr., and G. H. Wahl, Jr., *J. Chem. Educ.*, **49**, 790 (1972).
(17) F. A. Davis, E. R. Fretz, and C. J. Horner, *J. Org. Chem.*, **38**, 690 (1973).
(18) F. A. Davis, C. J. Horner, E. R. Fretz, and J. F. Stackhouse, *J. Org. Chem.*, **38**, 695 (1973).
(19) J. J. D'Amico, *J. Org. Chem.*, **26**, 3436 (1961).
(20) H. Z. Lecher and F. M. Hardy, *J. Org. Chem.*, **20**, 475 (1955).
(21) N. Kharasch and A. J. Havlik, *J. Amer. Chem. Soc.*, **75**, 374 (1953); D. I. Relyea, *J. Org. Chem.*, **31**, 3577 (1966); W. H. Mueller and P. E. Butler, *J. Amer. Chem. Soc.*, **90**, 2075 (1968).
(22) For leading references see G. M. Underwood, A. K. Chan, T. Green, C. T. Watts, and C. A. Kingsbury, *J. Org. Chem.*, **38**, 2735 (1973).
(23) F. A. Davis, S. Divald, and A. H. Confer, *Chem. Commun.*, 294 (1971).
(24) N. Kharasch in "Organic Sulfur Compounds," Vol. 1, N. Kharasch, Ed., Pergamon Press, New York, N. Y., 1961, Chapter 32.
(25) D. Ben-Ishai and R. Giger, *Tetrahedron Lett.*, 4523 (1965).
(26) The isolation of **13a,b** in the *E* configuration requires the formation of rotamer **22** since a trans elimination is required. Rotamer **22** would be formed by a trans addition of the sulfenyl chloride to the enamide form of **22**. The preference of the *Z* configuration for enamides **11a** and **11d** is, however, not clear. The formation of enamides **11a** and **11d** in the *Z* configuration requires exclusive elimination from rotamer **23a**.



22 23a 23b

(27) H. Bohme and H. Fisher, *Chem. Ber.*, **75**, 1310 (1942).
(28) E. M. Kosower, W. J. Cole, G. S. Wu, D. E. Cardy, and G. Meisters, *J. Org. Chem.*, **28**, 630 (1963).

Chemistry of the Neomycins. XIII. Synthesis of Aminocyclitols and Amino Sugars *via* Nitromethane Condensations[1,2]

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Received September 27, 1973

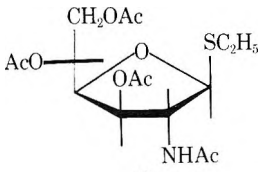
Base-catalyzed cylizations of 2-acetamido-2,6-dideoxy-6-nitro-α-D-gluco- (and -L-ido-) thiofuranosides with subsequent hydrogenations have given two known inosadiamines—streptamine and *myo*-inosadiamine-1,3—and two previously unknown optically active inosdiamines—L-*myo*-inosadiamine-1,5 and L-*epi*-inosadiamine-1,3. Starting from *myo*-inosadiamine-1,3, 2-deoxystreptamine was synthesized in three steps. Neosamines B and C have also been prepared. The structures of all new compounds were determined by their nmr spectra and the reaction sequences.

Neomycin remains one of the clinically important antibiotics.[4] When structural studies on this antibiotic, actually a complex of antibiotics including neomycins B and C, neamine (neomycin A),[4] and others,[5] were nearly completed, we commenced an investigation of the mode of biosynthesis of these antibiotics.[6] Although commercially available labeled compounds (glucose-*1*-^{14}C, glucose-*6*-^{14}C, glucosamine-*1*-^{14}C, ribose-*1*-^{14}C) sufficed for studies of early steps in the biosynthesis, specifically labeled units from the antibiotics themselves were desirable for studies of later steps. These units include deoxystreptamine (**28**), neosamine C (**9b**), and neosamine B (**24**). The synthesis of these three moieties of neomycin B, again specifically labeled but with stable isotopes, was also desirable for our study of their mass spectra.

A potentially useful method for introducing label into the three units would involve the condensation of nitromethane-^{14}C with an aldehyde generated by cleavage between C-5 and C-6 of glucosamine in the furanose form. This route could lead to neosamines B and C labeled at C-6 and, after cyclization, to deoxystreptamine labeled at a ring carbon bearing an amino group. Some of the synthetic operations described have, in fact, been reported earlier by the Wolfrom group in their synthesis of streptamine.[7] In the present report we describe our investigation of the nitromethane condensation route. This report includes the syntheses of neosamine C-*6*-^{14}C and deoxystreptamine-*1*-^{14}C, of the unequivocal synthesis of neosamine B, and of the preparation of a number of new diaminocyclitols of potential utility as substrates for incorporation into hybrimycins.[8,9]

Synthesis of 6-Nitro Sugar Derivatives. Since the yields reported by Wolfrom in his synthesis of streptamine, especially in the base-catalyzed cyclization of the nitro sugar, were too low to use those procedures directly for our purpose, our first goal was to obtain the aldehydothiofuranoside intermediate **4a** in a pure crystalline state, for the purpose of improving the yield in the base-catalyzed condensation reaction with nitromethane. Following Wolfrom's procedure,[7,10] 2-acetamido-2-deoxy-D-glucose diethyl dithioacetal (**1**) was converted by treatment with mercuric chloride followed by acetylation to ethyl 2-acetamido-3,5,6-tri-*O*-acetyl-2-deoxy-1-thio-α-D-glucofuranoside (**2a**) in 55% yield (Figure 1). A second isomer was isolated in pure form by fractional crystallization and chromatography from this reaction mixture. This was assigned the structure ethyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-1-thio-β-D-glucopyranoside (**3b**) (6% yield). In addition, a mixture of **3b** and the corresponding α-D-glucopyranoside (**3a**) was obtained in 7% yield.

The three compounds (**2a**, **3a**, and **3b**) were indicated to be isomeric by elemental analyses and mass spectral behavior. Both **2a** and **3a** gave molecular ions at *m/e* 391, that for **3a** being inferred from the spectrum of the mixture of **3a** and **3b** since the latter compound did not give a molecular ion peak. The highest mass ion in the spectrum of **3b** was at *m/e* 332 (M − OAc), but its trimethylsilyl derivative gave a strong ion at *m/e* 448 (M − CH_3). The melting point, 184–186°, and rotation, $[\alpha]^{28}D$ −56° (c 1, $CHCl_3$), of **3b** identify it as the second isomer reported by Wolfrom, *et al.* [lit. mp 179–180°, $[\alpha]^{22}D$ −42° (c 2, $CHCl_3$)],[7] who assigned to it the β-D-glucofuranoside structure (**2b**). However, the nmr spectrum of **3b** (see Experimental Section) identifies it as a glucopyranose derivative, with trans-diaxial coupling of all ring protons. The chemical shifts and coupling patterns of the protons of **2a** are quite different (see Experimental Section), in agreement with those expected for a furanoside. The purity of **3a** did not allow complete assignment of chemical shifts and coupling constants to its protons, but the anomeric proton was apparent, at δ 5.75 (J = 5.7 Hz).



2b

O-Deacetylation of **2a** with sodium methoxide in absolute methanol followed by oxidative cleavage between C-5 and C-6 with sodium metaperiodate[11a] gave ethyl 2-acetamido-2-deoxy-1-thio-α-D-*xylo*-pentodialdo-1,4-furanoside (**4a**), which was crystallized from ethanol to give its crystalline ethanol solvate, **4b**. Both the solvate and **4a** apparently exist as a hemiacetal, perhaps a dimer of the type described by Schaffer and Isbell for 1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdo-1,4-furanoside.[11b] No aldehyde carbonyl absorption was found in their infrared spectra, and both the nmr spectra contained little or no aldehyde absorption but displayed absorption for an extra hemiacetal proton at δ 5.4 (one proton). The solvate **4b** contained ethoxyl group absorption at δ 3.72 (q) and 1.21 (t). Reduction of **4b** with sodium borohydride in aqueous solution gave ethyl 2-acetamido-2-deoxy-1-thio-α-D-xylofuranoside (**5**).[11a] The yields of **1**, **2a**, and **4b** were 60, 65, and 71%, respectively, in their individual preparative steps. Thus, the overall yield of **4b** from *N*-acetylglucosamine was 29%.

Treatment of **4b** with an equimolar amount of nitromethane in the presence of sodium methoxide catalyst at 0–5° yielded two crystalline condensation products which could be separated either by fractional crystallization from absolute ethanol or on a specially prepared silica gel column.[12a] Compound **7**, shown below to be the D-gluco isomer, was isolated in 23% yield from **4b** (16% from **2a**) and had mp 115–118°; compound **6**, the L-ido isomer, was

Table I
Nmr Methyl Absorptions of Peracetyl-1,3-inosadiamines

Configuration	Chemical shift, δ[a]	Solvent[b]	Ref
scyllo-1,3 (**11**)	1.94 (4), 1.75 (2)	D	This work
	1.90 (4), 1.70 (2)	D	43
	2.03 (2), 1.98 (2), 1.91 (2)	C	43
	2.06 (4), 1.92 (2)	W	43
myo-1,3 (**12**)	2.19, 1.96 (2), 1.94, 1.78 (2)	D	This work
	2.14, 1.92 (2), 1.89, 1.74 (2)	D	43
	2.26, 2.06 (2), 2.03, 1.90 (2)	C	43
13	2.32, 2.15, 1.93 (4), 1.73	D	This work
	2.38, 2.33, 2.03 (2), 2.00 (2), 1.92	C	This work
	2.37, 2.32, 2.04 (2), 2.00 (2), 1.93	C	12b
myo-1,5 (**18**)	2.13, 1.93, 1.89 (2), 1.76, 1.71	D	This work
epi-1,3 (**19**)	2.16, 2.12, 1.97, 1.88, 1.80, 1.77	D	This work
	2.19, 2.14, 2.04, 1.97, 1.92, 1.89	C	This work
muco-1,3	2.08, 2.05, 2.00 (3), 1.96	C	16
myo-2,4	2.10, 2.05 (2), 2.01 (2), 1.93	W	42
chiro-1,3	2.16, 2.04 (3), 1.98 (2)	C	16
chiro-1,5	2.18, 2.01 (3), 1.98 (2)	C	16

[a] Number of methyl groups indicated in parentheses; one except as noted. [b] D = DMSO-d_6; C = $CDCl_3$; W = D_2O.

isolated in 32% yield from **4b** (23% from 2a) and had mp 206–208°.

Since isolation and purification of the low melting isomer (7) lowered its yield, an alternative sequence was employed in which fractional crystallization from ethanol gave the chromatographically pure high melting isomer **6** in 15% yield from **4b**, and the syrupy product obtained on evaporating the mother liquor, rich in **7**, was subjected directly to the next hydrolysis, involving a slight excess of mercuric chloride in hot water. This afforded the crystalline 2-acetamido-2,6-dideoxy-6-nitro-D-glucopyranose (**8**) in 35% yield. Compound **8**, identified by elemental analyses and infrared spectrum, was hydrogenated over platinum in acidic solution to give an oil (**9a**), which was hydrolyzed with 6 *N* hydrochloric acid to afford (almost quantitatively) 2,6-diamino-2,6-dideoxy-D-glucose (**9b**), also identified as its crystalline di-*N*-acetyl derivative (**9c**). The synthesis of diaminoglucose assigns the low melting isomer as ethyl 2-acetamido-2,6-dideoxy-6-nitro-1-thio-α-D-glucofuranoside (**7**); thus, the high melting isomer is the β-L-idofuranoside (**6**). Earlier work[7] had not assigned the stereochemistry of the two isomers.

Barium Hydroxide Cyclizations of 6-Nitro Sugars. Next, the base-catalyzed cyclization of the higher melting 2-acetamido-2,6-dideoxy-6-nitrohexose[7] was reexamined. The thioethyl group of **6** was hydrolyzed by mercuric chloride and the nitro sugar formed (**10**, Figure 1) was not isolated but was subjected to alkaline condensation using barium hydroxide at room temperature (Figure 2). The mixture of nitro compounds obtained was isolated as an amorphous mixture of barium salts which was hydrogenated in acidic solution over a platinum catalyst. The resultant diaminocyclitol derivatives were acetylated to give a mixture, from which three compounds were isolated by fractional crystallization from ethanol. Two of the derivatives obtained from **6** after the barium hydroxide cyclization were readily identified as hexaacetylstreptamine (**11**) and hexaacetyl-*myo*-inosadiamine-1,3 (**12**) by their melting point behavior and infrared spectra, as well as by the chemical shifts of their acetyl protons (Table I). The nmr spectra (Table I) of the third product, **13**, showed peaks for seven acetyl methyl groups at positions reported earlier for heptaacetylstreptamine,[12b] and the mass spectrum contained a protonated molecular ion at *m*/e 473.177 (M + H)$^+$ appropriate for a heptaacetylinosadiamine, with a much more intense ion at *m*/e 412 (M − HOAc). The structure of **13** was confirmed by its hydrolysis to streptamine.

Compounds **11**, **12**, and **13** were obtained in 10, 11, and 6% yields, respectively, from **6**; the total yield of *myo*-inosadiamine derivatives is thus 11% and of *scyllo*- 16%. It is of some interest to note here that the Wolfrom group isolated two products from the higher melting isomer in their streptamine synthesis, in very poor but approximately equal yields.[7] One was shown to be streptamine. From the optical inactivity of streptamine and Fischer's results,[13] which indicated that alkaline carbonyl reactions give only trans configurations, Wolfrom, Olin, and Polglase[7] deduced the configuration of streptamine as the all-trans isomer of 1,3-inosadiamine. They did not report the rotation of the second isomer and tentatively assigned to it the muco-1,3 configuration which would be the other product containing only trans configurations at the new asymmetric centers. However, had they observed that the second isomer, isolated from the reaction mixture in yield similar to that of streptamine, was also optically inactive, they could not have assigned the configuration of streptamine, although their assignment was subsequently shown to be correct by X-ray[14] and nmr[15] evidence.

The crystalline hydrolysis product **8**, from the D-gluco isomer **7**, was also subjected to barium hydroxide catalyzed cyclization, followed by reduction and acetylation (Figure 2). Two hexaacetylinosadiamines were isolated from the reaction mixture and were identified as hexaacetylstreptamine (**11**) and hexaacetyl-*myo*-inosadiamine-1,3 (**12**), respectively. The third product (**13**) was not isolated.

The isolation of **11** and **12** from **8** as well as from **6** requires an inversion of the stereochemistry found at C-5 in **8**. This could occur in the nitro sugars, but isomerization of the sugar would require loss of nitromethane and recondensation. Thus, it seems more likely that the isomerization occurs after cyclization to the nitrocylitol.

Sodium Methoxide Cyclization of 6-Nitro Sugars. The crude syrupy nitro sugar (**10**) obtained by hydrolysis of **6** with mercuric chloride was dissolved in absolute methanol and treated with an equimolar amount of sodium methoxide at 0–5° for 12 hr (Figure 2). Work-up yielded crude, crystalline **15**, which on recrystallization from methanol afforded the pure isomer in 67% yield. The structure of **15** was established by its hydrogenation to the corresponding inosadiamine, which on acetylation gave hexaacetyl-*myo*-inosadiamine-1,3 (**12**). No evidence was found for isomeric nitrocyclitols or hexaacetylinosadiamines. Thus, this base appears to be much more selective in catalyzing cyclizations than barium hydroxide. It is also of

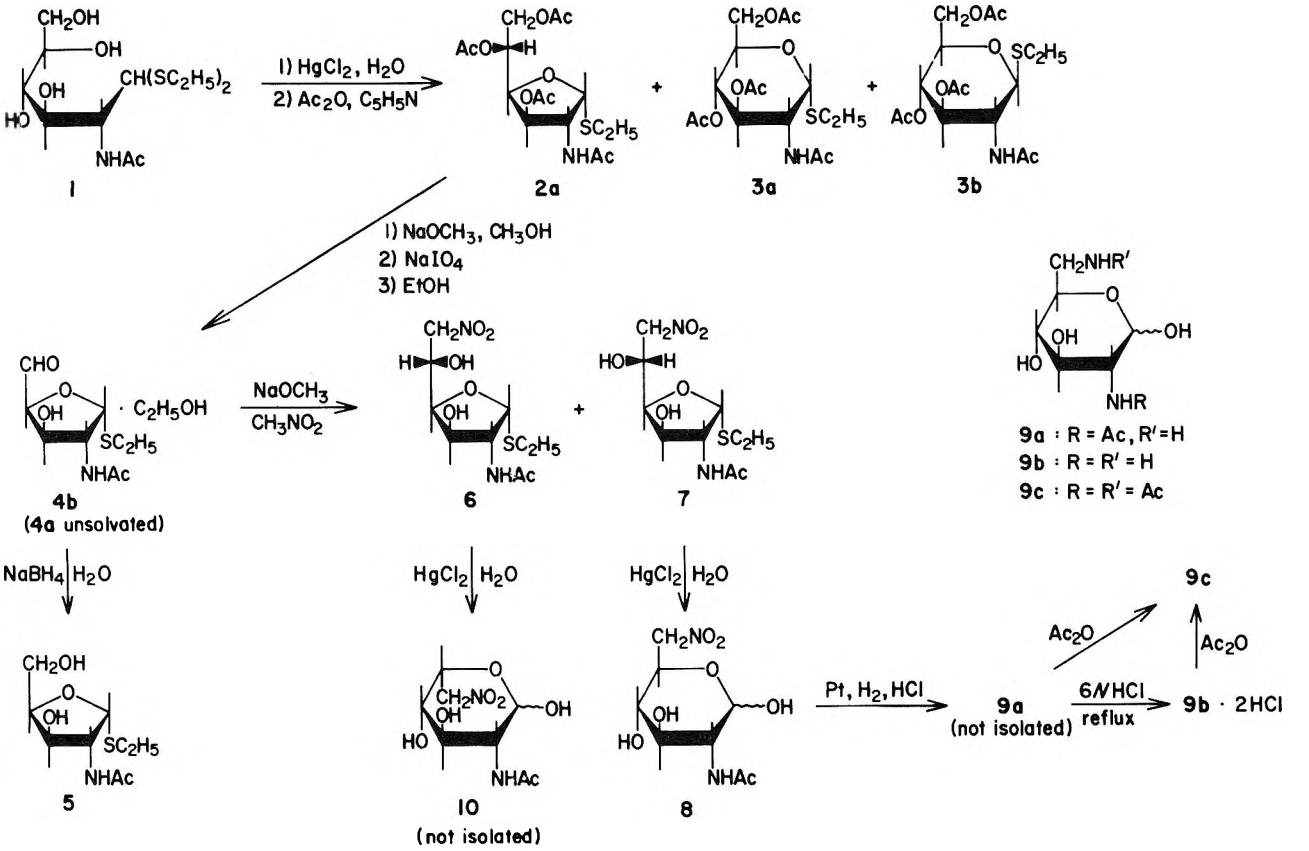


Figure 1. Synthesis of derivatives of 6-nitro-2-acetamido sugars from *N*-acetylglucosamine diethyl dithioacetal (1).

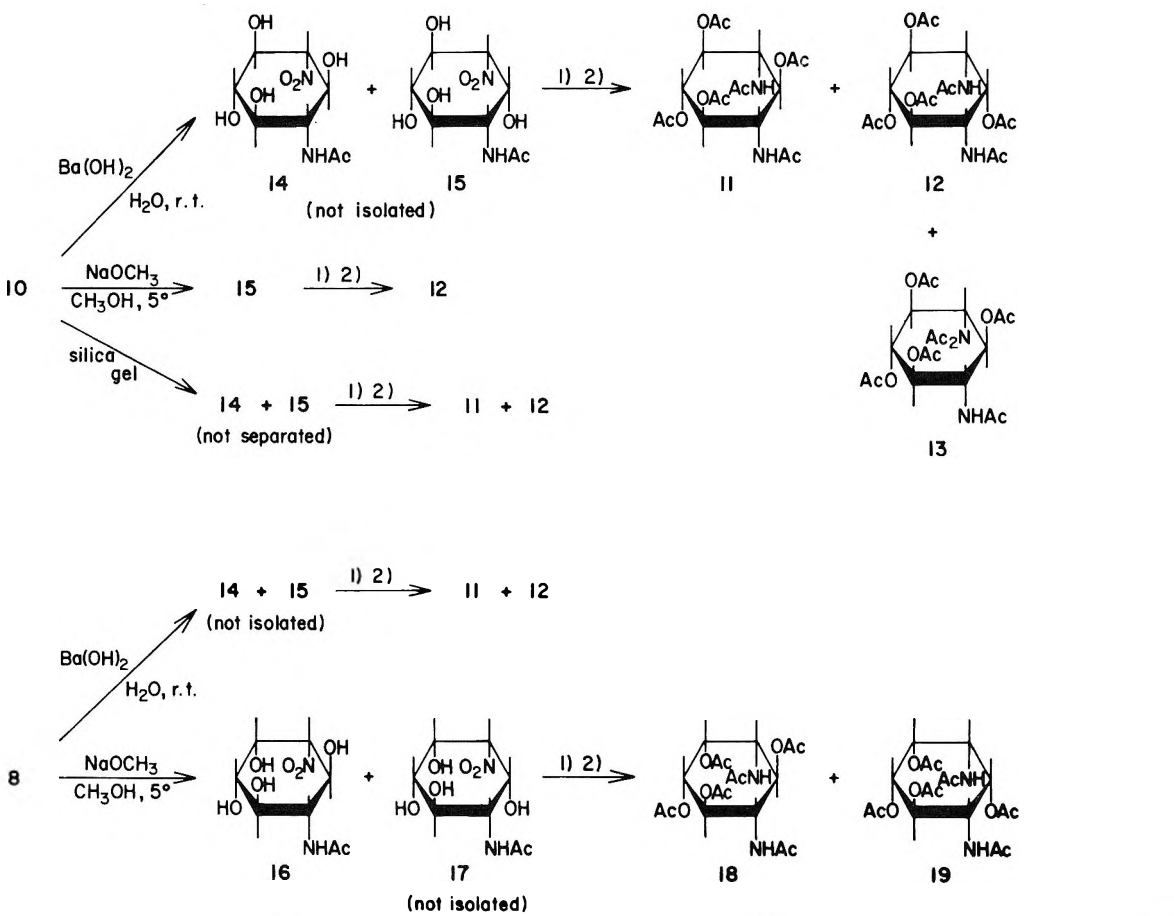


Figure 2. Preparation of diamino inositols from the D-*gluco*-6-nitro sugar derivative 8 and the L-*ido*-6-nitro sugar derivative 10. Conditions: (1) Pt, H_2, HCl; (2) Ac_2O, C_5H_5N.

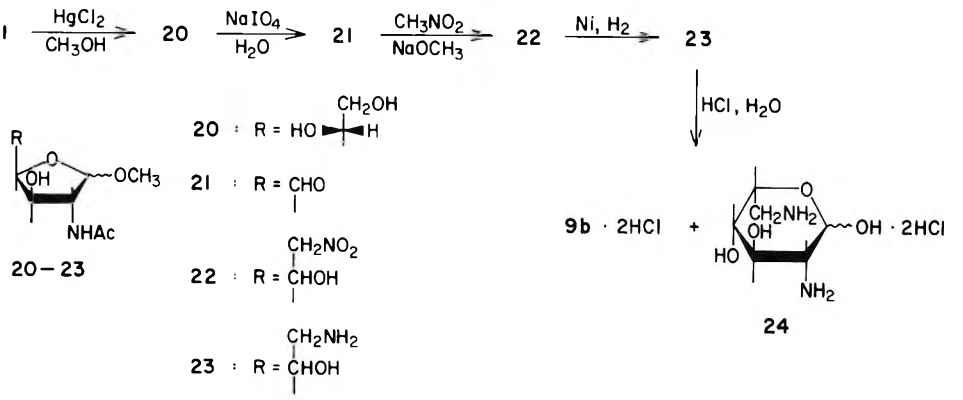


Figure 3. Synthesis of neosamine B (24) from *N*-acetylglucosamine diethyl dithioacetal (1).

interest that the preferred isomer is not that which is presumably most stable, the all-trans scyllo isomer **14**. Apparently some degree of kinetic control *obtains*.

When compound 8 was dissolved in absolute methanol and treated with equimolar sodium methoxide at 0–5° for 12 hr (Figure 2), work-up afforded a mixture of *N*-acetylnitrodeoxyinosamines—1L-5-acetamido-1,5-dideoxy-1-nitro-*myo*-inositol (**16**) and 1L-1-acetamido-1,3-dideoxy-3-nitro-*epi*-inositol (**17**)—in 72% combined yield. The mixture of **16** and **17** was hydrogenated catalytically and subsequent acetylation gave a mixture of hexaacetylinosadiamines, which could be separated by fractional crystallization from ethanol to afford 1L-hexa-*N,O*-acetyl-*myo*-inosadiamine-1,5 (**18**) and 1L-hexa-*N,O*-acetyl-*epi*-inosadiamine-1,3 (**19**) in 67 and 15% yields, respectively, from the mixture of **16** and **17**. In a separate experiment nitroinositol **16** was purified and converted separately to **18**.

In assigning the stereochemistry of **18** and **19** it was first assumed that the configurations at C-2, C-3, and C-4 of D-glucosamine must be retained and substituents at these positions of the inosadiamines must all be trans to one another. With that restriction there are eight theoretically possible isomers obtainable from the reaction,[13] six optically active forms—1L-myo-1,5, 1L-myo-2,4, 1L-epi-1,3, 1L-chiro-1,3, 1D-chiro-1,5, and 1L-muco-1,3—and two meso forms—scyllo-1,3 and myo-1,3. Six isomers have been previously reported, at least as racemates.[16-20]

Nmr spectra of **18** and **19** were determined in dimethyl sulfoxide-d_6, the solvent which gives the most reliable information relative to axial *vs.* equatorial acetoxyl and acetamido groups.[43] The nmr spectrum (Table I) of **18** in DMSO-d_6 showed five sharp signals with relative intensities of 1:1:2:1:1 at δ 2.13, 1.93, 1.89, 1.76, and 1.71, respectively. These can be ascribed to one axial acetoxyl group, three equatorial acetoxyl groups, and two equatorial acetamido groups, respectively.[19] Of the six optically active inosadiamines above, only the myo-1,5 configuration would satisfy these spectral data.

The nmr spectrum (Table I) of **19** in DMSO-d_6 showed six signals with relative intensities of 1:1:1:1:1:1 at δ 2.16, 2.12, 1.97, 1.88, 1.80, and 1.77, respectively. These can be assigned as two axial acetoxyl groups, two equatorial acetoxyl groups, and two equatorial acetamido groups, respectively.[19] Therefore, compound **19** is assigned the epi-1,3 configuration.

The configurations of the inosadiamines obtained from the sodium methoxide cyclizations at low temperature (0–5°) indicate that in this reaction, in contrast to the barium hydroxide reactions, isomerization of the nitroinositols (or nitro sugars) does not take place and that the original configuration at C-5 of the sugars is preserved during the reaction.

Synthesis of Neosamine B. In an attempt to prepare neosamine B, compound **6** was hydrolyzed in the presence of mercuric chloride. A thin layer chromatogram of the crude hydrolyzate showed a single major spot, along with a trace of starting material. An attempt was made to purify the nitro sugar (**10**) on a silica gel column; elution with chloroform containing 20% methanol gave homogeneous crystals accounting for a 77% yield. Although elemental analyses and an infrared spectrum were satisfactory for a nitroacetamido sugar, the compound's mobility in tlc was quite different from that of the original crude product. When the crystalline material was hydrogenated catalytically, compounds **11** and **12** were obtained after subsequent acetylation, in 9 and 78% yields, respectively. Apparently the crude L-ido nitro sugar had cyclized on the chromatographic column, to afford cyclitols, mainly of the myo-1,3 configuration.[22] The crystals isolated must then have been composed of 1L-1-acetamido-1,3-dideoxy-3-nitro-*scyllo*-inositol (**14**) and 1L-1-acetamido-1,3-dideoxy-3-nitro-*myo*-inositol (**15**) in the approximate ratio of 1:9.

Several additional attempts were made to prepare neosamine B from the 1-thio-L-idofuranoside. For instance, on hydrogenation of the crude nitro sugar (**10**) in acidic medium or on direct methanolysis of **6** in the presence of acidic catalyst and subsequent hydrogenation, neosamine B was sometimes detected by paper chromatography. However, many by-products, usually aminocyclitols, were also formed and the results were inconclusive.

In an effort to find an alternative route to neosamine B, that shown in Figure 3 was devised. Whitehouse and Kent[23] have reported the synthesis of methyl 2-acetamido-2-deoxy-β-D-glucofuranoside by treatment of **1** with mercuric chloride in anhydrous methanol. When this preparation was repeated in the present study, the product could not be crystallized and paper chromatography revealed the presence of two major components and traces of four NH-containing impurities. This mixture was separated by chromatography over charcoal; the major component was isolated in 30% yield, but could not be crystallized, although it was homogeneous by paper chromatography. Presumably it was a mixture of α and β anomers (**20**), not distinguishable by paper chromatographic techniques. Analytical periodate oxidation demonstrated a very rapid 1-mol uptake of oxidant, with formation of formaldehyde as expected for the furanoside structure.[23]

Glycol cleavage was accomplished on a preparative scale with a slight excess of sodium metaperiodate in aqueous solution. The deionized reaction mixture was strongly reducing to AHP, indicating the presence of the intermediate aldehyde (**21**). No attempt was made to isolate this aldehyde; rather, it was immediately condensed with excess nitromethane under basic catalysis to give the

Table II
Comparison of Natural and Synthetic 2,6-Diamino-2,6-dideoxy-L-idose

	Synthetic	Neosamine B	Ref
Dihydrochloride (**24**), $[\alpha]_D$	+23.9° (*c* 1.9, H_2O)	+17.5° (*c* 0.9, H_2O)	24
N-Acetyl derivative			
$[\alpha]_D$	+7.0° (*c* 1.9, H_2O)	+5.0°, +6.0° (*c* 1.0, H_2O)	25
R_f, PEaAW[a]	0.59	0.59	
R_f, BAW 415[a]	0.44	0.45	
M_g, borate electrophoresis[a]	0.42	0.42	
Mp, *p*-nitrophenylhydrazone	211–215°[b]	215–218°[b]	25

[a] See Experimental Section for details. [b] Mmp 212–217°.

crude mixture of epimers (**22**), in 86% yield. In view of the possible instability of the 6-nitro isomers and the facile separation procedure available for the final product diamines, it was decided to postpone epimer separation until the last stages of the synthesis. Accordingly, half of the crude mixture was immediately hydrogenated over Raney nickel. The crude primary amine mixture (**23**) gave a very strongly positive test with ninhydrin and on vigorous acidic hydrolysis gave a mixture of mono- and diamino sugars, which was separated into three diamine components (peaks I, II, III) by ion-exchange chromatography. The first (and major) diamine component was chromatographed over cellulose as its *N*-acetyl derivative to give two fractions. One of these was identified as 2,6-diacetamido-2,6-dideoxy-D-glucose (**9c**) by comparison of optical activity, melting point, and paper chromatographic behavior with those of an authentic sample of diacetylneosamine C (**9c**). This was isolated in 9% crude yield, with 3% obtained in crystalline form, based on the starting methyl furanoside **20**. The other N-acetylated component of peak I, isolated as a glass in approximately 7% yield, has not been identified. It resembled a diacetamidohexitol in its paper chromatographic mobility and lack of reaction with AHP, but was different from 2,6-diacetamido-2,6-dideoxy-D-glucitol in optical activity.

The second diamino component from the ion-exchange column (peak II), isolated as a glass in less than 1% yield, also behaved after N-acetylation as a diacetamidohexitol in paper chromatography and color tests. Insufficient material was available for further purification or comparison with known diacetamidohexitols.

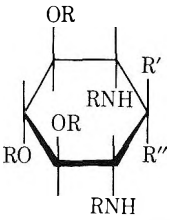
The third diamine component (peak III), 2,6-diamino-2,6-dideoxy-L-idose dihydrochloride (**24**), was obtained in 5% yield as a hygroscopic glass. This product was ninhydrin and AHP positive, indicative of the primary amine and reducing carbohydrate functions expected. Its point of elution on the gradient elution chromatography curve near 2,6-diamino-2,6-dideoxy-D-glucose indicates that there are two amino groups per molecule. L-Ido stereochemistry was adduced for this material on the basis of its mode of formation.

The synthetic material was compared with natural neosamine B as summarized in Table II: optical activity of the dihydrochloride; optical activity of the *N*-acetyl derivative; mobility of the borate complexes of the *N*-acetyl derivatives in electrophoresis, a technique previously shown[27] to be extremely sensitive to conformational differences; paper chromatographic behaviors of the *N*-acetyl derivatives; and melting point behavior of the *N*-acetyl derivatives.

Synthesis of Neosamine C-6-^{14}C and 2-Deoxystreptamine-1-^{14}C. Synthetic methods developed in previous sections of the present report appeared to lend themselves well to the preparation of specifically labeled subunits of the neomycins, and these expectations have already been realized for neosamine C and deoxystreptamine.

Neosamine C-6-^{14}C was prepared by the route shown in Figure 1 *via* compounds **4b** and **8**. Label was introduced *via* nitromethane-^{14}C. The overall yield of labeled **8** was 34% (from **4b**) and that of crude neosamine C-6-^{14}C (labeled **9b**) was 56% (from **8**).

Suami, *et al.*,[26,27] recently reported a two-step synthesis of 2-deoxystreptamine (**28**) starting from *myo*-inosadiamine 1,3-dihydrochloride (**25**) and we have followed that route in the preparation of labeled **28** from **6**. Labeled **12** was prepared as shown in Figure 2, by the silica gel cyclization. The hexaacetate **12** was easily hydrolyzed with boiling 6 *N* hydrochloric acid to give the dihydrochloride **25** in 96% yield. Under conditions slightly modified from



25, R = R′ = H; R″ = OH
26, R = Ac; R′ = Br; R″ = H
27, R = Ac; R′ = R″ = H
28, R = R′ = R″ = H

those earlier reported,[26,27] we obtained a somewhat better yield (81%) in the introduction of bromine into **25**. Debromination was effected by treating pentaacetyl-2-bromo-2-deoxystreptamine (**26**) with zinc, acetic anhydride, and water at room temperature to give pentaacetyl-2-deoxystreptamine (**27**) in 82% yield. Compound **27** was hydrolyzed with boiling 6 *N* hydrochloric acid to give deoxystreptamine dihydrochloride (**28**) in 96% yield. The overall yield (based on labeled nitromethane) was 5.0%.

Experimental Section[28]

2-Acetamido-2-deoxy-D-glucose diethyl dithioacetal (**1**) was prepared from 50.0 g of 2-acetamido-2-deoxy-D-glucose, mp 205–208° dec [lit.[34] mp 203–205° (dec)], by the procedure of Wolfrom and Anno[35] except that residual lead carbonate was removed by Amberlite MB-3 resin, and the filtrate was concentrated to yield 18.7 g of crystalline **1**, mp 128–129°, $[\alpha]^{27}D$ −30.5° (*c* 0.96, H_2O) [lit.[35] mp 130–131°; $[\alpha]^{23}D$ −35° (*c* 4.0, H_2O)]. The mother liquor yielded an additional 26.0 g of the diethyl dithioacetal, mp 124–127°. The total yield of **1** was thus 64%.

Reaction of 2-acetamido-2-deoxy-D-glucose diethyl dithioacetal (1) with mercuric chloride was carried out according to the procedure described by Wolfrom, *et al.*,[7,11a] employing 10.0 g of **1** and freshly prepared mercuric oxide.[36] The acetylated product began to crystallize when it was poured into ice and water. The crystals were filtered and washed with water; the yield was 6.88 g of ethyl 2-acetamido-3,5,6-tri-*O*-acetyl-2-deoxy-1-thio-α-D-glucofuranoside (**2a**), mp 123–125°. Recrystallization from ethanol and water gave pure needles: 6.09 g; mp 124–125°; $[\alpha]^{28}D$ +147° (*c* 3.95, $CHCl_3$) [lit.[7] mp 124.5–125.5°; $[\alpha]^{23}D$ +140° (*c* 4.0, $CHCl_3$)]. The mother liquor was evaporated and extracted with chloroform to give a second crop of crystals, 0.90 g, mp 120–122°. Recrystallization gave pure crystals, 0.63 g, mp 123–124°. The total yield of a slightly impure **2a** was thus 7.78 g (65%), that of pure crystals 6.72 g (56%). The nmr spectrum ($CDCl_3$) of **2a** contained the following absorptions, with assignments confirmed by spin decoupling: δ 1.29 (t, 3, *J* = 7.2 Hz, $SCCH_3$), 2.01 (s, 6, $COCH_3$), 2.06 (s, 6, $COCH_3$), 2.66 (q, 2, *J* = 7.2 Hz, SCH_2), 4.13 (d of d, *J* = 13.0,

5.8 Hz, H-4), 4.49 (m, 2, H-6), 4.57 (m, J = 7.8, 6.0, 4.1 Hz, H-2), 5.28 (m, H-5), 5.45 (d of d, J = 5.8, 4.1 Hz, H-3), 5.72 (d, J = 6.0 Hz, H-1), 6.70 (d, J = 7.8 Hz, NH). The infrared spectrum (Nujol) contained a strong band at 1750 cm^{-1} not found in the spectrum of **1**.

The mother liquor from the second crop of **2a** was concentrated to *ca.* 30 ml, and the mixture was kept for 3 days at room temperature. The precipitated crystals were collected by filtration and washed with a little water; yield 0.83 g (7%) of a mixture of ethyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-1-thio-α- (and β-) -D-glucopyranosides (**3a** and **3b**, respectively; mainly **3b**), mp 153–158°. Recrystallization from ethanol and water gave 0.62 g (5%) of colorless needles, mp 158–160°, $[\alpha]^{28}D$ −6° (*c* 1, $CDCl_3$). The nmr spectrum ($CDCl_3$) was the same as that of pure **3b** (see below) except for the following peaks due to minor amounts of **3a**: δ 1.29 (t, $SCCH_3$), 2.70 (q, SCH_2), 5.75 (d, J = 5.7 Hz, H-1).

Anal. Calcd for $C_{16}H_{25}NO_8S$: C, 49.09; H, 6.44; N, 3.58; S, 8.19; mol wt, 391. Found: C, 49.11; H, 6.47; N, 3.53; S, 8.19; mol wt, 391 (mass spectrum).

The mother liquor from the preceding crystallization was further concentrated to 3.4 g of syrup, most of which (3 g) was chromatographed over Celite employing benzene–ethanol (99:1, v/v) as development solvent, extrusion, alkaline permanganate detection,[37] and elution with acetone to yield 0.69 g (6%) of **3b**, mp 165–173°. Recrystallization from ethanol–water gave 0.43 g (4%) of **3b**, mp 184–186°, $[\alpha]^{28}D$ −56° (*c* 1, $CDCl_3$). The nmr spectrum ($CDCl_3$) of **3b** contained the following absorptions, with assignments confirmed in part by spin decoupling: δ 1.26 (t, 3, J = 7.4 Hz, $SCCH_3$), 1.93 (s, 3), 2.02 (s, 6), 2.07 (s, 3), 2.72 (q, 2, J = 7.4 Hz, SCH_2), 3.78 (m, H-5), 4.10 (m, H-2), 4.23 (m, 2, H-6), 4.75 (d, J = 10.0 Hz, H-1), 5.11 (t, J = 10.0 Hz, H-3), 5.31 (t, J = 9.0 Hz, H-4), 6.35 (d, J = 9.4 Hz, NH).

Anal. Calcd for $C_{16}H_{25}NO_8S$: C, 49.09; H, 6.44; N, 3.58; S, 8.19. Found: C, 48.93; H, 6.36; N, 3.67; S, 8.46.

A sample of the β-D-glucopyranoside **3b** (97.8 mg) was dissolved in absolute methanol (2 ml), and sodium (25 mg) was added. The solution was allowed to stand for 2 hr at room temperature, and then was neutralized with Amberlite IR-120 (H^+) cation-exchange resin, filtered, and concentrated to a syrup which crystallized on removal of the last traces of methanol under reduced pressure. Thin layer chromatography [silica gel G, benzene–methanol (8:2)] showed a single spot, R_f 0.14. A mixture of 25 mg of this de-*O*-acetylated product, 1 ml of barium oxide dried pyridine, and 0.5 ml of *N,O*-bis(trimethylsilyl)acetamide in a 5-dram vial fitted with a Teflon-lined screw cap was allowed to stand at room temperature with occasional shaking until the *N*-acetyl derivative had entirely dissolved. Excess silylating reagent and solvent were evaporated in a stream of dry nitrogen, the residue was dissolved in sodium-dried hexane, and the solution was evaporated in a stream of dry nitrogen. The residue was stored *in vacuo* over phosphorus pentoxide at about 40° for 10 hr, mp 164–168° dec. The mass spectrum contained a peak at m/e 448 ($M - CH_3$).

Ethyl 2-acetamido-2-deoxy-1-thio-α-D-*xylo*-pentodialdo-1,4-furanoside (4a) and its ethanol solvate (4b) were prepared by a modification of the procedure of Wolfrom and Winkley[11a] from 1.957 g of **2a**. Tlc [silica gel G, benzene–methanol (8:2)] showed a single spot, R_f 0.26, for the intermediate from deacetylation of **4a**. After periodate cleavage, barium chloride treatment, and filtration, the filtrate was evaporated under reduced pressure to a crude residue which was dried by codistillation with absolute ethanol several times and then dissolved in 30 ml of absolute ethanol. The solution was kept in a refrigerator for 3 hr, filtered, and evaporated to a crystalline residue. Tlc on silica gel G showed a major spot at R_f 0.63 and a minor spot at 0.31 in chloroform–methanol (17:3). The crude crystals were recrystallized from ethanol–ether to give 0.985 g (71%) of ethyl 2-acetamido-2-deoxy-1-thio-α-D-*xylo*-pentodialdo-1,4-furanoside ethanol solvate (**4b**): white needles, mp 132–133°, $[\alpha]^{24}D$ +165° (*c* 0.65, CH_3OH), tlc R_f 0.63 (silica gel G). The nmr spectrum (D_2O) of **4b** contained signals at δ 5.7 (H-1), 5.4 (H-5), 4.7–3.9 (H-2, H-3, H-4), 3.72 (q, $-OCH_2CH_3$), 2.75 (q, $-SCH_2CH_3$), 2.00 (s, $NCOCH_3$), 1.28 (t, $-SCH_2CH_3$), 1.21 (t, $-OCH_2CH_3$). Addition of ethanol to the nmr solution enhanced the signals at 3.72 and 1.21. The nmr spectra of **4b** in acetone-d_6 and dimethyl sulfoxide-d_6 both showed only a trace of aldehyde proton absorption. The total yield of **4b** was 0.985 g (71%).

Anal. Calcd for $C_9H_{15}NO_4S \cdot C_2H_5OH$: C, 47.31; H, 7.58; N, 5.02; S, 11.45; mol wt, 141. Calcd for $(C_9H_{15}NO_4S)_2 \cdot 2C_2H_5OH$: mol wt, 187. Found: C, 47.39; H, 7.08; N, 5.01; S, 11.77; mol wt, 203 (osmometric, in acetone).

When **4b** was dried at 100° (5 mm) over phosphorus pentoxide, it slowly melted to a glass, whose nmr spectrum ($CDCl_3$) lacked the signals at δ 3.72 and 1.21 but otherwise was identical with the nmr spectrum ($CDCl_3$) of **4b**.

Ethyl 2-acetamido-2-deoxy-1-thio-α-D-xylofuranoside (5) was prepared by the procedure of Wolfrom and Winkley[11a] but employing 92 mg of purified **4b**. The yield was 28 mg (35%) of **5**, mp 158–160° after sintering at 156°, $[\alpha]^{30}D$ +236° (*c* 0.60, water) [lit.[11a] mp 153–155°, $[\alpha]^{22}D$ +212 ± 3° (*c* 6.45, water)]. The mother liquor yielded 38 mg (48%) of **5**, mp 150–157° after sintering at 145°. The total yield was 83%.

Preparation of Ethyl 2-Acetamido-6-nitro-2,6-dideoxy-1-thio-β-L-ido- and -α-D-glucofuranosides (6 and 7). A. From 4b. Compound **4b** (2.22 g) was dissolved in 95% ethanol (42 ml), and equimolar nitromethane (0.555 ml) was added to the solution. The solution was cooled in an ice bath, and an equimolar amount of sodium methoxide (20% solution in absolute methanol) was added dropwise under agitation. The reaction was stirred 30 min at the same temperature and then allowed to stand in a refrigerator for 18 hr. The slightly yellow solution was neutralized with Amberlite IR-120 (H^+) and then evaporated under reduced pressure to yield a crystalline residue which showed two major spots on tlc [silica gel G, chloroform–methanol (19:1)]. One recrystallization from hot absolute ethanol gave colorless needles (**6**), mp 184–192° dec, which tlc showed to be contaminated by a small amount of the D-gluco isomer (**7**). Further recrystallization from the same solvent gave almost pure L-ido isomer (**6**) (0.925 g, 32%, based on nitromethane), mp 206–208° dec, $[\alpha]^{24}D$ +176° (*c* 2, methanol [lit.[7] mp 190–193°, $[\alpha]^{26}D$ +171° (c 2, methanol)].

Anal. Calcd for $C_{10}H_{18}N_2O_6S$: C, 40.80; H, 6.16; N, 9.52; S, 10.89. Found: C, 41.03; H, 6.04; N, 9.43; S, 10.91.

An oily product was obtained on evaporation of the mother liquor. Thin layer chromatography showed that it consisted mainly of the D-gluco isomer (**7**). Column chromatography (silica gel; chloroform containing 5% methanol) of the crude oily product gave pure crystalline **7** (0.670 mg, 23%), mp 115–118° (lit.[7] 114–115°).

Anal. Calcd for $C_{10}H_{18}N_2O_6S$: C, 40.80; H, 6.16; N, 9.52; S, 10.89. Found: C, 41.08; H, 6.24; N, 9.38; S, 10.76.

B. From 2a. The procedure of Wolfrom and Winkley[11a] was employed for the deacetylation of **2a** (1.957 g) and periodate oxidation as far as the removal of barium iodate by filtration. The filtrate and washings were combined and concentrated *in vacuo* to a thick oil, which was azeotroped several times with absolute ethanol, freed of sodium chloride by precipitation with ethanol, and filtered. The filtrate was concentrated *in vacuo* to a thick syrup which was dissolved in 10 ml of 95% ethanol and cooled to 0–5°. Nitromethane (2 ml) was added, followed, dropwise, by a solution of 2 *N* sodium methoxide in methanol to pH 11. The reaction mixture stood 15 hr at 0–5° and 3 hr at room temperature, Amberlite IR-120 (H^+) ion-exchange resin (~8 g) was added to remove sodium ions, and the product was concentrated to a thick yellow oil weighing 1.40 g.

The crude material was chromatographed by the method of Bhalla,[12a] employing a column 4.7 × 25 cm packed with 250 g of silica gel and developed with chloroform–methanol (17:3). Two zones, located by iodine vapor about 7–8 cm from the origin, were removed. Elution of the adsorbent from the upper region (faster moving band) yielded a yellow material which on careful crystallization from a small volume of ethanol gave 0.185 g (13%) of **6**, mp 206–208° dec, $[\alpha]^{24}D$ +176° (c 2, methanol).

Elution of the slower moving band gave on careful crystallization from chloroform–benzene–di-*n*-butyl ether (2:1:2, volume) 0.169 g (12%) of **7**, mp 115–116°.

Preparation of Ethyl 2-Acetamido-6-nitro-2,6-dideoxy-1-thio-β-L-idofuranoside (6) and 2-Acetamido-6-nitro-2,6-dideoxy-D-glucopyranose (8) from 4b. Nitromethane (1.335 g) was added to a solution of 6.12 g of **4b** in 95% ethanol (97 ml) at 0–5°, then 10.9 ml of 2 *N* sodium methoxide in methanol was added drop by drop during 15 min with stirring. The reaction mixture stood 16 hr in a refrigerator, then was neutralized with Dowex 50W-X8 (H^+) and evaporated under reduced pressure to give a crystalline residue. Tlc [silica gel G, chloroform–methanol (19:1)] showed two main spots running near one another, with traces of impurities. Recrystallization from absolute ethanol gave three crops weighing 0.894 g (mp 190–194° dec), 0.724 g (mp 184–192° dec), and 0.299 g (mp 180–190° dec), respectively. Tlc [silica gel G, chloroform–methanol (85:15)] showed that the first crop (except for two trace contaminants at R_f 0.53 and 0.28) was almost pure **6** but that the second and third crops were somewhat contaminated, with three spots at R_f 0.53, 0.36, and 0.28. Fractional

crystallization then gave pure **6**: 978 mg (15%); mp 206–208° dec; $[\alpha]^{24}D$ +176° (c 2, CH_3OH).

All the mother liquors were combined and evaporated to give a thick oily residue which was dissolved in 70 ml of water and warmed to 50–60°. When 4.0 g of mercuric chloride in 140 ml of water was added, fine white crystals of ethylmercaptomercuric chloride precipitated immediately. The reaction mixture stood at room temperature for 12 hr; then the precipitate was filtered and the filtrate was stirred with 5.0 g of fresh silver acetate for 2–3 hr. White crystals of silver chloride were removed by centrifugation. Excess silver acetate was removed by passing hydrogen sulfide through the filtrate for 25 min, the resulting black precipitate was removed by filtration through Celite, and the filtrate was evaporated under reduced pressure to afford a crystalline residue. The crystals were digested with methanol and chloroform and filtered; yield, 1.043 g. Second and third crops were obtained from the mother liquor; weight, 0.668 and 0.231 g, respectively. Tlc showed a single spot for each crop. The total yield of **8** was 1.942 g (35%). Recrystallization from methanol and chloroform gave the analytical sample, mp 193–195° dec, $[\alpha]^{18}D$ +71° (5 min) → +49° (10 hr) (c 1.0, water).

Anal. Calcd for $C_8H_{14}N_2O_7$: C, 38.40; H, 5.64; N, 11.20. Found: C, 38.01; H, 5.67; N, 11.32.

Ethyl 2-acetamido-2,6-dideoxy-6-nitro-1-thio-β-L-idofuranoside-6-^{14}C (6) and 6-nitro-6-deoxy-*N*-acetyl-D-glucosamine-6-^{14}C (8) were prepared as described in the preceding section, from 3.82 g of **5b** and 25.6 mg of nitromethane-^{14}C (2.38 mCi/mmol) diluted with 978.9 mg of cold nitromethane. The first and second crops of crystals from ethanol (890 mg and 449 mg, respectively) were combined and recrystallized from ethanol to give needles (707 mg, 15%). Tlc showed a single spot, for **6**. Evaporation of the mother liquors and hydrolysis of the residue with mercuric chloride (3.2 g) as in the preceding section gave crude crystals of **8** (1.387 g, 34%). The radioactivity of the recrystallized material was 52.5 μCi/mmol.

Hexaacetylinosadiamines from Ethyl 2-Acetamido-6-nitro-2,6-dideoxy-1-thio-β-L-idofuranoside (6). A. Barium Hydroxide Catalyzed Cyclization. The method of Wolfrom[7] was employed directly to hydrolyze **6** (287.2 mg) with mercuric chloride (260 mg). The resultant crude oily nitro sugar (**10**) was then subjected to barium hydroxide catalyzed cyclization, again following the method of Wolfrom except that the barium hydroxide solution was neutralized with Amberlite IR-120 (H^+) after 1–2 days. The crude barium salt of mixed nitrodeoxyinosamines was hydrogenated over 200 mg of platinum catalyst, and the mixture of hexa- and heptaacetylinosadiamines was separated by multiple fractional recrystallization from ethanol: hexaacetylstreptamine (**11**), 42.5 mg (10%), mp 237–245°, identical with an authentic sample;[38] hexaacetyl-*myo*-inosadiamine-1,3 (**12**), 47.3 mg (11%), mp 287–289° (lit.[21] 283.5–285°), infrared spectrum superimposable on that of an authentic sample;[21] and heptaacetylstreptamine (**13**), 23.9 mg (6%), mp 240–252° (lit.[11b] 258–259°); the total yield was 27%.

In addition to the M + H ion, compound **13** also gave strong ions at *m/e* 455.1674 (M + H − H_2O, calcd 455.1665), *m/e* 429.1509 (M − $COCH_3$, calcd 429.1509), and *m/e* 412.1477 (M − HOAc, calcd 412.1481), as well as a weak peak at *m/e* 514.1788 (calcd 514.1798), indicative of a small amount of octaacetylinosadiamine impurity. The ir spectrum showed bands at 1750, 1700, 1680, and 1650 cm^{-1}. Hydrolysis of 10 mg of **13** with 6 *N* hydrochloric acid for 2 hr on the steam bath, followed by neutralization, gave a product which gave identical tlc behavior with that of streptamine (R_f 0.66) but differed from that of *myo*-inosadiamine-1,3 (R_f 0.58).

B. Sodium Methoxide Catalyzed Cyclization. A solution of **6** (285 mg) in water (73 ml) was hydrolyzed with mercuric chloride (275 mg) according to the Wolfrom procedure.[7] The crude hydrolyzate was dissolved in absolute methanol (35 ml) and cooled to 0–5°, then 1 ml of a 1 *N* solution of sodium methoxide in methanol was added. The solution stood in a refrigerator overnight, then was neutralized with Dowex 50W-X8 (H^+) and evaporated *in vacuo* to give a crystalline residue of L-1-acetamido-1,3-dideoxy-3-nitro-*myo*-inositol (**15**). The crystals were digested with chloroform and methanol and collected by filtration; yield 0.163 g (67%), mp 208–213° dec. The analytical sample was obtained by recrystallization from ethanol; plates, mp 207–210° dec or needles, mp 210–215° dec, $[\alpha]^{21}D$ +95° (c 1.0, water).

Anal. Calcd for $C_8H_{14}N_2O_7$: C, 38.40; H, 5.64; N, 11.20. Found: C, 38.60; H, 5.52; N, 11.26.

A solution of 157.9 mg of crude **15** in 15 ml of water containing 5 ml of 0.5 *N* hydrochloric acid was hydrogenated over platinum catalyst. The resultant crystalline amine hydrochloride was treated with acetic anhydride and pyridine to afford 221.5 mg (82%) of hexaacetyl-*myo*-inosadiamine-1,3 (**12**).

C. Silica Gel Catalyzed Cyclization. Compound **6** (452 mg) was dissolved in 110 ml of water and treated with 412 mg of mercuric chloride in water (27 ml) at 50–60°. The crude hydrolyzate was chromatographed on a silica gel column (30 g) packed with chloroform–methanol (4:1), eluting with chloroform–methanol (3:1). The fractions which showed a single spot on tlc (silica gel) were collected and evaporated. The major fraction, a white crystalline powder, mp 202–206°, contained a mixture of **14** and **15** (280 mg, 77% based on unrecovered **6**); the minor fraction contained 24 mg of **6**. A 106-mg portion of the mixture of **14** and **15** was dissolved in water (10 ml) containing 3 ml of 0.5 *N* hydrochloric acid and hydrogenated over platinum for 4.5 hr; hydrogen uptake was 32 ml. The catalyst was filtered and the filtrate was evaporated *in vacuo* to give a white crystalline residue. The residue was treated overnight with a mixture of 5 ml of acetic anhydride and 5 ml of pyridine. The reaction mixture was evaporated *in vacuo* and a trace of acetic anhydride and pyridine were removed by codistillation with ethanol and toluene. The partly crystallized oil was triturated with 10 ml of methanol to give 17 mg (9%) of **11**. The mother liquor was evaporated, and the residue was crystallized from ethanol to afford 143 mg (78%) of **12**, which contained a trace of **11**.

D. Silica Gel Catalyzed Cyclization to Give Hexaacetylstreptamine-1-^{14}C (11) and Hexaacetyl-*myo*-inosadiamine-1,3-1-^{14}C (12) from 6. The sample of ^{14}C-labeled **6** (707 mg) prepared above was hydrolyzed with mercuric chloride (687 mg) and chromatographed on silica gel as described in the preceding section to give a white crystalline powder (labeled **14** and **15**, 398 mg, 66%). The powder was hydrogenated (uptake 120 ml), and the product was worked up as in the preceding section to give 561 mg (54%) of crude crystals, which were recrystallized from chloroform to yield 89.3 mg (9%) of pure crystalline labeled **11**. The mother liquor was evaporated and the residue was recrystallized from ethanol to afford 354 mg (34%) of pure crystalline labeled **12**.

E. "Spontaneous Cyclization." Compound **6** was hydrolyzed with mercuric chloride to give a 30% yield of a crystalline product, mp 210–213°, single spot on tlc at the position of the 6-nitro-*N*-acetylhexose (**10**). A 38.5-mg portion of **10** was catalytically hydrogenated to an oil (single spot on tlc), which was N-acetylated to give 13 mg of a colorless, crystalline di-*N*-acetyl derivative, mp 320–323°. The mother liquor was evaporated to yield an oily product which was treated with acetic anhydride and pyridine to give a white powder, sintering 235–240°. The infrared spectrum of this compound was superimposable on that of authentic hexaacetylstreptamine (**11**).

Hexaacetylinosadiamines from 2-Acetamido-2,6-dideoxy-6-nitro-D-glucose (8). A. Barium Hydroxide Catalyzed Cyclization. A mixture of 255 mg of **8**, 5 ml of water, and 5 ml of 0.2 *N* barium hydroxide solution was allowed to stand at room temperature for 20 hr. Hydrogenation, acetylation, and work-up were as described above. The products isolated were 31 mg (7%) of hexaacetylstreptamine (**11**) and 38.3 mg (9%) of hexaacetyl-*myo*-inosadiamine-1,3 (**12**).

B. Sodium Methoxide Catalyzed Cyclization. 1. Isolation of 16 and Its Conversion to 18. A solution of 672 mg of **8** in 105 ml of absolute methanol was cooled to 0–5°, and then 2.75 ml of 1 *N* sodium methoxide in absolute methanol was added, with stirring. The reaction mixture was kept in a refrigerator overnight, neutralized with Dowex 50W-X8 (H^+) and filtered. The filtrate was evaporated under reduced pressure to give a crystalline residue of 5-acetamido-1,5-dideoxy-1-nitro-L-*myo*-inositol (**16**). Recrystallization from ethanol gave fine needles: 244 mg (36%); mp 190.5–193° dec; $[\alpha]^{24}D$ +19° (c, 1.05, H_2O).

Anal. Calcd for $C_8H_{14}N_2O_7$: C, 38.40; H, 5.64; N, 11.20. Found: C, 38.32; H, 5.67; N, 11.27.

The nitroinositol (**16**, 105 mg) was then hydrogenated in 11 ml of water containing 2 ml of 0.5 *N* hydrochloric acid in the presence of platinum catalyst at room temperature. Hydrogen uptake (23 ml) ceased after 3 hr. The catalyst was filtered, and the filtrate was evaporated under reduced pressure to give a white crystalline residue which was allowed to stand overnight with acetic anhydride (7 ml) and pyridine (7 ml) at room temperature and then was heated on a steam bath for 30 min. The reaction mixture was evaporated under reduced pressure; remaining traces of pyridine were removed by codistillation with toluene. The crystalline residue of L-hexaacetyl-*myo*-inosadiamine-1,5 (**18**) was digested with ethanol and the crystals were collected by filtration; yield 145 mg (81%), mp 284.5–285.5°. Recrystallization from

ethanol gave the analytical sample: mp 285.5–286.5°; $[\alpha]^{20}D$ +1° (*c* 1.0, pyridine); $[\alpha]^{20}D$ +8° (c 1.0, water).

Anal. Calcd for $C_{18}H_{26}N_2O_{10}$: C, 50.23; H, 6.09; N, 6.51. Found: C, 50.62; H, 6.26; N, 6.78.

2. Direct Conversion to 18 and 19. A solution of 1.52 g of 8 in 240 ml of absolute methanol was cooled by ice while 6.2 ml of 1 *N* sodium methoxide in methanol was added drop by drop, with shaking. The reaction mixture was allowed to stand in a refrigerator overnight, then was neutralized with Dowex 50W-X8 (H^+), and evaporated under reduced pressure to afford a crystalline product. The crystals were digested with 5 ml of ethanol, filtered, and washed with a mixture of ethanol and ether; needles, 1.17 g (72%), mp 169–173° dec after sintering at 140°. The crude nitrodeoxyinosamine (0.934 g) was hydrogenated and acetylated as described in run 1 to yield 842 mg (52%) of **18**, mp 282–284°, identified by the infrared spectrum.

The mother liquor was evaporated *in vacuo* and the oily residue was dissolved in chloroform and chromatographed over alumina. Elution with chloroform gave a thick oily product which crystallized gradually after 1 or 2 weeks. The crystalline mass was digested with a small amount of ethanol, filtered, and washed with a mixture of ether and ethanol to give 194 mg (7%) of L-hexa-*N,O*-acetyl-*epi*-inosadiamine-1,3 (**19**) as colorless needles. The crystals were recrystallized from ethanol–ether to afford fine needles, mp 149–152°. The crystals contain 1 mol of water of crystallization, while the anhydrous product is hygroscopic, $[\alpha]^{18}D$ +31° (*c* 1.1, chloroform).

Anal. Calcd for $C_{18}H_{26}N_2O_{10}\cdot H_2O$: C, 48.21; H, 6.29; N, 6.28. Found: C, 48.24; H, 6.59; N, 6.38.

***myo*-Inosadiamine-1,3 Dihydrochloride.** A solution of 479 mg of hexaacetyl-*myo*-inosadiamine-1,3 (**12**) was heated in 6 *N* hydrochloric acid on a boiling water bath for 2 hr and then evaporated under reduced pressure to a crystalline residue. Crystallization from ethanol–water gave 270 mg (93%) of *myo*-inosadiamine-1,3 dihydrochloride; recrystallization yielded the analytically pure sample, mp 222–240.5° (lit.[21] 221–241.5°). The infrared spectrum was superimposable on that of an authentic sample.[21]

***myo*-Inosadiamine-1,3-*l*-^{14}C Dihydrochloride.** Hexaacetyl-*myo*-inosadiamine-1,3-*l*-^{14}C (**12**, 567 mg) was heated for 2 hr with 30 ml of refluxing 6 *N* hydrochloric acid. The reaction mixture was evaporated *in vacuo* and a trace of hydrochloric acid was removed by repeated codistillation with water. The glassy residue was triturated with water and ethanol to afford fine needles [291 mg (88%) after drying over phosphorus pentoxide *in vacuo* at 100°].

Preparation of Di-*N*-acetylneosamine C from 7. The crystalline D-*gluco*-nitrothiofuranoside (**7**) was hydrolyzed with mercuric chloride in aqueous solution to give colorless crystals (**8**), mp 180–183°, in 70% yield. The crude nitro sugar (**8**), which showed a single spot on tlc, was hydrogenated in an acidic solution in the presence of platinum catalyst to give an oily product, which showed a single spot on paper chromatography (R_f 0.19, BPW 643). The crude product was converted to its di-*N*-acetyl derivative (**9c**), which was identified as di-*N*-acetylneosamine C by its paper chromatographic behavior (R_f 0.32, BEW 415; R_f 0.51, BPW 643). A trace of di-*N*-acetylneosamine B could also be detected by paper chromatography (R_f 0.48, BEW 415; R_f 0.54, BPW 643).

Di-*N*-acetylneosamine C-6-^{14}C was prepared from labeled **8** by the micro N-acetylation method: mp 200–207°; R_f 0.52 (BPW); radioactivity, 53.0 μCi/mmol.

Neosamine C-6-^{14}C Dihydrochloride (9b). A sample of labeled **8** (298.3 mg) was hydrogenated over platinum at room temperature in 30 ml of water containing 12 ml of 0.5 *N* hydrochloric acid. Hydrogen uptake (85 ml) ceased after 3 hr, the catalyst was filtered, and the filtrate was evaporated *in vacuo* to an oily residue. The residue was heated in 6 *N* hydrochloric acid (20 ml) at reflux for 2 hr. After it had been decolorized with carbon, the solution was evaporated *in vacuo* and dried by codistillation with absolute ethanol; the crude dihydrochloride (**9b**) weighed 167 mg (56%). The product was purified by preparative thin layer chromatography (cellulose powder, 15 g, 20 × 20 cm plate, BAW 221). Spots were detected by ninhydrin spray. Radioactivity of the sample was 54.8 μCi/mmol. The purity of chromatographed **9b** was determined by paper chromatography of its di-*N*-acetyl derivative (**9a**) obtained by the microacetylation technique. Paper chromatography showed one major spot, R_f 0.51, and a minor spot, R_f 0.61, in BPW 643. By radioanalysis, the relative intensities of the spots were 91.7 and 8.3%, respectively.

Methyl 2-Acetamido-2-deoxy-D-glucofuranoside (20). A slurry of 20.1 g of mercuric oxide, 24.9 g of mercuric chloride, and 14.9 g of *N*-acetylglucosamine diethyl dithioacetal (**1**) in 150 ml of methanol was stirred at room temperature for 6 hr and then treated with 6 ml of pyridine, stirred briefly in an ice bath, and filtered through Celite. The filtrate was shaken over liquid mercury for 60 hr. After the precipitate had settled, the yellow methanolic solution was decanted and filtered. Additional methanol was used to wash the mercury and salts. Evaporation of solvent from the combined filtrates left 9.6 g of a yellow gum, which was triturated with 200 ml of boiling 2-propanol. The resultant solution was filtered while hot and then evaporated to a thick oil, which was dissolved in methanol, filtered, and assayed by paper chromatography. The major CLOR-positive component of the mixture had R_f 0.63 in PEaW (R_{NAG} 1.39), a minor component had R_f 0.54, and trace components had R_f 0.33, 0.47, 0.70, and 0.78. The respective R_f values in BEW are 0.45, 0.35, 0.08, 0.26, 0.51, and 0.62.

A portion (620 mg) of the crude methyl furanoside mixture was chromatographed over a charcoal-Celite column (30 × 420 mm), eluting with 5% ethanol in water. The 20-ml fractions were analyzed by CLOR and residue weight. The first half of the major peak (tubes 43 through 59) contained the methyl pyranoside and furanoside; the balance (tubes 60 through 100) contained nearly pure furanoside (R_f 0.63, BEW). Combination of tubes 60–100, and removal of solvent, gave 260 mg (30%, based on **1**) of methyl 2-acetamido-2-deoxy-D-glucofuranoside (**20**), homogeneous by paper chromatography. A second pure methyl furanoside peak was obtained by washing the column with 7.5% ethanol in water. All efforts to crystallize this compound were unsuccessful.

Quantitative periodate oxidation by the method of Argoudelis[39] showed a 1-mol uptake in 7 min with slight subsequent overoxidation. Chromotropic acid determination[39] of formaldehyde fromation, using mannitol as a standard, showed 0.72 to 0.80 mol of formaldehyde produced per mole of sample oxidized.

Preparation of Neosamines B and C (24 and 10) from 20. A solution of 1.47 g (6.17 mmol) of methyl 2-acetamido-2-deoxy-D-glucofuranoside (**20**) and 1.47 g (6.80 mmol) of sodium metaperiodate in 40 ml of water was kept at 0–5° for 1 hr and then dripped slowly through a column containing 20 ml (12.5 mequiv) of Amberlite MB-3 mixed bed (H^+ and OH^-) ion-exchange resin. The pale yellow eluate was strongly AHP-reducing at first, gradually decreasing in intensity as the column was washed with 1 l. of water. Removal of the water under reduced pressure at 40° left **21** as a yellow syrup which was dried by repeated evaporation from methanolic solution; weight 1.58 g.

The thick syrup of crude **21** dissolved in 20 ml of absolute ethanol and 20 ml of nitromethane was chilled; sodium methoxide in absolute ethanol was then added until the sugar solution gave an alkaline test (pH 8 to 9) when applied to moist pH test paper. The stoppered flask was refrigerated at 10° for 33 hr and then a large excess of dry Dowex-50 (H^+ form) ion-exchange resin was stirred in. The resin was removed by filtration and washed well with methanol. The pale yellow filtrate was freed of solvent and the residue was dried over phosphorus pentoxide *in vacuo* to give 1.40 g (86% based on **20**) of a yellow glass assumed to be a mixture (**22**) of C-5 epimers of the 6-nitrofuranoside.

Half of this yellow glass was hydrogenated at atmospheric pressure in aqueous solution over approximately 2 g of Raney nickel. Hydrogen uptake amounted to only 115 ml (57.5% of theory) in 40 hr. The catalyst was removed by filtration and washed liberally with water. The combined filtrate and washings, strongly ninhydrin-positive, were freed of solvent and dried, leaving 549 mg of crude **23** as a yellow-brown syrup.

This was dissolved in 40 ml of 1.5 *N* hydrochloric acid and heated 4 hr at 50°, then 2 hr at 95–100°. The dark brown solution was slurried a few minutes with charcoal and filtered. The clear, almost colorless, filtrate was freed of solvent and dried over sodium hydroxide to 450 mg of a glass which retained the odor of hydrochloric acid.

A small sample of this was N-acetylated in phosphate buffer and subjected to paper electrophoresis: M_g 0.18, 0.29, and 0.55 (in decreasing order of intensity to AHP), corresponding to *N,N'*-diacetylneosamine C (M_g 0.20), *N*-acetylglucosamine (M_g 0.30), and *N,N'*-diacetylneosamine B (M_g 0.56), respectively.

The crude amine mixture was gradient eluted (0.5 to 2.0 *N* hydrochloric acid) from a 50-ml column of Dowex-50 (H^+ form) resin. Semiquantitative NIN colorimetry showed three peaks, which were collected, freed of solvent, and assayed separately.

Peak I yielded 168 mg of a glass, $[\alpha]^{28}D$ +52.0° (c 1.68, water), which was N-acetylated by the phosphate method and analyzed by paper chromatography and electrophoresis. This mixture was combined with an equal amount of corresponding material from a

second run and separated by cellulose powder chromatography with BAW 415. Two CLOR-positive fractions were obtained.

Solvent removal from the first fraction gave 146 mg (9%, based on **20**) of a glass, $[\alpha]^{28}D$ +29.5° (c 2, water), R_f of 0.52 in PEaAW, R_f 0.40 in BAW 415 (CLOR spray). Crystallization from ethanol–ether gave, after prolonged standing, 50 mg (3%) of colorless needles: mp 211–214° dec; $[\alpha]^{25}D$ +32° (c 1.06, water) [lit.[40] mp 209–215° dec; $[\alpha]D$ +36° (c 0.7, water)]. A mixture melting point with authentic 2,6-diacetamido-2,6-dideoxy-D-glucose (**9a**) showed no depression.

Solvent removal from the second fraction from peak I gave 121.5 mg of a glass: $[\alpha]^{28}D$ +18° (c 2, water), AHP-negative, R_f 0.44 in PEaAW (CLOR)[41] (7% from **20**, based on a diacetamidodideoxyhexitol structure).

Evaporation of peak III and extensive drying over sodium hydroxide at 0.2 mm left 38 mg (5%) of 2,6-diamino-2,6-dideoxy-L-idose dihydrochloride (**24**) as a glass, $[\alpha]^{28}D$ +23.9° (c 1.9, water) [lit.[24] $[\alpha]D$ +17.5° (c 0.9, water)]. Treatment with acetic anhydride and phosphate solution gave the *N*-acetyl derivative, which was purified by preparative paper chromatography in BAW 415 to give a glass; 20.6 mg, $[\alpha]^{25}D$ +7.0° (c 1.9, water) [lit.[25] $[\alpha]D$ +5° (c 1, water)]. Electrophoresis in borate solution of alternate spots of the synthetic material and *N,N'*-diacetylneosamine B showed no differentiation, M_g 0.42. Approximately 6 mg of the N-acetylated derivative was converted to its *p*-nitrophenylhydrazone with 6 mg of *p*-nitrophenylhydrazine in boiling methanol. Crystallization from methanol and absolute ethanol gave small yellow needles, mp 211–215° dec [lit. mp for *N,N'*-diacetylneosamine B *p*-nitrophenylhydrazone 215–218° dec[25]]. A mixture melting point with an authentic sample had mp 212–217° dec.

Pentaacetyl-2-bromo-2-deoxystreptamine (26). Anhydrous *myo*-inosadiamine-1,3 dihydrochloride (**25**, 882 mg, dried over phosphorus pentoxide *in vacuo* at 100°, obtained by hydrolysis of **12** in refluxing 6 *N* hydrochloric acid), acetyl bromide (1.2 ml), and acetic anhydride (2.6 ml) were heated in a sealed tube at 140° for 5 hr. The tube was cooled, then opened carefully and ethanol (6 ml) was added gradually with cooling in an ice bath. The mixture was allowed to stand in a refrigerator overnight, evaporated *in vacuo* to a glassy residue, then dried thoroughly in a vacuum desiccator. Acetic anhydride (15 ml) and pyridine (15 ml) were added, and the mixture stood at room temperature for 10 hr. Colorless crystals were filtered and washed with pyridine, and the filtrate and washing were combined and evaporated *in vacuo* to afford a white solid residue, which was recrystallized from ethanol to give pentaacetyl-2-bromo-2-deoxystreptamine (**26**) as colorless needles (660 mg, 42%), mp 257–258.5° dec (lit.[27] 256.5–258.5° dec). A second crop of crystals (270 mg, 17%), mp 255–256° dec, was obtained from the mother liquor. The mother liquor was finally diluted with methanol, treated with Amberlite IRA-400 (hydroxide phase), concentrated, and passed through an activated alumina column. Elution with chloroform yielded a third crop of crystals (240 mg, 15%), mp 245–252° dec. The second and third batches of crystals were combined and recrystallized from ethanol to give colorless needles (367 mg, 23%), mp 257–258.5° dec. The total yield of **21** was thus 1.027 g (65%). The ir spectra of the three crops of crystals were all superimposable on that of an authentic sample.[27]

Pentaacetyl-2-bromo-2-deoxystreptamine-1-^{14}C (26). Anhydrous *myo*-inosadiamine-1,3-1-^{14}C dihydrochloride (**25**-^{14}C, 290 mg, obtained by hydrolysis of labeled **12**) was heated in a sealed tube with acetyl bromide (0.41 ml) and acetic anhydride (0.88 ml) and worked up as described in the preceding section for the unlabeled compound. The first crop weighed 221 mg (42%), the second crop 139 (27%), and the third crop 64 mg (total yield 81%), mp 257–258.5° dec.

Pentaacetyl-2-deoxystreptamine (27). A slurry of pentaacetyl-2-bromo-2-deoxystreptamine (**26**, 440 mg) and acetic anhydride (15.4 ml) was stirred vigorously with pulverized zinc metal (7.8 g). Water (0.38 ml) was added after 1 and 2 hr, stirring was continued for 1 hr longer, and the remaining solids were filtered and washed thoroughly with acetic anhydride. The filtrate and washings were then combined and evaporated under reduced pressure to a crystalline residue which was recrystallized from ethanol to give fine crystals, 269.5 mg (74%), mp 322–323° (lit.[27] mp above 300°). The infrared spectrum was superimposable on that of an authentic sample.[27]

Pentaacetyl-2-deoxystreptamine-1-^{14}C (27). A slurry of labeled **26** (220 mg), acetic anhydride (7.7 ml), and pulverized zinc (3.9 g) was treated as for the unlabeled material in the preceding section. The recrystallized product weighed 149.9 mg (82%), mp 322–323°. The ir spectrum was superimposable on that of an authentic sample derived from neomycin B. Radioactivity of the sample was 53.2 μCi/mmol.

2-Deoxystreptamine Dihydrochloride (28). A mixture of pentaacetyl-2-deoxystreptamine (**27**, 129 mg) and 6 *N* hydrochloric acid (15 ml) was heated at reflux for 2 hr and then evaporated under reduced pressure to give a thick oil, which crystallized gradually during codistillation with ethanol. The crystals were digested with ethanol and collected by filtration; yield 77.9 mg (96%). The infrared spectrum was superimposable on that of an authentic sample.[27]

2-Deoxystreptamine-1-^{14}C Dihydrochloride (28). Labeled **27** (129 mg) was hydrolyzed with 6 *N* hydrochloric acid (15 ml) and worked up as in the preceding section; yield 79.4 mg (96%). Tlc (cellulose powder, BAW 221) showed a single spot. Radioactivity of the sample was 50.6 μCi/mmol.

Acknowledgment. This work was supported by Public Health Service Grant No. AI 01278 from the National Institute of Allergy and Infectious Diseases. We thank Professor T. Suami, Keio University, Yokohama, for providing authentic samples. We also thank Dr. F. C. Falkner, Dr. J. M. Malik, Dr. C. Mabuni, Mr. E. T. Iwamoto, and Mr. R. M. Stroshane, University of Illinois, and Mr. R. D. Birkenmeyer, The Upjohn Company, for assistance.

Registry No.—**1**, 6838-16-0; **2a**, 7115-40-4; **3a**, 49810-41-5; **3b**, 4239-72-9; **4a**, 49810-43-7; **5**, 7115-38-0; **6**, 49810-45-9; **7**, 49810-46-0; **8**, 49810-47-1; **9c**, 10536-74-0; **11**, 7380-63-4; **12**, 6255-71-6; **13**, 18376-9; **15**, 49810-52-8, **16**, 49810-53-9; **18**, 49810-54-0; **19**, 49810-55-1; **20**, 49810-56-2; **21**, 49810-57-3; **24**, 49810-58-4; **24** *N,N'*-diacetyl *p*-nitro-phenylhydrazone, 49810-59-5; **25**, 16656-63-6; **25** ^{14}C-labeled, 49810-61-9; **26**, 18783-89-6; **26** ^{14}C-labeled, 49775-26-0; *muco*-1,3-peracetylinosadiamine, 49810-62-0; *myo*-2,4-peracetylinosadiamine, 19046-76-5; *chiro*-1,3-peracetylinosadiamine, 16020-11-4; *chiro*-1,5-peracetylinosadiamine, 49810-65-3; 2-acetamido-2-deoxy-D-glucose, 7512-17-6.

References and Notes

(1) Paper XII in the series: M. Hichens and K. L. Rinehart, Jr., *J. Amer. Chem. Soc.*, **85**, 1547 (1963).
(2) Presented in part at the 156th National Meeting, American Chemical Society, Atlantic City, N. J., Sept 8–13, 1968; Abstract ORGN 024.
(3) National Science Foundation Predoctoral Fellow, 1959–1960, 1961–1963; Dow Chemical Co. Fellow, 1960–1961.
(4) Recent reviews: K. L. Rinehart, Jr., *J. Infect. Dis.*, **119**, 345 (1969); K. L. Rinehart, Jr., "The Neomycins and Related Antibiotics," Wiley, New York, N. Y., 1964.
(5) E. J. Hessler, H. K. Jahnke, K. Tsuji, J. H. Robertson, K. L. Rinehart, Jr., and W. T. Shier, *J. Antibiot.*, **23**, 464 (1970).
(6) Preliminary reports of portions of the biosynthetic studies have appeared: (a) K. L. Rinehart, Jr., M. Hichens, and A. D. Argoudelis, *Antimicrob. Ag. Chemother.*, 268 (1962); (b) K. L. Rinehart, Jr., M. Hichens, and J. L. Foght *Ind. Chim. Belge*, **27**, 552 (1962); (c) K. L. Rinehart, Jr., M. Hichens, J. L. Foght, and W. S. Chilton, *Antimicrob. Ag. Chemother.*, 193 (1963); (d) K. L. Rinehart, Jr., Symposium on the Chemistry of Microbial Products, Institute of Applied Microbiology Symposium No. 6, University of Tokyo, April 24–25, 1964; Abstracts, pp 48–71; (e) K. L. Rinehart, Jr., and R. F. Schimbor, in "Antibiotics," Vol. II, D. Gottlieb and P. D. Shaw, Ed., Springer-Verlag, Berlin, 1967, p 359.
(7) M. L. Wolfrom, S. M. Olin, and W. J. Polglase, *J. Amer. Chem. Soc.*, **72**, 1724 (1950).
(8) W. T. Shier, K. L. Rinehart, Jr., and D. Gottlieb, *Proc. Nat. Acad. Sci. U. S.*, **63**, 198 (1969).
(9) W. T. Shier, D. Gottlieb, and K. L. Rinehart, Jr., *J. Antibiot.*, **23**, 51 (1970).
(10) M. L. Wolfrom and K. Anno, *J. Amer. Chem. Soc.*, **75**, 1038 (1953).
(11) (a) M. L. Wolfrom and M. W. Winkley, *J. Org. Chem.*, **31**, 1169 (1966); (b) R. Schaffer and H. S. Isbell, *J. Amer. Chem. Soc.*, **79**, 3864 (1957).
(12) (a) V. K. Bhalla, U. R. Nayak, and S. Dev, *J. Chromatogr.*, **26**, 54 (1967); (b) N. Kurihara, T. Kurokawa, and M. Nakajima, *Agr. Biol. Chem.*, **31**, 1166 (1967).
(13) J. M. Grosheintz and H. O. L. Fischer, Abstracts, 108th National Meeting of the American Chemical Society, 1944, No. 9R; *J. Amer. Chem. Soc.*, **70**, 1476, 1749 (1948).
(14) S. Neidle, D. Rogers, and M. B. Hursthouse, *Tetrahedron Lett.*, 4725 (1968).
(15) F. W. Lichtenthaler and H. O. L. Fischer, *J. Amer. Chem. Soc.*, **83**, 2005 (1961).
(16) M. Nakajima, A. Hasegawa, and F. W. Lichtenthaler, *Justus Liebigs Ann. Chem.*, **669**, 75 (1963).
(17) F. W. Lichtenthaler, *Angew. Chem., Int. Ed. Engl.*, **3**, 211 (1964).
(18) T. Suami and S. Ogawa, *Bull. Chem. Soc. Jap.*, **38**, 758 (1965).
(19) (a) T. Suami, F. W. Lichtenthaler, and S. Ogawa, *Bull. Chem. Soc. Jap.*, **39**, 170 (1966); (b) *ibid.*, **40**, 1488 (1967).
(20) S. Ogawa, T. Abe, H. Sano, K. Kotera, and T. Suami, *Bull. Chem. Soc. Jap.*, **40**, 2405 (1967).

(21) T. Suami, S. Ogawa, S. Naito, and H. Sano, *J. Org. Chem.*, **33**, 2831 (1968).
(22) Crude **8** was purified over a silica gel column without cyclization.
(23) M. W. Whitehouse and P. W. Kent, *Tetrahedron*, **4**, 425 (1958).
(24) K. L. Rinehart, Jr., A. D. Argoudelis, W. A. Goss, A. Sohler, and C. P. Schaffner, *J. Amer. Chem. Soc.*, **82**, 3938 (1960).
(25) S. Horii, *J. Antibiot., Ser. A*, **14**, 249 (1961).
(26) T. Suami, S. Ogawa, and H. Sano, *Tetrahedron Lett.*, 2671 (1967).
(27) T. Suami, F. W. Lichtenthaler, S. Ogawa, Y. Nakashima, and H. Sano, *Bull. Chem. Soc. Jap.*, **41**, 1014 (1968).
(28) Nuclear magnetic resonance spectra were obtained on Varian Associates spectrometers, Models HA100 and A-60, by R. L. Thrift, D. H. Johnson, and their associates. Chemical shifts are expressed in ppm from tetramethylsilane (δ scale) throughout. Infrared absorption spectra were recorded on Perkin-Elmer spectrophotometers, Models 237 and 21B. Colorimetric and ultraviolet analyses were performed on a Beckman spectrophotometer, Model DB. High resolution mass spectral data were obtained on a Varian MAT 731 mass spectrometer by Mr. J. C. Cook, Jr. Melting points were determined on a Kofler micro hot stage or in a Hershberg apparatus and are uncorrected. Optical rotations were measured with Rudolf and Zeiss polarimeters. Microanalyses were performed by Mr. J. Nemeth and associates. Paper chromatography employed as spray reagents[29,30] ninhydrin (NIN), aniline hydrogen phthalate (AHP), Tollens silver nitrate (TOL) and Pan-Dutcher (CLOR) reagents and as solvent systems[3c,31] pyridine–ethyl acetate–acetic acid–water (5:5:1:3) (PEaAW); 1-butanol–pyridine–water (6:4:3) (BPW); 1-butanol–acetic acid–water (4:1:5) (BAW 415); *tert*-butyl alcohol–acetic acid–water (2:2:1) (BAW 221); 1-butanol–ethanol–water (4:1:5) (BEW); 2-propanol–ethyl acetate–water (7:1:2) (PrEaW). The values R_{NAG} and R_{Gn} are the ratios of the distance traveled by a component to the distance traveled by *N*-acetylglucosamine and glucosamine hydrochloride, respectively. Paper electrophoresis in 0.05 *M* borate buffer[32,33] employed an LKB electrophoresis apparatus, Model 3276 BN, with an LKB D-C power supply, Model 3290B, operated at an applied voltage of 200 V. Reasonable separations were obtained in 8–12 hr. 2,3,4,6-Tetra-*O*-methyl-D-glucose and D-glucose were used as reference substances; the value M_g is defined as the ratio of the distance between the sugar and tetramethylglucose to the distance between glucose and tetramethylglucose. Thin layer chromatography used plates, applicator, and template obtained from Brinkmann Instruments, Inc., and silicic acid obtained from E. Merck, A. G. Organic material was detected with iodine vapor. Small samples of amino sugars were N-acetylated, to provide paper chromatography and electrophoresis samples, by treating one part of a 5% solution of the sugar with ten parts of 3 *M* aqueous potassium hydrogen phosphate and five parts of acetic anhydride, then shaking until droplets of the anhydride were no longer visible.
(29) W. S. Chilton, Ph.D. Thesis, University of Illinois, 1963.
(30) V. F. German, Ph.D. Thesis, University of Illinois, 1963.
(31) R. Kuhn, W. Bister, and H. Fischer, *Justus Liebigs Ann. Chem.*, **617**, 109 (1958).
(32) A. B. Foster, *Advan. Carbohyd. Chem.*, **12**, 81 (1957).
(33) R. J. Block, E. L. Durrum, and G. Zweig, "Paper Chromatography and Paper Electrophoresis," 2nd ed, Academic Press, New York, N. Y., 1958.
(34) D. Horton, *Biochem. Prep.*, **11**, 1 (1966).
(35) M. L. Wolfrom and K. Anno, *J. Amer. Chem. Soc.*, **74**, 6150 (1952).
(36) E. Pacsu and E. J. Wilson, *J. Amer. Chem. Soc.*, **61**, 1450 (1939).
(37) W. H. McNeely, W. W. Binkley, and M. L. Wolfrom, *J. Amer. Chem. Soc.*, **67**, 527 (1945).
(38) R. L. Peck, C. E. Hoffhine, Jr., E. W. Peel, R. P. Graber, F. W. Holly, R. Mozingo, and K. Folkers, *J. Amer. Chem. Soc.*, 68, 776 (1946).
(39) A. D. Argoudelis, Ph.D. Thesis, University of Illinois, 1959.
(40) K. L. Rinehart, Jr., M. Hichens, K. Striegler, K. R. Rover, T. P. Culbertson, S. Tatsuoka, S. Horii, T. Yamaguchi, H. Hitomi, and A. Miyake, *J. Amer. Chem. Soc.*, **83**, 2964 (1961).
(41) 2,6-Diacetamido-2,6-dideoxy-D-glucitol has R_f 0.44, $[\alpha]^{25}D$ −7.0° (*c* 1.97, water). *N,N'*-Diacetylneosaminol B has R_f 0.41, $[\alpha]D$ −18 to −19° (*c* 2, water).
(42) T. Suami, S. Ogawa, Y. Nakashima, and H. Sano, *Bull. Chem. Soc. Jap.*, **40**, 2958 (1967).
(43) F. W. Lichtenthaler and P. Emig, *Carbohyd. Res.*, **7**, 121 (1968).

γ Condensation of an Allylic Phosphonium Ylide

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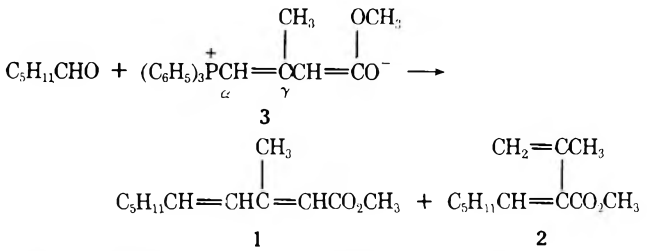
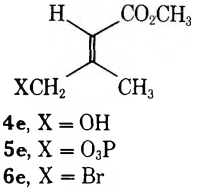
Received June 26, 1973

The Wittig reaction of (*E*)-3-methoxycarbonyl-2-methylallyltriphenylphosphonium bromide with *n*-hexanal furnished all four geometric isomers of methyl 3-methyl-2,4-decadienoate, the normal α-condensation product, and both geometric isomers of methyl 2-isopropenyl-2-octenoate, the unprecedented γ-condensation product. The α:γ product ratio varied from 1:9 to 9:1 in response to the tertiary amine base and the group IIB metal halide present. In contrast, the analogous trans phosphonate provided only the trans-2,trans-4 and the cis-2,trans-4 isomers of the α-condensation product in 6:1 ratio.

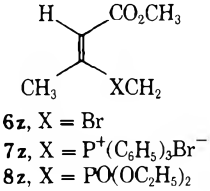
Aldehydes normally condense with allylic phosphonium ylides at the ylide α-carbon atom.[1-5] The Wittig reaction of *n*-hexanal with the stabilized allylic phosphonium ylide **3**, however, generates not only all four geometric isomers of methyl 3-methyl-2,4-decadienoate (**1**), the normal α-condensation product, but also both geometric isomers of methyl 2-isopropenyl-2-octenoate (**2**), the unprecedented γ-condensation product. Under the appropriate reaction conditions, either ester can be produced in >90% relative yield.



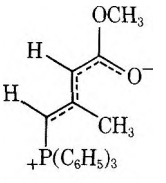
The crystalline trans phosphonium bromide[2,3] **7e** was obtained in 84% yield on heating equimolar quantities of methyl 4-bromo-3-methyl-2-butenoate (**6e:6z** = 86:14) and triphenylphosphine in acetonitrile. This salt slowly isomerized in dry dimethyl sulfoxide near 25°; the isomer ratio at equilibrium was **7e:7z** = 47:53. Treatment of the trans phosphonium salt **7e** with excess sodium hydroxide furnished the phosphonium ylide **3** as yellow crystals in 68% yield. A $CDCl_3$ solution of this ylide near 25° contained two isomeric species in 2:1 ratio. The major and minor species are assigned the structures **3z** and **3e**, respectively,



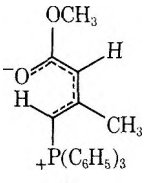
4e, X = OH
5e, X = O_3P
6e, X = Br
7e, X = $P^+(C_6H_5)_3Br^-$
8e, X = $PO(OC_2H_5)_2$



6z, X = Br
7z, X = $P^+(C_6H_5)_3Br^-$
8z, X = $PO(OC_2H_5)_2$

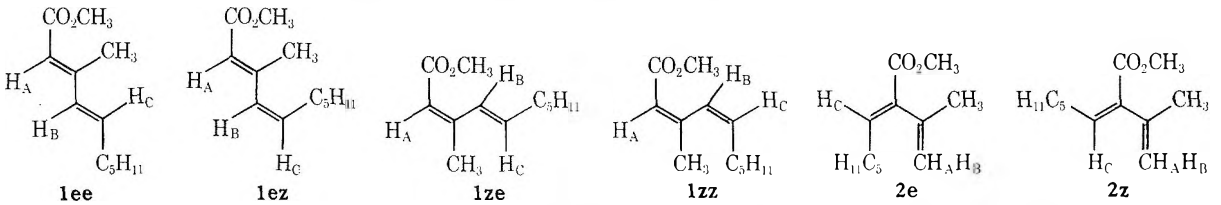


3e



3z

Table I
Infrared, Nmr, and Glc Data for Esters 1 and 2



1ee 1ez 1ze 1zz 2e 2z

Compd	Ir, λmax (CCl4), μ (intensity) νC=O	νC=C	ν-CH[a]	Nmr (CCl4), δ (ppm), multiplicity, and J (Hz) CCH3 (b s, 3 H)	OCH3 (s, 3 H)	HA (b s)	HB (1 H)	HC (1 H)	Glc[b]
1ee	5.81 (s)	6.10 (w), 6.19 (m)	10.36 (m)	2.25	3.65	5.63	6.08, s	6.08, m	100
1ez	5.79 (s)	6.11 (w), 6.24 (w)		2.23	3.66	5.63	5.85, d, 12	5.55, d, 12, t, 7	61
1ze	5.81 (s)	6.10 (m), 6.24 (m)	10.22 (m)	1.97	3.64	5.55	7.63, d, 15.5	6.05, d, 15.5, t, 7	91
1zz				1.80	3.71		7.40, m		65
2e	5.78 (s)	6.12 (w)	11.09 (m)	1.85	3.67	4.68	5.07, b s	6.69, t, 7.5	38
2z	5.76 (s)	6.15 (w)	11.26 (m)	1.87	3.73	4.80	4.92, b s	5.71, t, 7.5	42

[a] Ethylenic out-of-plane wagging mode. [b] Relative retention time on column A at 170°; the retention time of **1ee** was 28.1 min.

Table II
Formation of the Esters 1 and 2 from the Trans Phosphonium Salt 7e and *n*-Hexanal

Reactant, ratio[a] Amine	Halide	DMF[b]	Time,[c] hr	Yield, %	Relative glc yield, % 1ee	1ez	1ze	1zz	2e	2z	1:2
3[d]			0.5	65	12	7	17	6	47	10	42:57
DBN, 1.05		1.5	2.3	73[e]	11	16	12	4	40	12	43:52
DBN, 1.0	$ZnCl_2$, 1.0	2.0	48	72	29	9	5	4	37	16	47:53
DBN, 1.0	CdI_2, 1.0	2.0	50	76	23	15	11	13	27	11	62:38
DBN, 1.0	CdI_2, 2.0	2.0	45	68	35	20	16	21	4	2	92:6
DIEA, 1.0	CdI_2, 1.0	4.0	12	26	45	20	21	4	4	1	90:5
DBN, 1.0	$HgCl_2$, 1.0	2.0	50	74	4	10	5	5	53	20	24:73
DIEA, 1.05		1.0	170[f]	74	2	2	3	2	68	22	9:90
DIEA, 1.01		2.0	370[g]	75	3	2	2	1	69	23	8:92

[a] Millimoles per millimole of *n*-hexanal. [b] Milliliters of dry dimethylformamide per millimole of *n*-hexanal. [c] Clear yellow-orange solution of *n*-hexanal (1.00 mmol), **7e** (1.00 mmol), amine, and halide in DMF was stirred at 25°, except as noted. [d] Solution of the ylide **3** (1.12 mmol) and *n*-hexanal (1.00 mmol) in CH_2Cl_2 (12 ml). [e] Substitution of dry dimethyl sulfoxide for DMF gave a product mixture of identical composition in 57% yield. [f] The salt **7e** (1.10 mmol) remained undissolved in part for about 26 hr. [g] Reaction temperature was 0–5°; the mixture remained heterogeneous for several days.

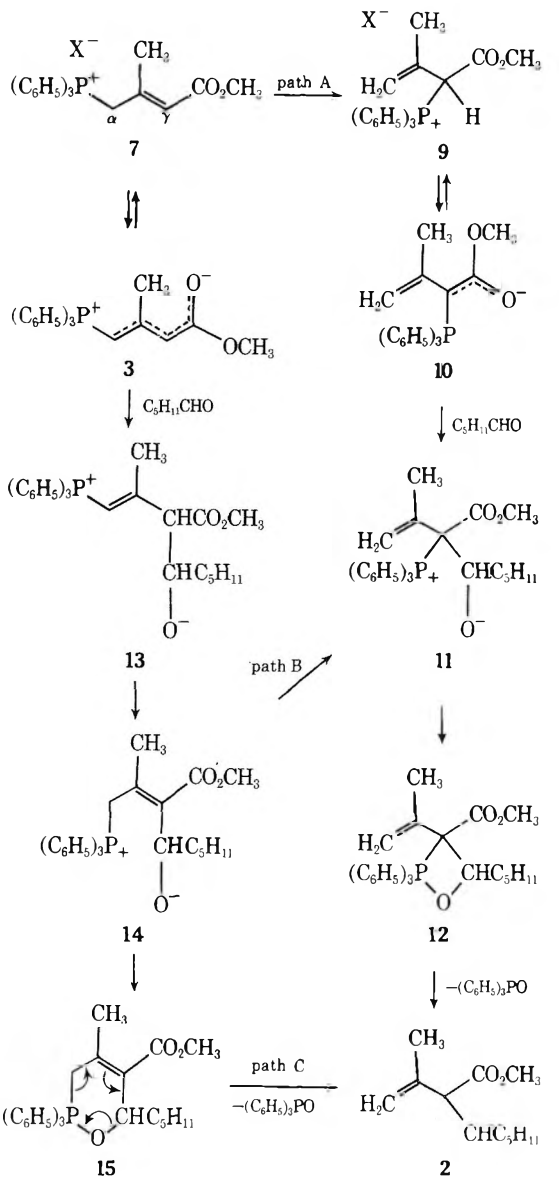
in analogy with the conformers observed by Howe[5] for the homologous *O*-ethyl phosphonium ylide.[6]

Reaction of *n*-hexanal with a dichloromethane solution of the phosphorane **3** for 30 min at 25° afforded in 65% yield a mixture of six isomeric esters. Preparative gas–liquid chromatography provided five fractions, four of which contained >93% of a single isomer by glc assay; the fifth fraction consisted of the esters **1ez** and **1zz** in the ratio 84:14. Each fraction was characterized by infrared and nmr spectroscopy; the distinguishing data are given in Table I.[7] Isomers of the linearly conjugated dienoate **1** exhibited two olefinic stretching vibrations; both isomers of the cross-conjugated dienoate **2** showed only one. The out-of-plane wagging deformation of the ethylenic hydrogens was observed near 10.3 μ for the vicinal trans-4 hydrogens of **1ee** and **1ze** and near 11.2 μ for the isopropenyl methylene groups of **2e** and **2z**. The methoxycarbonyl group deshielded proton H_B of the cis-2 isomers of **1**, the C(3)-methyl protons of the trans-2 isomers of **1**, and the H_C proton of **2e** and the trans-4 isomers of **1**.

The same six isomers were formed in essentially the same ratio both from the preformed ylide **3** and by generation of this ylide *in situ* by deprotonation of the trans phosphonium bromide **7e** with 1,5-diaza-5-bicyclo-[4.3.0]nonene (DBN) in dimethylformamide (DMF) (see Table II). The presence of zinc chloride caused little change in this product ratio. Cadmium iodide, however, favored formation of the α-condensation product; ester **1** constituted more than 90% of the product mixture when diisopropylethylamine (DIEA) was used with an equimolar amount of cadmium iodide or when DBN was employed with 2 equiv of the iodide. In contrast, the cross-conjugated ester **2** comprised 73% of the product mixture when DBN was used with an equimolar amount of mercuric chloride. Finally, when a DMF slurry of the crystalline, sparingly soluble trans phosphonium salt **7e** was treated with *n*-hexanal and the weaker base DIEA, the γ-condensation product **2** was formed in >90% relative yield at both 0 and 25°.

Substantial precedent[1] exists for formation of the α-condensation product **1** by electrophilic attack of *n*-hexanal at the α carbon of ylide **3** and fragmentation of the adduct *via* a cyclic four-center phosphorane. Formally, generation of the γ-condensation product **2** involves electrophilic attack of *n*-hexanal at the γ carbon and double-bond formation with loss of triphenylphosphine oxide. Three possible mechanisms for γ condensation are shown in Scheme I. Path A would involve allylic rearrangement of the triphenylphosphorus moiety before normal Wittig condensation. Thus isomerization of the allylic ylide **3** *via* the phosphonium salts **7** and **9** would give the ylide **10**, which would condense with the aldehyde through the cyclic four-center phosphorane **12**.[8] Path B would involve attachment of *n*-hexanal to the γ carbon of allylic ylide **3**,[9] tautomerization of the initial adduct **13**, allylic rearrangement of the triphenylphosphorus group of the adduct **14**, and elimination of triphenylphosphine oxide from the resulting betaine **11** as in path A. Finally, path C would

Scheme I



avoid the unprecedented allylic rearrangement of the triphenylphosphorus group required by path A or B. Thus the zwitterion **14** obtained by tautomerization of the initial γ adduct **13** would directly fragment to the observed γ-condensation product **2** and triphenylphosphine oxide *via* the cyclic six-center phosphorane **15.** The present data are explicable by competition of any of these pathways for γ condensation with the usual Wittig pathway for α condensation.

Aldehydes normally condense with stabilized phosphonate carbanions to form predominantly the trans olefin.[10,11] Pattenden and Weedon[12] reported that the allylic trans phosphonate **8e** condenses position specifically and stereospecifically with *trans*-geranial and benzaldehyde to form only the all-trans esters. In contrast, the allylic cis phosphonate **8z** was observed to condense position specifically but not stereospecifically with propanal, benzaldehyde, and *trans*-geranial; in each case the product ratio of the cis-2,trans-4 isomer to the trans-2,trans-4 isomer was 1:3.

The trans phosphonate[12] **8e** is formed in 96% yield by heating an equimolar mixture of the trans bromo ester **6e** and triethyl phosphite at 165–170° for 5 min. The stereochemical purity of the phosphonate is strictly dependent on that of the bromo ester, since neither compound is isomerized under the conditions of this Arbuzov reaction.[13] Free-radical bromination[14–19] of methyl 3-methylbutenoate with *N*-bromosuccinimide afforded a mixture of the starting ester, the trans bromo ester **6e,** the cis bromo ester **6z,** and methyl 4-bromo-3-bromomethyl-2-butenoate (**16**) in the ratio 12:42:37:11 by nmr assay. Fractional distillation of this mixture through a Teflon spinning band column provided the pure trans bromo ester in 17% yield. Alternatively, free-radical bromination of 3-methyl-2-butenoic acid afforded a similar mixture of bromo acids from which the trans bromo acid can be obtained either by crystallization[19] from hydrocarbon solvents or by selective lactonization[20] of the cis bromo acids with aqueous alkali; subsequent esterification furnishes the trans bromo ester **6e** in low overall yield. As both of these routes require the purification of lachrymatory allylic bromides that can cause pronounced dermatitis on contact with the skin, a third route to the trans bromo ester was developed that avoids the purification of allylic bromide intermediates.

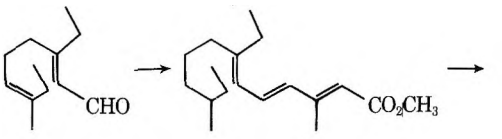
Table III
Formation of the Bromo Ester 6e from the Hydroxy Ester 4e *via* the Phosphite 5e

Time, hr (temp, °C)[a]	Product distribution,[b] mol % 4e	5e	6e
1.3 (0)	26	49	25
6.0 (0)	4	55	41
13.5 (0)	2	46	52
19 (0)	0	39	61
32 (0)	0	25	75
32 (0), 12 (20)	0	10	90

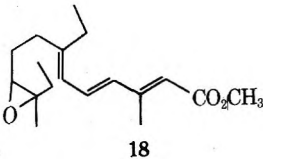
[a] Solution of **4e** (3.0 mmol), PBr_3 (1.1 mmol), and ether (30 ml) under argon. [b] By nmr assay.

The trans hydroxy ester **4e,** prepared in good yield by the method of Epstein and Sonntag,[21] was treated[22] with phosphorus tribromide in 1:1 ether–hexane for 6 hr at 25° to produce the pure trans bromo ester **6e** in 83% yield.[23] This reaction proceeds *via* the trans phosphite **5e,** which is formed in ether faster than it is converted to the bromide (Table III). The trans bromo ester prepared in this manner contained none of the cis isomer by nmr assay.

Treatment of the trans phosphonate **8e** with *n*-hexanal and lithium diisopropylamide for 6 hr below −50° provided isomers **lee** and **lze** in the ratio 86:14, respectively. The 4,5 double bond was formed stereospecifically, since neither of the cis-4 isomers was detected in the product mixture. The partial loss of the trans-2 stereochemistry is evidently due to the nature of the phosphonate carbanion, since the recovered phosphonate **5** was extensively isomerized (cis:trans 63:37). Under carefully selected conditions, however, loss of the trans-2 stereochemistry can be suppressed. Thus during the synthesis[24] of the dehydro analog **18** of the C_{18}-Cecropia juvenile hormone, Wittig reaction of the trans phosphonate **8e** with the appropriate aldehyde provided the trans-2,trans-4,trans-6,cis-10 isomer of the tetraene **17** in about 99% purity under carefully chosen reaction conditions.



17



18

Table IV
Nmr Data for Eight Compounds of the Type $XCH_2C(CH_3)=CHCO_2CH_3$

Compd	X	Chemical shift (ppm), multiplicity, and coupling constant (Hz): CCH_3 (3 H)	OCH_3 (3 H)	CH_2 (2 H)	=CH (1 H)	X
4e	OH	2.02, d, 1	3.67, s	4.05, d, 2	5.90, m	4.65, s, 1 H
5e	O_3P	2.13, b, s	3.69, s	4.54, b d, 9	5.90, m	
6e	Br	2.26, d, 1.5	3.69, s	3.95, s	5.89, b s	
7e	$P(C_6H_5)_3Br$	2.02, d, 3, d, 1	3.62, s	5.04, b d, 16	5.87, b d, 5	7.6–8.1, m, 15 H
8e	$PO(OC_2H_5)_2$	2.25, d, 3.4, d, 1.3	3.65, s	2.67, d, 23.5, d, 0.7	6.74, b d, 5.5	1.29, 6 H, t, 7.0; 4.06, 4 H, d, 8.5, q, 7.0
6z	Br	2.05, d, 1.5	3.69, s	4.54, s	5.70, b s	
7z	$P(C_6H_5)_3Br$	2.12, d, 3.5, d, 1	3.37, s	5.53, b d, 18	5.86, b d, 5	7.6–8.1, m, 15 H
8z	$PO(OC_2H_5)_2$	2.03, d, 3.6, d, 3	3.65, s	3.37, b d, 24.5	6.74, b d, 5.5	1.27, 6 H, t, 7.0; 4.03, 4 H, d, 8, q, 7.0

Experimental Section

Melting points and boiling points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 137 Infracord spectrophotometer. Nuclear magnetic resonance (nmr) spectra were measured with a Varian Associates A-60 spectrometer; chemical shifts are expressed in parts per million (ppm) downfield from internal tetramethylsilane (b = broad). The infrared and nmr spectra were observed in CCl_4 solution. Mass spectra were observed in these laboratories with an AEI-MS 9 spectrometer at 70 eV.

Analytical gas–liquid phase chromatography (glc) was performed with column A, a stainless-steel column (15 ft × 0.125 in.) containing 10% Carbowax 20M on Diatoport S (80–100 mesh), on a Hewlett-Packard (F & M) research gas chromatograph, Model 5750, using flame ionization detectors and prepurified nitrogen (30 ml/min) as the carrier gas. Product percentages were calculated from peak-area ratios without correction for detector response. Preparative glc was conducted with column B, a brass column (12 ft × 0.375 in.) containing 16% Carbowax 20M on Diatoport S (60–80 mesh), on a Wilkins Aerograph Model A-700 instrument using thermal conductivity detectors and helium (200 ml/min) as the carrier gas.

Diisopropylamine and hexamethylphosphoric triamide (HMPA) were dried by distillation from calcium hydride; tetrahydrofuran (THF) was freshly distilled from lithium aluminum hydride; and *n*-hexanal, bp 32–34° (1 Torr), was freshly distilled from sodium sulfate.

Methyl (*E*)-4-Bromo-3-methyl-2-butenoate (6e). A. Bromination of Methyl 3-Methyl-2-butenoate. *N*-Bromosuccinimide (46.0 g, 0.258 mol) was added to a solution of methyl 3-methyl-2-butenoate, bp 73.5° (88 Torr) (28.5 g, 0.250 mol), and azobis(isobutyronitrile) (0.41 g, 2.5 mmol) in CCl_4 (250 ml). The slurry was heated at reflux for 10 hr, cooled, and filtered to remove solid succinimide (25.43 g, 99% yield). The filtrate contained four esters by nmr assay, compound (rel mol %): the trans bromo ester **6e** (42), the cis bromo ester **6z** (37), the dibromo ester **16** (11), and the starting ester (10). It was freed of solvent and distilled through a 45-cm stainless-steel spinning-band column to provide the bromo ester **6** (*E*:*Z* = 23:77, 12.4 g, 26% yield), bp[25] 56 (2.2 Torr)–64° (3.5 Torr). As the isomers of **6** were not separated under these conditions, the undistilled material was filtered and distilled without column to give a colorless liquid (26.2 g, 51% yield), bp 40–70° (0.1 Torr), consisting of **6e**:**6z**:**16** (71:12:17).

This mixture was redistilled at reduced pressure through an annular 60-cm Teflon spinning-band column. The first fraction (0.2 g, 4% yield) was the cis bromo ester **6z**, pure by nmr assay: bp 83–89° (9 Torr); ir 5.79 (s, C=O), 6.07 (m, C=C), 6.94 (w, sh), 6.99 (m), 7.29 (m, CCH_3), 7.40 (m, CO_2CH_3), 7.88 (m, sh), 8.00 (s, CO), 8.22 (m), 8.41 (m), 8.62 (vs, CO), 9.60 (m), 10.07 (w), 10.82 (w), 11.25 (w, sh), and 11.58 μ (m); nmr, see Table IV; mass spectrum *m/e* 191.9875 (calcd for $C_6H_9BrO_2$, 191.9786).

After many intermediate fractions, several fractions afforded the trans bromo ester **6e** (8.0 g, 16.5% yield), pure by nmr assay, as a colorless liquid: bp 67–68° (0.45 Torr) [lit.[19] bp 82–83° (10 Torr)]; ir 5.78 (s, C=O), 6.08 (m, C=C), 6.99 (m), 7.26 (w, CCH_3), 7.39 (m, CO_2CH_3), 7.81 (w), 8.11 (s, CO), 8.27 (m), 8.62 (vs, CO), 8.81 (m), 9.66 (m), 10.78 (w), 11.31 (w), and 11.63 μ (w); nmr, see Table IV; mass spectrum *m/e* 191.9781 (calcd for $C_6H_9BrO_2$, 191.9786).

The residual red-black liquid (9.5 g) was mostly 4-hydroxy-3-methyl-2-butenoic acid lactone (**19**) and 4-hydroxy-3-bromomethyl-2-butenoic acid lactone (**20**) by ir and nmr characterization: ir 5.59 (s, C=O), 5.69 (vs, C=O), and 6.08 μ (w, C=C). They were evidently formed during distillation by thermal elimination of CH_3Br from the cis bromo ester **6z** and the dibromo ester **16**, respectively. Nmr data for **16** follow: 3.74 (s, 3, OCH_3), 4.16 (s, 2, trans CH_2), 4.74 (s, 2, cis CH_2), and 6.07 ppm (m, 1, CH=C). **19** nmr: 2.11 (b s, 3, CH_3), 4.69 (b s, 2, CH_2O), and 5.74 ppm (m, 1, CH=C) (lit.[21] 2.12, 4.73, and 5.78 ppm). **20** nmr: 4.34 (b s, 2, CH_2O), 5.90 (b s, 2, CH_2Br), and 6.07 ppm (m, 1, CH=C).

B. Bromination of Methyl (*E*)-4-Hydroxy-3-methyl-2-butenoate (4e). A solution of the trans hydroxy ester[21] **4e**, bp 77° (0.27 Torr), in hexane (100 ml) and ether (100 ml) was stirred under argon at −10° and was treated dropwise over 2 min with phosphorous tribromide (3.0 g, 1.11 mmol, 1.1 equiv). The solution was stirred in the dark for 6.0 hr at 25°, washed with aqueous sodium bicarbonate and brine, dried, and freed of solvent. The residual colorless liquid (4.90 g, 83% yield), the pure trans bromo ester **6e** by nmr assay,[26] was used without further purification.

(*E*)-3-Methoxycarbonyl-2-methylallyltriphenylphosphonium Bromide (7e). A solution of the bromo ester **6** (*E*:*Z* = 86:14; 3.01 g, 15.6 mmol) and triphenylphosphine (4.10 g, 15.6 mmol) in acetonitrile (50 ml) was heated at reflux for 20 min, cooled, and allowed to stand at 25° for 6 hr. A white, crystalline solid was obtained in two crops (3.44 and 1.72 g, 84% combined yield) that was the pure trans phosphonium bromide by nmr assay: mp 183–184° with prior sintering and decomposition to a red liquid (lit.[2] mp 160°, lit.[3] mp 179°); ir 5.82 (s, C=O), 6.09 (m, C=C), 6.20, 6.31, and 6.77 (all w), 6.98 (vs), 7.26 and 7.39 (w), 8.2 (s, broad), 8.70 (s), 9.02 (vs), 9.7 (w), 10.02 (m), 11.36 (w), and 14.75 μ (s, C_6H_5); nmr, see Table IV.

Dilution of the remaining solution with hexane precipitated a white solid, about 90% of which was the cis phosphonium bromide **7z** by nmr assay; for nmr, see Table IV.

An 0.22 *M* solution of trans phosphonium bromide **7e** in dry dimethyl sulfoxide was kept near 25°; the isomer ratio after 7 and 31 days was *E*:*Z* = 47:53 by nmr assay.

(3-Methoxycarbonyl-2-methylallylidene)triphenylphosphorane (3). A solution of the trans phosphonium bromide **7e** (0.495 g, 1.09 mmol) in acetonitrile (5 ml) was shaken with 40% aqueous sodium hydroxide (1.0 ml) for 5 min. The organic phase was washed with brine (1 ml) and freed of solvent. The residual viscous orange liquid (0.36 g) was crystallized from ethyl acetate to furnish yellow crystals (0.275 g, 68% yield) that sintered near 120° and melted near 135° to a deep red liquid. A solution of these crystals in $CDCl_3$ contained two isomers in 2:1 ratio by nmr spectroscopy: broadened methyl singlets at 1.67 (CCH_3, major), 2.50 (CCH_3, minor), 3.40 (OCH_3, minor), and 3.57 ppm (OCH_3, major), olefinic multiplets at 3.2–3.7 and 4.6–5.0 ppm, and an aromatic multiplet at 7.1–7.9 ppm.

Diethyl (*E*)-3-Methoxycarbonyl-2-methylallylphosphonate (8e). A mixture of the trans bromo ester **6e** (1.67 g, 8.65 mmol) and redistilled triethyl phosphite (1.45 g, 8.7 mmol) was heated at 165–170° for 5 min. The resulting material was vacuum distilled through a 5-cm Vigreux column to provide the trans phosphonate **8e** (2.09 g, 96%), pure by nmr assay,[27] as a colorless liquid: bp 112° (0.12 Torr), 117–119° (0.35 Torr) [lit.[28] bp 118–120° (0.55 Torr), lit.[29] bp 120–122° (0.6 Torr)]; ir 5.79 (s, C=O), 6.05 (m, C=C), 6.99 (m), 7.21 (m), 7.38 (m), 7.99 (s), 8.27 (s), 8.68 (s), 9.11 (m), 9.47 (s), 9.71 (vs), 10.35 (s), and 11.38 μ (m); nmr, see Table IV; mass spectrum *m/e* 250.0968 (calcd for $C_{10}H_{19}O_5P$, 250.0970).

Isomerization of the Phosphonate 8. A. With Lithium Diisopropylamide. A solution of diisopropylamine (1.081 g, 10.7 mmol) in dry tetrahydrofuran (12 ml) was cooled under argon to −75°, treated with 1.60 *M* *n*-butyllithium in pentane (Foote Mineral Co.; 6.25 ml, 10.0 mmol), and warmed to 0°. The phosphonate 8 (*E*:*Z* = 55:45; 2.47 g, 9.90 mmol) was added, which immediately colored the solution a deep blood-red. After 10 min at 0° part of this solution was added to 3 *M* aqueous ammonium chloride; extractive work-up furnished the isomers of phosphonate 8 in the ratio *E*:*Z* = 35:65 by nmr assay. After 13 hr at 0° or 15 hr at 0° and 10 hr at 30°, the isomer ratio was *E*:*Z* = 23:77.

B. With Heat. The phosphonate 8 (*E*:*Z* = 86:14) was sealed under argon in a glass tube and heated at 130° for 10 hr; the isomer ratio of the recovered phosphonate was *E*:*Z* = 77:23 by nmr assay.

Methyl 3-Methyl-2,4-decadienoate (1) and Methyl 2-Isopropenyl-2-octenoate (2). Solid trans phosphonium bromide **7e** (1.000 g, 2.20 mmol) and a solution of 1,5-diaza-5-bicyclo[4.3.0]nonene (0.25 ml, 2.1 mmol) in dry dimethylformamide (2.0 ml) was stirred under argon for 5 min at 25°. The resulting clear orange solution was treated with *n*-hexanal (0.24 ml, 2.0 mmol), stirred at 25° for 2.3 hr, diluted with 2:1 hexane–dichloromethane (30 ml), washed with 0.5 *M* aqueous hydrochloric acid, water, 0.5 *M* aqueous sodium bicarbonate, and brine (25 ml each), dried, and freed of solvent. The solid residue, which contained much triphenylphosphine oxide, was triturated with hexane (four 3-ml portions). The hexane triturate was filtered, freed of solvent, and retriturated with hexane (three 1-ml portions). The triturate was filtered and freed of solvent to furnish a clear yellow liquid (0.287 g, 73%) that was a mixture of the ester 1 (four isomers) and the ester 2 (two isomers) by nmr assay. By glc assay this mixture contained the six isomers in the ratio **1ee**:**1ez**:**1ze**:**1zz**:**2e**:**2z** = 11:16:12:4:40:12. The results of eight related experiments are given in Table II.

The product mixtures from several experiments were pooled and separated by preparative glc on column B at 150° into five fractions that were assayed by analytical glc on column A at 170°, isomer (rel %): **1ee** (96) and **1ze** (4); **1ez** (84) and **1zz** (14); **1ze** (94) and **1ee** (6); **2e** (93) and **2z** (7); **2z** (98) and **2e** (2). Diagnostic data from the infrared and nmr spectra of these fractions are given in Table I. The first four fractions gave mass spectral molecular ions at *m*/*e* 196.1452, 196.1450, 196.1443, and 196.1439, respectively (calcd for $C_{12}H_{20}O_2$, *m*/*e* 196.1463).

Methyl 2-Isopropenyl-2-octenoate (2). Solid trans phosphonium bromide **7e** (1,000 g, 2.20 mmol) and a solution of diisopropylethylamine (0.400 ml, 21.1 mmol) and *n*-hexanal (0.24 ml, 2.0 mmol) in dry dimethylformamide (2.0 ml) were stirred under argon at 25° for 170 hr. After 26 hr the initial slurry became a clear yellow solution. The reaction was worked up as described in the previous experiment to provide a clear light yellow liquid (0.288 g, 74% yield) that consisted of the trans isomer **2e**, the cis isomer **2z**, and isomers of the ester 1 in the ratio 68:22:9, respectively, by glc assay.

Methyl (*E*,*E*)- and (*Z*,*E*)-3-Methyl-2,4-decadienoate (1ee and 1ze). A solution of diisopropylamine (0.528 g, 5.24 mmol) in dry THF (5.0 ml) was stirred at −75° under argon and treated with 1.60 *M* *n*-butyllithium in pentane (3.1 ml, 4.95 mmol). The solution was warmed to −60°, diluted with dry HMPA (5.0 ml), and treated with a solution of *n*-hexanal (0.400 g, 4.00 mmol) and the trans phosphonate **8e** (1.10 g, 4.40 mmol) in THF (16 ml) and HMPA (5 ml) precooled to −70°. The reaction solution was stirred for 6.0 hr at −60 to −50° (9:1 acetonitrile–acetone slurry), poured into 0.5 *M* aqueous sodium bicarbonate (50 ml), and extracted with 1:1 hexane–ether. The extracts were washed with 0.5 *M* aqueous sodium bicarbonate and brine, dried, and freed of solvent.

The resulting clear yellow liquid (1.04 g) contained the phosphonate 8 and two isomers of the ester **1** (**1ee**:**1ze** = 9:1) by nmr assay. It was separated into two fractions by chromatography on a 2.0-mm layer of Merck silica gel using dichloromethane as eluent and uv visualization. The faster moving liquid (R_f 0.45–0.75, 0.128 g, 13% recovery) was the phosphonate 8 (*E*:*Z* = 37:63) by nmr assay. The slower moving liquid (R_f 0–0.45, 0.378 g, 48% yield) consisted of only two isomers of the ester 1 in the ratio **1ee**:**1ze** = 86:14 by glc assay.

Registry No.—**1ee**, 50428-75-6; **1ez**, 50428-76-7; **1ze**, 50428-77-8; **1zz**, 50428-78-9; **2e**, 50428-79-0; **2z**, 50428-80-3; **3e**, 50432-30-9; **3z**, 50432-31-0; **4e**, 13866-57-4; **5e**, 50428-82-5; **6e**, 19041-17-9; **6z**, 27652-13-7; **7e**, 50557-81-8; **7z**, 50557-82-9; **8e**, 19945-56-3; **8z**, 19945-48-3; 16, 50428-87-0.

References and Notes

(1) Reviews: (a) A. Maercker in "Organic Reactions," Vol. **14**, R. Adams, Ed., Wiley, New York, N. Y., 1965, p 270; (b) A. W. Johnson, "Ylid Chemistry," Academic Press, New York, N. Y., 1966.

(2) G. Wittig and H. Pommer, German Patent 950,552 (1956); *Chem. Abstr.*, **53**, 436 (1959). H. Pommer, G. Wittig, and W. Sarnecki, German Patent 1,026,745 (1958); *Chem. Abstr.*, **54**, 11074 (1960).

(3) J. B. Davis, L. M. Jackman, P. T. Siddons, and B. C. L. Weedon, *J. Chem. Soc. C*, 2154 (1966).

(4) H. Oediger, H. J. Kabbe, F. Moller, and K. Eiter, *Chem. Ber.*, **99**, 2012 (1966).

(5) R. K. Howe, *J. Amer. Chem. Soc.*, **93**, 3457 (1971).

(6) For the *O*-ethyl ylide, Howe[5] observed the *C*-methyl and *O*-methylene protons at 1.60 and 4.15 ppm, respectively, for the major cisoid-2 conformer and at 2.54 and **3**.93 ppm, respectively, for the minor transoid-2 conformer. For the homologous *O*-methyl ylide, we observed the *C*-methyl and O-methyl protons as broad singlets at 1.67 and 3.57 ppm, respectively, for the major conformer assigned the cisoid-2 structure **3z** and at 2.50 and 3.40 ppm, respectively, for the minor conformer assigned the transoid-2 structure **3e**.

(7) For a complete discussion of the structural assignments, see B. W. Erickson, Ph.D. Thesis, Harvard University, 1970, pp 151–159; *Diss. Abstr. Int., B*, **31**, 6500 (1971).

(8) The ylide **10** (OCH_3 = H), formed from the aldehydic analog of **9**, condenses with 4-nitrobenzaldehyde to form the cross-conjugated dienal related to **2** in 89% yield: M. J. Berenguer, J. Castells, R. M. Galard, and M. Moreno-Manas, *Tetrahedron Lett.*, 495 (1971).

(9) Three laboratories have recently observed bonding of an aldehyde or an α,β-unsaturated ketone to the γ carbon of an allylic phosphorane, but the initial adducts subsequently underwent other reactions than the condensation described here. See G. Büchi and H. Wüest, *Helv. Chim. Acta*, **54**, 1767 (1971); E. Vedejs, K. A. J. Snoble, and P. L. Fuchs, *J. Org. Chem.*, **38**, 1178 (1973); W. G. Dauben and J. Ipaktschi, *J. Amer. Chem. Soc.*, **95**, 5088 (1973).

(10) Reviews: (a) ref 1b, pp 203–212; (b) A. V. Dombrovskii and V. A. Dombrovskii, *Russ. Chem. Rev.*, **35**, 733 (1966).

(11) Formation of the cis olefin predominates when either reagent is sterically hindered: T. H. Kinstle and B. Y. Mandanas, *Chem. Commun.*, 1699 (1968).

(12) G. Pattenden and B. C. L. Weedon, *J. Chem. Soc. C*, 1984, 1997 (1968).

(13) After 10 hr at 130°, about 10% of the trans phosphonate **8e** was converted into the cis isomer.

(14) D. Ziegler, A. Spath, E. Schaaf, W. Schumann, and E. Winkelmann, *Justus Liebigs Ann. Chem.*, **551**, 80 (1942).

(15) K. Sisido, K. Kondo, H. Nozaki, M. Tuda, and Y. Udo, *J. Amer. Chem. Soc.*, **82**, 2286 (1960).

(16) M. U. S. Sultanbawa, P. Veeravagu, and T. Padmanathan, *J. Chem. Soc.*, 1262 (1960).

(17) I. K. Sarycheva, G. A. Shatenshtein, M. G. Pleshakov, and N. A. Preobrazhenskii, *J. Gen. Chem. USSR*, **30**, 2522 (1960).

(18) M. Halmos and T. Mohácsi, *J. Prakt. Chem.*, [4] **12**, 50 (196[illegible]).

(19) I. Ahmad, R. N. Gedye, and A. Nechvatal, *J. Chem. Soc. C*, 185 (1968).

(20) W. S. Johnson, T. Li, D. J. Faulkner, and S. F. Campbell, *J. Amer. Chem. Soc.*, **90**, 6225 (1968).

(21) W. W. Epstein and A. C. Sonntag, *J. Org. Chem.*, **32**, 3390 (1967).

(22) After a procedure by J. M. Osbond, *J. Chem. Soc.*, 5270 (1961).

(23) A glc-pure sample of the corresponding trans chloro ester has been prepared[19] in 35% yield by treatment of the trans hydroxy ester **4e** with neat thionyl chloride.

(24) E. J. Corey, J. A. Katzenellenbogen, S. A. Roman, and N. W. Gilman, *Tetrahedron Lett.*, 1821 (1971).

(25) Reported values: bp 74–78° (6 Torr),[16] 78–85° (8.0 Torr),[15] 80–88° (12 Torr),[19] 84–89° (12 Torr),[14] 92–94° (11 Torr).[17]

(26) The *C*-methyl region of the nmr spectrum was expanded to detect the doublet at δ 2.05 due to the cis bromo ester **6z**. Although as little as 1% of the cis isomer could have been detected, the cis doublet was absent.

(27) The presence of as little as 1% of the cis isomer would have been detected in the expanded *C*-methyl region of the nmr spectrum, but none was observed.

(28) W. S. Wadsworth, Jr., and W. D. Emmons, *J. Amer. Chem. Soc.*, **83**, 1733 (1961).

(29) L. Horner, H. Hoffmann, and H. G. Wippel, *Chem. Ber.*, **91**, 61 (1958).

Reaction of Tosylhydrazones with Phenyltrimethylammonium Perbromide. Synthesis of Tosylazoalkenes[1]

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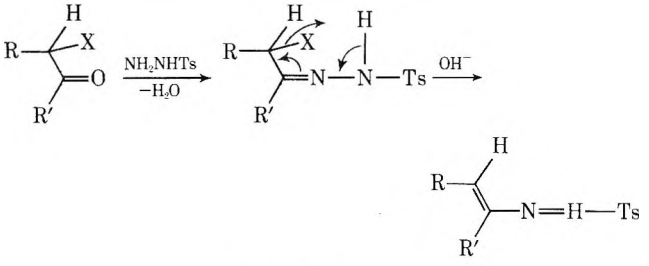
Received June 20, 1973

Tosylhydrazones 1-6 undergo oxidation to tosylazoalkenes in mild conditions using phenyltrimethylammonium perbromide followed by basic treatment effected *in situ*. A mechanistic pathway of the reaction is proposed. The procedure appears to be a convenient method for preparing tosylazoalkenes.

Tosylazoalkenes are a new class of unstable compounds that have been the subject of considerable study[2-10] and have been proposed as intermediates in a number of organic reactions.[11-16]

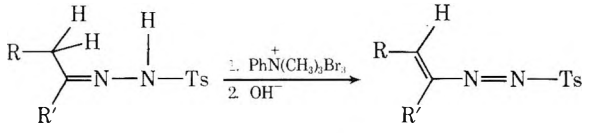
The preparation of tosylazoalkenes by treatment with alkali of tosylhydrazones of the corresponding ketones and aldehydes containing a leaving group on the α carbon is an established preparative reaction.[2,5-8,10]



X = Cl, Br, F, OAc, epoxy, OSO_2CH_3

However, using some α-halo carbonyl compounds, substitution and/or dehydrohalogenation has been observed as reported for α-halo ketones upon treatment with ammonia or primary or secondary amines.[17,18]

Herein we wish to report that aldehyde and ketone tosylhydrazones can be directly converted into tosylazoalkenes in fair to good yields in mild conditions using phenyltrimethylammonium perbromide (PTAB) followed by basic treatment effected *in situ*.



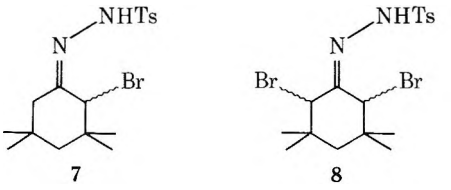
Some results given by our process are shown in Table I where the yields refer to analytically pure products obtained by crystallization from reactions in tetrahydrofuran.

Phenyltrimethylammonium perbromide (PTAB) is a mild and extremely efficient reagent for the α-bromination of ketones and cyclic ketals.[19-25]

However, all attempts to oxidize tosylhydrazones to tosylazoalkenes performed with molecular bromine, dioxane dibromide, and *N*-bromosuccinimide in a range of solvents failed.

Tosylhydrazones of nonenolizable ketones such as benzophenone did not react with PTAB. When 1,3-diphenylpropanone tosylhydrazone (**2**) was treated with 2 mol of PTAB, it was possible to isolate bromotosylazoalkene **2b** after basic treatment of the reaction mixture. Tosylazoalkene **6a** was prepared by reaction of 3,3,5,5-tetramethylcyclohexanone tosylhydrazone (**6**) with 1 mol of PTAB at −20°. At room temperature, **6** gave bromotosylazoalkene **6b** also using only 1 mol of PTAB; the yield of **6b** was increased when 2 mol of PTAB was used.

All attempts to isolate brominated intermediates from the reactions performed between tosylhydrazones **1-5** and PTBA were unsuccessful. However, when the reaction of **6** with 1 mol of PTAB was performed at −20°, the corresponding α-bromo ketone tosylhydrazone **7** was isolated in 55% yield. The reactions performed with 2 mol of PTAB at room temperature gave the α,α'-dibromo ketone tosylhydrazone **8** in 83% yield (see Experimental Section).

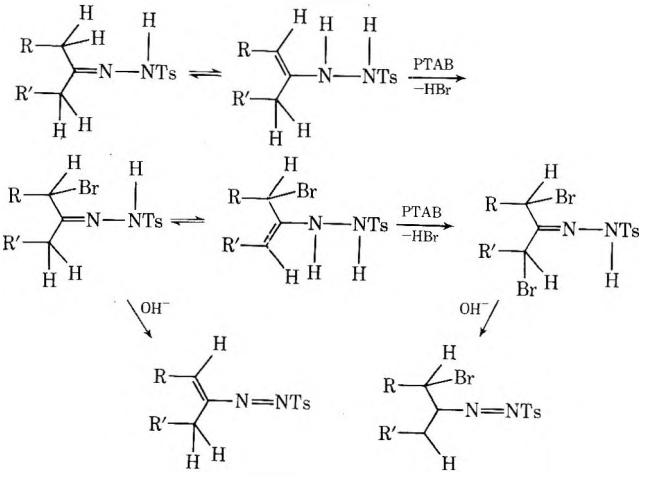


7 **8**

Compound **7** dissolved in tetrahydrofuran and added with another mole of PTAB gave dibromo derivative **8** in 87% yield. Compounds **7** and **8** underwent 1,4-dehydrobromination by treatment with an aqueous solution of sodium carbonate to afford tosylazoalkenes **6a** and **6b**.

The detailed mechanism of the oxidation of enolizable ketone and aldehyde tosylhydrazones with PTAB and basic treatment has not been established; however, in order to explain the above results and observations, the following reaction sequence is proposed for this new reaction of tosylhydrazones (Scheme I).

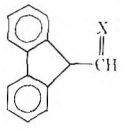
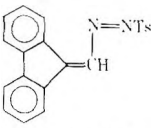
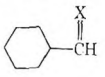
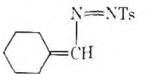
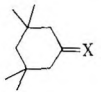
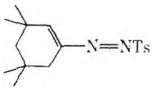
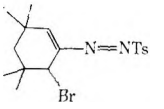
Scheme I



This reaction of tosylhydrazones with PTAB appears similar to the acid-catalyzed bromination of enolizable ketones.[26] The isomerization of tosylhydrazones to ene hydrazine tautomers can be considered the key step of the reaction and the formation of α,α'-dibromo derivatives can be rationalized assuming a further acid-catalyzed bromination on the other side of the keto imino group.[27]

The basic treatment performed after addition of 1 or 2 mol of PTAB to tosylhydrazone dissolved in tetrahydrofu-

Table I

No.	Tosylhydrazones (NNHTs)=X	No.	Tosylazoalkenes	PTAB, mol	Mp, °C, dec	Yield, %
1	$PhCH_2\overset{X}{\overset{\|\|}{C}}Ph$	1a	$PhCH{=}\overset{N=NTs}{\overset{\|}{C}}Ph$	1	84–85	65
2	$PhCH_2\overset{X}{\overset{\|\|}{C}}CH_2Ph$	2a	$PhCH{=}\overset{N=NTs}{\overset{\|}{C}}CH_2Ph$	1	84–85	60
		2b	$PhCH{=}\overset{N=NTs}{\overset{\|}{C}}CHBrPh$	2	90–92	72
3	$(Ph)_2CH\overset{X}{\overset{\|\|}{C}}H$	3a	$(Ph)_2C{=}\overset{N=NTs}{\overset{\|}{C}}H$	1	82	72
4		4a		1	138	75
5		5a		1	54–55	64
6		6a		1[a]	87	82
		6b		2	85–86	74

[a] Reaction performed at −20°.

ran induces a 1,4 elimination of hydrogen bromide to give tosylazoalkene or bromotosylazoalkene.

This new route to tosylazoalkenes is remarkable for its simplicity. Easily accessible starting materials such as tosylhydrazones and PTAB are used. The reactions are performed under mild conditions and generally are free from reaction by-products which might interfere with easy isolation of the tosylazoalkenes.

Experimental Section

All melting points are uncorrected. Spectra were recorded on Perkin-Elmer 257, Unicam SP-800, and Joel C 60 HL spectrometers. Nmr spectra were recorded using TMS as internal standard. Microanalyses were performed using the C, H, N, Analyzer Model 185 of the Hewlett-Packard Co. Deoxybenzoin, 1,3-diphenylpropanone, diphenylacetaldehyde, cyclohexanecarboxaldehyde, 3,3,5,5-tetramethylcyclohexanone, and tosylhydrazine are commercial materials. 9-Formylfluorene[28] and phenyltrimethylammonium perbromide (PTAB)[19,20] were prepared as previously reported. Analytical grade tetrahydrofuran was purified by the standard method.[29]

Preparation of Tosylhydrazones. General Procedure. The tosylhydrazones 1–6 were readily prepared in good yields from the carbonyl compounds by addition of equimolar quantities of tosylhydrazine in methanol or ethanol at temperatures not exceeding 50° (1–2 hr). The corresponding tosylhydrazone, which crystallized from the solution after cooling, was isolated by filtration, dried *in vacuo*, and used in the next step without further purification. An analytical sample was prepared by recrystallization from methanol or ethanol. These derivatives all showed ir absorption (KBr) at approximately 3200, 1600, 1360, 1170, and 820 cm^{-1}.

Deoxybenzoin Tosylhydrazone (1). Deoxybenzoin gave **1** in 87% yield, mp 141–142°.

Anal. Calcd for $C_{21}H_{20}N_2O_2S$: C, 69.21; H, 5.53; N, 7.69. Found: C, 69.30; H, 5.85; N, 7.31.

1,3-Diphenylpropanone Tosylhydrazone (2). 1,3-Diphenylpropanone gave **2** in 85% yield, mp 183–184°.

Anal. Calcd for $C_{22}H_{22}N_2O_2S$: C, 69.82; H, 5.86; N, 7.40. Found: C, 69.90; H, 5.85; N, 7.31.

Diphenylacetaldehyde Tosylhydrazone (3). Diphenylacetaldehyde gave **3** in 87% yield, mp 143–145°.

Anal. Calcd for $C_{21}H_{20}N_2O_2S$: C, 69.21; H, 5.53; N, 7.69. Found: C, 69.12; H, 5.46; N, 7.83.

9-Formylfluorene Tosylhydrazone (4). 9-Formylfluorene[28] gave **4** in 94% yield, mp 169–170°.

Anal. Calcd for $C_{21}H_{18}N_2O_2S$: C, 69.60; H, 4.85; N, 7.73. Found: C, 69.58; H, 4.81; N, 7.79.

Cyclohexanecarboxaldehyde Tosylhydrazone (5). Cyclohexanecarboxaldehyde gave **5** in 95% yield, mp 99–100°.

Anal. Calcd for $C_{14}H_{20}N_2O_2S$: C, 59.98; H, 7.19; N, 9.99. Found: C, 59.81; H, 7.05; N, 9.88.

3,3,5,5-Tetramethylcyclohexanone Tosylhydrazone (6). 3,3,5,5-Tetramethylcyclohexanone gave **6** in 87% yield, mp 160–162°.

Anal. Calcd for $C_{17}H_{26}N_2O_2S$: C, 63.33; H, 8.13; N, 8.69. Found: C, 63.39; H, 8.17; N, 8.56.

Preparation of Tosylazoalkenes. General Procedure. A solution containing 1.0×10^{-2} mol of tosylhydrazone in anhydrous tetrahydrofuran (100 ml) was stirred at room temperature under nitrogen and PTAB (1 or 2 equiv) was slowly added. The orange color of PTAB rapidly disappeared and phenyltrimethylammonium salt precipitated. After another 10 min, diethyl ether was added and the mixture was shaken with a saturated aqueous solution of sodium carbonate. A yellow color rapidly appeared. The layers were separated and the resulting ethereal solution was dried (Na_2SO_4) and concentrated under reduced pressure at a temperature not exceeding 40°. Generally the crystallization of tosylazoalkenes was accomplished by addition of *n*-hexane.

Tosylazostilbene (1a). Tosylhydrazone **1** (3.64 g, 1.0×10^{-2} mol) by reaction with PTAB (3.79 g, 1.0×10^{-2} mol) gave **1a** (2.3 g, 65% yield), mp 95° dec; spectroscopic data are in agreement with those recorded on a sample independently prepared.[8]

Anal. Calcd for $C_{21}H_{18}N_2O_2S$: C, 69.60; H, 5.0; N, 7.73. Found: C, 69.85; H, 4.95; N, 7.83.

2-Tosylazo-1,3-diphenylpropene (2a). Tosylhydrazone **2** (3.78 g, 1×10^{-2} mol) with PTAB (3.79 g, 1.0×10^{-2} mol) gave **2a** (2.25 g, 65% yield), mp 84–85° dec; spectroscopic data are in agreement with those recorded on a sample independently prepared.[8]

Anal. Calcd for $C_{22}H_{20}N_2O_2S$: C, 70.2; H, 5.36; N, 7.44. Found: C, 69.86; H, 5.05; N, 7.68.

3-Bromo-1,3-diphenyl-2-tosylazoprop-1-ene (2b). 1,3-Diphenylpropanone tosylhydrazone (**2**) (3.78 g, 1.0×10^{-2} mol) was dissolved in anhydrous tetrahydrofuran (100 ml) and stirred at room temperature. PTAB (7.58 g, 2×10^{-2} mol) was added during a

period of 30 min. After another 10 min, the mixture was treated as reported above and an orange product was isolated (3.30 g, 72% yield): mp 90–92° dec; uv max (C_6H_6) 363 mμ (ε 13,100); nmr ($CDCl_3$) δ 7.85–7.00 (m, 15 H, aromatic and 1 vinylic protons), 6.27 (s, 1 H, -CHBr), 2.47 (s, 3 H, p-$CH_3C_6H_4$).

Anal. Calcd for $C_{22}H_{19}BrN_2O_2S$: C, 58.02; H, 4.16; N, 6.29. Found: C, 58.18; H, 4.25; N, 6.21.

2,2-Diphenyl-1-tosylazoethylene (3a). Tosylhydrazone **3** (3.64 g, 1.0×10^{-1} mol) with PTAB (3.79 g, 1.0×10^{-2} mol) gave **3a** (2.60 g, 72% yield), mp 82° dec; spectroscopic data are in agreement with those recorded on a sample independently prepared.[9]

Anal. Calcd for $C_{21}H_{18}N_2O_2S$: C, 69.61; H, 4.97; N, 7.73. Found: C, 69.56; H, 5.05; N, 7.78.

9-Tosylazomethylenefluorene (4a). Tosylhydrazone **4** (3.62 g, 1.0×10^{-2} mol) with PTAB (3.79 g, 1.0×10^{-2} mol) gave **4a** (2.79 g, 75% yield): mp 138° dec; uv max ($CHCl_3$) 227 mμ (ε 22,100); nmr ($CDCl_3$) δ 7.9–7.1 (m, 13 H, aromatic and 1 vinylic protons), 2.5 (s, 3 H, p-$CH_3C_6H_4$).

Anal. Calcd for $C_{21}H_{16}N_2O_2S$: C, 69.99; H, 4.48; N, 7.77. Found: C, 69.73; H, 4.52; N, 7.81.

Tosylazomethylenecyclohexane (5a). Tosylhydrazone **5** (2.8 g, 1.0×10^{-2} mol) with PTAB (3.79 g, 1.0×10^{-2} mol) gave **5a** (1.8 g, 64% yield): mp 53–54° dec; uv max (*n*-hexane) 280 mμ (ε 15,000) and 420 (80); nmr ($CDCl_3$) δ 7.55 (*AA'BB'* pattern, 4 H, *J* = 8 Hz, p-C_6H_4), 3.5 (s, 1 H, vinylic proton), 2.45 (s, 3 H, p-$CH_3C_6H_4$), 2.00–1.00 (m, 10 H, other aliphatic protons).

Anal. Calcd for $C_{14}H_{18}N_2O_2S$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.36; H, 6.60; N, 10.12.

2-Bromo-3,3,5,5-tetramethylcyclohexanone Tosylhydrazone (7). 3,3,5,5-Tetramethylcyclohexanone tosylhydrazone (3.22 g, 1.0×10^{-2} mol) was dissolved in anhydrous tetrahydrofuran (100 ml) and stirred at −20°. PTAB (3.79 g, 1.0×10^{-2} mol) was added during a period of 15 min. After another 10 min, the precipitate was collected by filtration and the resulting solution was evaporated under reduced pressure at a temperature not exceeding 40°. The residue was dissolved with diethyl ether, and methanol was added until precipitation of a white product occurred. The crystals of **7** were collected and dried (2.20 g, 55% yield): mp 122–123° dec; nmr ($CDCl_3$) δ 8.18 (broad s, 1 H, -SO_2NH-), 7.50 (*AA'BB'* pattern, 4 H, *J* = 8 Hz, p-C_6H_4), 4.35 (s, 1 H, -CHBr), 2.40 (s, 3 H, p-$CH_3C_6H_4$), 2.42–2.17 (AB systems, q, 2 H, $|J_{AB}|$ = 14 Hz, C_6H_2, partially overlapped with singlet of $CH_3C_6H_4$), 1.72–1.12 (AB system, q, 2 H, $|J_{AB}|$ = 14 Hz, C_4H_2, partially overlapped with signals of methyl protons), 1.1–0.7 (m, 12 H, methyl protons).

Anal. Calcd for $C_{17}H_{24}N_2O_2S$: C, 63.16; H, 7.50; N, 8.75. Found: C, 50.98; H, 6.52; N, 6.99.

3,3,5,5-Tetramethyl-1-tosylazocyclohexene (6a). The ethereal solution of **7** (4.0 g, 1.0×10^{-2} mol) was shaken with a saturated aqueous solution of sodium carbonate and then washed several times with water, dried (Na_2SO_4), and filtered. The ether was evaporated and a yellow compound, **6a**, was obtained by addition of *n*-hexane (2.62 g, yield 82%): mp 87° dec; uv max (*n*-hexane) 275 mμ (ε 20,000); nmr (CCl_4) δ 7.40 (*AA'BB'* pattern, 4 H, *J* = 7.5 Hz, p-C_6H_4), 6.60 (s, 1 H, vinylic proton), 2.45 (s, 3 H, p-$CH_3C_6H_4$), 2.00 (s, 2 H, C_6H_2) 1.40 (s, 2 H, C_4H_2), 1.15 [s, 6 H, $C_3(CH_3)_2$], 1.00 [s, 6 H, $C_5(CH_3)_2$].

Anal. Calcd for $C_{17}H_{24}N_2O_2S$: C, 63.16; H, 7.50; N, 8.75. Found: C, 63.22; H, 7.38; N, 8.87.

6-Bromo-3,3,5-5-tetramethyltosylazocyclohex-1-ene (6b). Tosylhydrazone **6** (3.22 g, 1.0×10^{-2} mol) with PTAB (7.58 g, 2.0×10^{-2} mol) gave **6b** (2.86 g, 74% yield): mp 85–86° dec; uv max (*n*-hexane) 2.79 mμ (ε 17,300) and 420 (125); nmr (CCl_4) δ 7.5 (*AA'BB'* pattern, 4 H, *J* = 8 Hz, p-C_6H_4), 6.7 (s, 1 H, vinylic proton), 4.5 (m, 1 H, -CHBr), 2.5 (s, 3 H, p-$CH_3C_6H_4$), 1.98–1.32 (AB system, q, 2 H, $|J_{AB}|$ = 14 Hz: C_4H_2, partially overlapped with other aliphatic protons), 1.3–1.0 (m, 18 H, other aliphatic protons).

Anal. Calcd for $C_{17}H_{23}BrN_2O_2S$: C, 51.13; H, 5.77; N, 7.01. Found: C, 51.43; H, 5.82; N, 7.14.

The same reaction performed at room temperature using 1 equiv of PTAB gave a 30% yield of **6b**.

2,6-Dibromo-3,3,5,5-tetramethylcyclohexanone Tosylhydrazone (8). 3,3,5,5-Tetramethylcyclohexanone tosylhydrazone (3.22 g, 1.0×10^{-2} mol) was dissolved in anhydrous tetrahydrofuran (100 ml) and stirred at room temperature. PTAB (7.58 g, 2.0×10^{-2} mol) was added during a period of 15 min. After another 10 min, the precipitate was collected and the solution was evaporated under reduced pressure at a temperature not exceeding 40°. The residue was dissolved with diethyl ether and allowed to stand in a refrigerator until precipitation of a white product occurred. The crystals of **8** were collected and dried (4.08 g, yield 85%): mp 112–113° dec; nmr ($CDCl_3$) δ 7.50 (*AA'BB'* pattern, 4 H, *J* = 8 Hz, p-C_6H_4), 7.67 (broad a partially covered by *AA'BB'* pattern, 1 H, -SO_2NH-), 5.05 (s, 1 H, C_6 HBr), 4.7 (m, 1 H, C_2 HBr), 2.40 (s, 3 H, p-$CH_3C_6H_4$), 1.42 (AB system, q, 2 H, $|J_{AB}|$ = 15 Hz, C_4H_2), 1.3–0.2 (m, 12 H, other aliphatic protons).

Anal. Calcd for $C_{17}H_{24}Br_2N_2O_2S$: C, 42.50; H, 5.00; N, 5.84. Found: C, 42.63; H, 4.91; N, 5.91.

The same reaction performed on compound **6** using 1 mol of PTAB at room temperature gave a 35% yield of **8**.

Dehydrobromination of 8. The ethereal solution of **8** was shaken with a saturated aqueous solution of sodium carbonate, washed several times with water, dried (Na_2SO_4), and filtered, and after evaporation of the solvent, afforded compound **6b** (83% yield).

Acknowledgment. We wish to thank Professor Luciano Caglioti for his interest in this work.

Registry No.—**1**, 19816-85-4; **1a**, 29127-96-6; **2**, 19816-88-7; **2a**, 29127-97-7; **2b**, 42449-02-5; **3**, 42449-03-6; **3a**, 34220-14-9; **4**, 35432-46-3; **4a**, 42449-06-9; **5**, 34266-29-0; **5a**, 42449-08-1; **6**, 42449-09-2; **6a**, 42449-10-5; **6b**, 42449-11-6; **7**, 42449-12-7; **8**, 42407-03-4; PTAB, 4207-56-1.

References and Notes

(1) This work was done with financial support of the Italian National Research Council (C. N. R.).
(2) L. Caglioti, P. Grasselli, F. Morlacchi, and G. Rosini, *Chem. Ind. (London)*, 25 (1968).
(3) L. Caglioti, A. Dondoni, and G. Rosini, *Chim. Ind. (Milan)*, 122 (1968).
(4) A. Dondoni, G. Rosini, G. Mossa, and L. Caglioti, *J. Chem. Soc. B*, 1404 (1968).
(5) L. Caglioti and G. Rosini, *Chem. Ind. (London)*, 1098 (1969).
(6) W. Barbieri, L. Bernardi, P. Masi, L. Caglioti, and G. Rosini, *Tetrahedron Lett.*, 1347 (1970).
(7) W. Barbieri, L. Bernardi, P. Masi, A. Vigevani, L. Caglioti, and G. Rosini, *Tetrahedron*, **27**, 5505 (1971).
(8) G. Rosini and R. Ranza, *J. Org. Chem.*, **36**, 1915 (1971).
(9) G. Rosini and S. Cacchi, *J. Org. Chem.*, **37**, 1856 (1972).
(10) L. Caglioti, F. Gasparrini, G. Paolucci, G. Rosini, and P. Masi, *J. Org. Chem.*, **38**, 920 (1973).
(11) A. Eshenmoser, D. Felix, and G. Ohlaff, *Helv. Chim. Acta*, **50**, 7088 (1967).
(12) J. Schreiber, D. Felix, A. Eshenmoser, N. Winter, F. Gautshi, K. H. Schute-Elte, E. Sund, G. Ohloff, J. Kalvoda, H. Haufmann, P. Wieland, and G. Anner, *Helv. Chim. Acta*, **50**, 2101 (1967).
(13) M. Tanabe, D. F. Growe, R. L. Dehn, and C. Detre, *Tetrahedron Lett.*, 3739 (1967).
(14) M. Tanabe, D. F. Growe, and R. L. Dehn, *Tetrahedron Lett.*, 3943 (1967).
(15) P. Wieland, *Helv. Chim. Acta*, **53**, 171 (1970).
(16) A. M. Foster and W. C. Agosta, *J. Org. Chem.*, **37**, 61 (1972).
(17) B. Tchoubar, *Bull. Soc. Chim. Fr.*, 1363 (1955).
(18) N. H. Cromwell and P. H. Hess, *J. Amer. Chem. Soc.*, **83**, 1237 (1961).
(19) D. Vorlander and E. Sietert, *Chem. Ber.*, **52**, 283 (1919).
(20) W. S. Johnson, D. J. Boss, and K. L. Williamson, *Tetrahedron*, **19**, 861 (1963).
(21) A. Marquet and J. Jacques, *Tetrahedron Lett.*, 24 (1959).
(22) A. Marquet, M. Dovolaitsky, H. B. Kagan, L. Mamlok, C. Onannes, and J. Jacques, *Bull. Soc. Chim. Fr.*, 1822 (1961).
(23) A. Marquet and J. Jacques, *Bull. Soc. Chim. Fr.*, 90 (1962).
(24) C. Berger, M. Franck-Neuman, and G. Ourisson, *Tetrahedron Lett.*, 3451 (1968).
(25) M. Fetizon, M. Jurion and N. T. Anh, *Chem. Commun.*, 112 (1969).
(26) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, New York, N. Y., 1965, p 144.
(27) E. W. Garbisch, Jr., *J. Org. Chem.*, **30**, 2109 (1965); C. Rappe, *Acta Chem. Scand.*, **16**, 2467 (1962); C. Rappe and L. Schotte, *ibid.*, **16**, 2060 (1962); D. Lloyd, D. R. Marshall, and M. Ranoal, *Chem. Ind. (London)*, 1132 (1960); G. Hesse and F. Urbank, *Chem. Ber.*, **91** 2733 (1958); E. J. Corey, *J. Amer. Chem. Soc.*, **75**, 3297 (1953).
(28) F. D. Miller and E. C. Wagner, *J. Org. Chem.*, 16, 279 (1951).
(29) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Vol. 1, Wiley, New York, N. Y. 1967, p 1140.

Bridged Polycyclic Compounds. LXXVIII. Reaction of Chromyl Chloride with Cyclopropanes[1]

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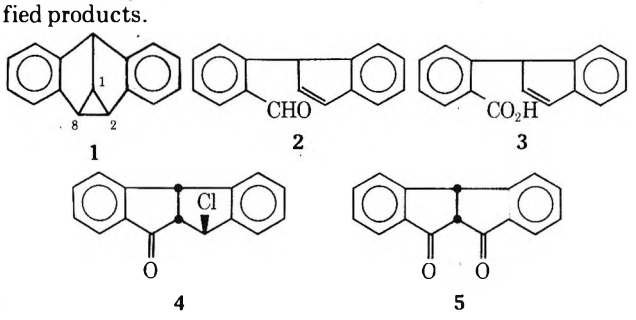
Received August 2, 1973

Treatment of 3,6-dibenzotricyclo[3.3.0.0^{2,8}]octadiene (**1**) with chromyl chloride involves reaction of the cyclopropane ring in the hydrocarbon. The nature of the products depends upon the ratio of reactants and upon the solvent. With limited amounts of chromyl chloride, in carbon tetrachloride, 2-(3-indenyl)benzaldehyde (**2**) is the principal product, while, in acetone, 8-chloro-3,6-dibenzo-2-bicyclo[3.3.0]octadienone (**4**) is the principal product. With excess chromyl chloride, in carbon tetrachloride, **2** is not isolated, but **4** and 3,6-dibenzo-2,8-bicyclo[3.3.0]octadienedione (**5**) are formed in modest amounts; in acetone these are major products. The unconjugated cyclopropane 6,8-dibenzotricyclo[3.2.2.0^{2,4}]nonadiene (**11**) is substantially less reactive toward chromyl chloride than is **1**; reaction under forcing conditions leads to 9,10-anthraquinone. These results are discussed briefly.

Our interest in the stereochemistry and mechanisms of electrophilic additions to cyclopropanes[2] led us to consider whether chromyl chloride might add to cyclopropanes, a reaction which, to the best of our knowledge, has not been reported. This reagent, which is best known for the oxidation of methylarenes to arenecarboxaldehydes,[3] also reacts readily with olefins. Although reactions with terpenes had been studied by Étard[4] and by Henderson[5] with confusing results (mixtures of ketones, aldehydes, and chlorinated compounds, generally of unidentified structures, were observed), it was not until study was carried out[6] with simpler olefins that the reaction course began to become clear. Additions of chromyl chloride in carbon tetrachloride led to α-chlorohydrins of such regioselectivity that it can be assumed that chromyl chloride donates an electrophilic oxygen species and a nucleophilic chloride ion; *i.e.*, the product has the opposite orientation of that of hypochlorous acid addition. Subsequent studies by several groups,[7,8] most notably that of Freeman, have expanded our original findings[6] and have brought this complex system to a new stage of understanding and utility. Thus it is now clear[9] that carbonyl compounds result from hydride or alkide migrations from carbenium-ion intermediates.

3,6-Dibenzotricyclo[3.3.0.0^{2,8}]octadiene (**1**) has been a useful cyclopropane for our studies[2a] of electrophilic additions, as, in simple additions, the stereochemistry of both electrophilic and nucleophilic attack can be observed, with all additions proceeding with C-2–C-8 bond cleavage. When **1** was treated with chromyl chloride (mole/mole) in carbon tetrachloride at 0°, the reaction occurred as rapidly as the chromyl chloride was added. After 20 min, the reaction was quenched (aqueous sodium bisulfite or zinc). The product mixture was examined by nmr spectroscopy and by isolation. The principal product was shown to be 2-(3′-indenyl)benzaldehyde (**2**), characterized by spectral properties and by oxidation to **3**, accompanied by unreacted **1** and by trace amounts of *anti*-8-chloro-3,6-dibenzo-2-bicyclo[3.3.0]octadienone (**4**), as well as of other unidentified products.

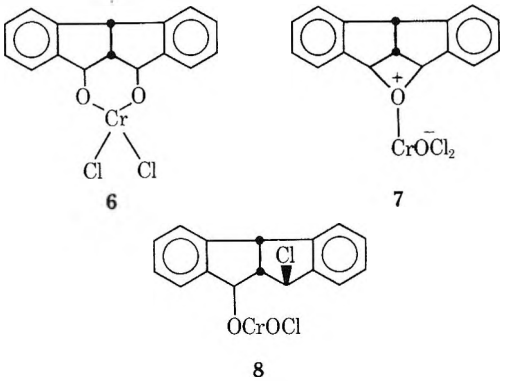


1 **2** **3** **4** **5**

Recently, the reaction of olefins with an excess of chromyl chloride in acetone was reported to give excellent yields of α-chloro ketones.[10] Using this procedure, we obtained three products from **1**; the chloro ketone **4** and the diketone **5** were formed in about 30% yield each, with perhaps 5% of **2** indicated by pmr analysis of the product mixture.

The results described above demonstrate that the cyclopropane ring in **1** is sensitive to attack by chromyl chloride. While the formation of **4** demonstrates that at least that portion of attack by nucleophile which gives **4** proceeds with inversion, the formation of **2** or of **4** gives no information regarding the stereochemistry of electrophilic attack. For this reason we decided to try the Sharpless procedure, but without an excess of chromyl chloride, in the hope that chlorohydrins could be obtained. However, when 2.0 mmol of **1** was treated with 0.70 mmol of chromyl chloride in acetone–carbon tetrachloride, no chlorohydrin was obtained, a substantial amount of **1** was recovered, and no diketone **5** was formed. The principal product was the chloro ketone **4**.

While the facts available do not permit detailed mechanistic considerations, it seems possible to assume that addition of chromyl chloride to **1** gives a 1:1 addition product similar to that with olefins,[11] *e.g.*, **6** or **7**, or perhaps the equivalent ion pairs, *i.e.*, species with one or more chloride ions separated. The formation of chloro ketone **4** seems attributable to ring opening of **6** or **7** (or their equivalents) by chloride ion, giving **8**, which by further oxidation–reduction is transformed to **4**. The benzylic carbon atom in **4** is then oxidized by excess Cr(VI) in acetone to **5**. These processes would appear to be the principal modes of reaction in acetone.

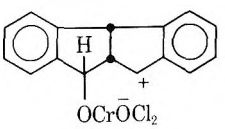


6 **7**

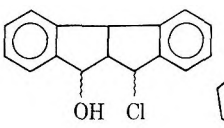
8

In carbon tetrachloride, however, **6** or **7** must be transformed to **9**, which by bond migration and cleavage of the oxygen–chromium bond becomes the aldehyde **2**. When

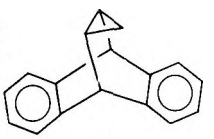
excess chromyl chloride is present, **2** is not found (presumably it is further oxidized by excess reagent), and a mixture of at least nine compounds results. We have not attempted the identification of these substances, except for **4** and **5**.



9



10



11

The nature of the products identified in these reactions, and, in particular, the absence of chlorohydrin species **10**, do not permit us to learn anything about the stereochemistry of electrophilic attack,[12] so that our experiments only demonstrate that cyclopropane rings may react with chromyl chloride. **1** is a very reactive cyclopropane, being activated by two benzene rings, and we therefore decided to look at the unconjugated cyclopropane 6,8-dibenzotricyclo[3.2.2.0^{2,4}]nonadiene (**11**). It was completely inert to chromyl chloride in 5.5 hr at 0°, and, when treated at room temperature for 5 days, 61% of **11** was recovered and the only reaction product which was found was 9,10-anthraquinone (60% based upon **11** consumed). Clearly in this case the primary reaction products are oxidized more rapidly than is the cyclopropane ring.

Experimental Section

Reaction of 1 with Chromyl Chloride in Carbon Tetrachloride. A solution of 520 mg (2.5 mmol) of **1**[13] in 25 ml of carbon tetrachloride was cooled to 0°. Then 450 mg (2.4 mmol) of chromyl chloride (CrO_2Cl_2) in 3 ml of carbon tetrachloride was added dropwise with stirring and cooling. The solution was stirred at 0° for 20 min, and 40 ml of a 2.3% aqueous solution of sodium bisulfite was added followed by additional stirring for 1 hr at 0°. The solution was diluted with carbon tetrachloride, washed two times with saturated aqueous sodium chloride, and dried over magnesium sulfate and the solvent was removed *in vacuo*. Column chromatography on silica gel eluted with 25% benzene–petroleum ether (bp 60–70°) yielded 210 mg (38%) of 2-(3′-indenyl)benzaldehyde (**2**): pmr ($CDCl_3$) δ 5.86 (1 H, t, H-3), 6.62 (1 H, d, d, H-2), 6.92 (1 H, d, d, H-1), 7.1–8.0 (8 H, m, aromatics), 10.22 (1 H, s, aldehyde H), $J_{2,3}$ = 2, $J_{1,3}$ = 2, $J_{1,2}$ = 5.5 Hz; mol wt (mass spectrum) 220 (calcd, 220).

A second sample of 210 mg of **1** in carbon tetrachloride was treated as above. However, 0.10 g of zinc was added rather than sodium bisulfite to reduce any remaining oxidizing agent. The mixture was stirred for 5 min, then 40 ml of ice water was added and stirring was continued for 20 min. The rest of the work-up was identical with that described above. Pmr analysis of the crude reaction mixture showed essentially the same product composition as above. In some experiments trace amounts of the chloro ketone **4** (see below) were noted.

Reaction of 1 with Excess Chromyl Chloride in Carbon Tetrachloride. A solution of 255 mg (1.25 mmol) of **1** in 12.5 ml of carbon tetrachloride was cooled to 0°. Then 404 mg (2.6 mmol) of chromyl chloride in 8 ml of carbon tetrachloride was added dropwise with stirring and cooling. The solution was stirred at 0° for 20 min, and 250 mg of zinc powder was added. The mixture was stirred for 15 min, then 25 ml of ice water was added and stirring was continued for 30 min. The mixture was red-orange at this point and enough 2.3% aqueous sodium bisulfite was added with stirring to complete the reduction of any remaining oxidizing agent. The mixture was filtered through Celite to break up the thick emulsion and transferred to a separatory funnel. The yellow organic layer was quickly washed with dilute aqueous sodium bisulfite followed by saturated aqueous sodium chloride and dried over anhydrous sodium sulfate. Removal of the solvent *in vacuo* afforded a pink oily residue.

The residue was taken up in a small volume of carbon tetrachloride and precipitated with hexane to give 67 mg (23%) of 3,6-dibenzo-2,8-bicyclo[3.3.0]octadienedione (**5**), mp 256–258° dec (lit.[2a] mp 257–259°).

The mother liquors were concentrated and examined by tlc, which revealed eight additional products, one of which was identified as *exo*-8-chloro-3,6-dibenzo-2-bicyclo[3.3.0]octadienone (**4**) by its R_f value compared with that of an authentic sample.

The complex product mixture was examined further by pmr spectrometry, which confirmed the presence of **4** as the principal component of the mother liquor mixture (see below). **2** was not observed in the mixture, and the remaining products were not identified.

Oxidation of 2 with Jones Reagent. Treatment of **2** with Jones reagent[14] in acetone at 0° gave 2-(3′-indenyl)benzoic acid (**3**), mp 141–142° after several recrystallizations from aqueous ethanol.

Anal. Calcd for $C_{16}H_{12}O_2$: C, 81.33; H, 5.12, mol wt, 236. Found: C, 81.21; H, 5.11, mol wt, 236 (mass spectrum).

Reaction of 3,6-Dibenzotricyclo[3.3.0.0^{2,8}]octadiene (1) with Chromyl Chloride in Acetone.[10] A solution of 203 mg (0.9 mmol) of **1** in 15 ml of acetone (distilled from $KMnO_4$) was cooled to −75°. Then 349 mg (2.25 mmol) of chromyl chloride in 3 ml of carbon tetrachloride was added dropwise with cooling and stirring. The solution was stirred at −75° for 90 min and then allowed to come to room temperature for 2 hr. The mixture was poured into an ice-cold solution of 360 mg (3.6 mmol) of sodium bisulfite in 11 ml of water and stirred for 30 min. The mixture was extracted two times with petroleum ether–ethyl acetate (50:50 v/v), washed with water and saturated aqueous sodium chloride, and dried over sodium sulfate. The solvent was removed *in vacuo* to give a solid residue. The residue was taken up in a minimal amount of hot benzene and treated with petroleum ether to give 68 mg (32%) of 3,6-dibenzo-2,8-bicyclo[3.3.0]octadienedione (**5**), mp 255–257°, mol wt, 234 (mass spectrum).

The mother liquors afforded 64 mg (28%) of *exo*-8-chloro-3,6-dibenzo-2-bicyclo[3.3.0]octadienone (**4**): mp 120–121° (lit.[15] mp 120–121.5°) after recrystallization from petroleum ether (bp 30–65°); pmr ($CDCl_3$) δ 3.82 (1 H, d, d, H-1), 5.15 (1 H, d, H-5), 5.8 (1, H, d, H-8), 7.2–8.0 (8 H, m, aromatics), $J_{1,5}$ = 6.5, $J_{1,8}$ = 1.3 Hz.

Reaction of 6,8-Dibenzotricyclo[3.2.2.0^{2,4}]nonadiene (11) with Chromyl Chloride in Carbon Tetrachloride. A solution of 273 mg (1.25 mmol) of **11**[16] in 15 ml of carbon tetrachloride was treated with 194 mg (1.25 mmol) of chromyl chloride in carbon tetrachloride at room temperature. The solution was stirred at room temperature for 5 days, poured into 20 ml of 2.3% aqueous sodium bisulfite, and stirred for 1 hr. The aqueous layer was extracted with carbon tetrachloride, the organic phases were combined, dried over magnesium sulfate, and filtered, and solvent was removed *in vacuo*. The residue obtained was placed on preparative-scale tlc plates (E. Merck, silica gel G, 20 × 20 × 0.5 cm) and eluted with benzene–methanol (98:2). Two bands were observed with uv light; the more mobile band afforded 168 mg (61%) of recovered **11**, while the other band gave 60 mg of 9,10-anthraquinone, mp 283° (lit.[17] mp 286°), mol wt (mass spectrum) 208 (calcd, 208).

Acknowledgment. The authors are indebted to the National Science Foundation for generous support of this work.

Registry No.—**1**, 2199-28-2; **2**, 50546-25-3; **3**, 50415-38-8; **4**, 50415-39-9; **5**, 29746-51-8; **11**, 30122-20-4; 9,10-anthraquinone, 84-65-1; CrO_2Cl_2, 7791-14-2.

References and Notes

(1) Paper LXXVII: S. J. Cristol and J. I. Maxwell, *J. Org. Chem.*, **39**, 228 (1974).
(2) (a) S. J. Cristol, W. Y. Lim, and A. R. Dahl, *J. Amer. Chem. Soc.*, **92**, 4013 (1970); (b) S. J. Cristol, J. K. Harrington, T. C. Morrill, and B. E. Greenwald, *J. Org. Chem.*, **36**, 2773 (1971).
(3) A. Etard, *Ann. Chim. Phys.*, [5], **22**, 218 (1881).
(4) A. Etard, *C. R. Acad. Sci.*, **116**, 434 (1893).
(5) G. G. Henderson and R. W. Smith, *J. Chem. Soc.*, **55**, 45 (1893); G. G. Henderson and T. Gray, *ibid.*, **83**, 1299 (1903); G. G. Henderson and I. M. Heilbron, *ibid.*, **93**, 288 (1908); **99**, 1887 (1911); G. G. Henderson, J. M. Robertson, and D. C. Brown, *ibid.*, **121**, 2717 (1922); G. G. Henderson and D. Chisholm, *ibid.*, **125**, 107 (1924).
(6) S. J. Cristol and K. R. Eilar, *J. Amer. Chem. Soc.*, **72**, 4353 (1950).
(7) R. H. Stairs, D. G. M. Diaper, and A. L. Gatze, *Can. J. Chem.*, **41**, 1059 (1963).
(8) F. Freeman and K. W. Arledge, *J. Org. Chem.*, **37**, 2656 (1972), and references cited therein.
(9) F. Freeman, P. J. Cameron, and R. H. Dubois, *J. Org. Chem.*, **33**, 3970 (1968).
(10) K. B. Sharpless and A. Y. Taranishi, *J. Org. Chem.*, **38**, 185 (1973).
(11) F. Freeman, P. D. McCart, and N. J. Yamachika, *J. Amer. Chem. Soc.*, **92**, 4621 (1970).
(12) The assumption that **6** or **7** is the intermediate obviously assumes

attack with retention. On the other hand, 9 or its epimer could be the first intermediate, leading on the one hand to 2 and on the other to 4.
(13) E. Ciganek, *J. Amer. Chem. Soc.*, **88**, 2883 (1966).
(14) R. G. Curtis, I. Heilbron, E. R. H. Jones, and G. F. Woods, *J. Chem. Soc.*, 457 (1953).
(15) G. C. Schloemer, Ph.D. Thesis, University of Colorado, 1972.
(16) A. L. Noreen, Ph.D. Thesis, University of Colorado, 1970.
(17) "Handbook of Chemistry and Physics," 40th ed, Chemical Rubber Publishing Co., Cleveland, Ohio, 1958, p 811.

Fluorinated Bicyclics. IV.[1] Ionic and Free-Radical Bromination of 5-(Difluoromethylene)-6,6-difluoro-2-norbornene

B. E. Smart

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Received October 31, 1973

Ionic bromination of 5-(difluoromethylene)-6,6-difluoro-2-norbornene (1) in methylene dichloride at 25° gave 1-(bromodifluoromethyl)-3-bromo-7,7-difluorotricyclo[2.2.1.$0^{2,6}$]heptane (2) and 2,7-dibromo-5,5-difluoro-6-(difluoromethylene)norbornane in the ratio of 4:1. In contrast, free-radical bromination gave 29% 2, 22% *exo*-2-bromo-*endo*-3-bromo-5-(difluoromethylene)-6,6-difluoronorbornane, and 49% *exo-cis*-2,3-dibromo-5-(difluoromethylene)-6,6-difluoronorbornane. The nature of the ionic and free-radical intermediates is discussed. Dominant homoallylic participation from the exocyclic difluoromethylene moiety is further support for the stability of α-fluorinated electron-deficient carbon.

Previous investigations from this laboratory have demonstrated the importance of γ-fluorine polar and steric effects on additions to the norbornene double bond.[1-3] In particular, fluorine substituents at the 5,6 positions deactivate the norbornene double bond toward electrophilic addition and only free-radical addition is observed. Furthermore, 5,6-endo fluorine substituents shield the endo side of the system from attack in comparison with norbornene itself.

These studies are extended here to a more complex molecule, 5-(difluoromethylene)-6,6-difluoro-2-norbornene (1).[2] Unlike other fluorinated norbornenes, *e.g.*, 5,5,6,6-tetrafluoro- or 5,5,6-trifluoro-2-norbornene, 1 readily undergoes ionic bromination. The importance of homoallylic participation from the difluoromethylene moiety will be discussed.

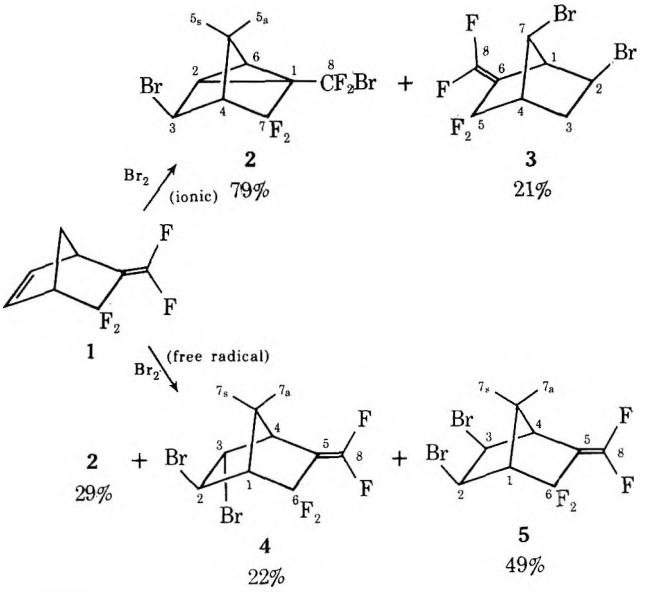
Free-radical bromination of 1 was also investigated. Studies with other methylenenorbornenes have shown that products can arise from initial radical attack at either the exocyclic[4-6] or endocyclic double bond,[7] and homoconjugate addition is often observed.[6] In this regard, the free bromination product distribution was examined and also compared with the ionic addition results.

Results

Olefin 1 rapidly consumed bromine in methylene dichloride solvent in the dark and under oxygen at 25° (ionic conditions) to afford a mixture of 79% 2 and 21% 3 by glpc.

Bromination of 1 under free-radical conditions[2] gave a mixture of 38% 2, 3.5% 3, 18% 4, and 40.5% 5 by glpc and nmr analysis (see Experimental Section). With the assumption that 3 arose only *via* an ionic pathway (*vide infra*), 17% superimposed ionic reaction was present. Correction of the observed results gave a free-radical product distribution of 29% 2, 22% 4, and 49% 5.

The reported dibromides accounted for >98% of the observed products. *No 1,2-dibromides resulting from addition across the difluoromethylene functionality were detected in either the ionic or free-radical reaction.* All dibromides were stable to the reaction and analytical conditions, and the respective product distributions are those of the kinetically controlled addition reactions.



Structural Assignments. The respective dibromide structures were established by ^1H and ^{19}F nmr and ir analyses. Appropriate double-resonance experiments at 100 and 220 MHz allowed for the assignment of long-range couplings. The chemical shift data are presented in Table I.

The dibromide 2 gave a narrow downfield resonance at δ 4.41 for a *single* proton geminal to bromine (Figure 1). The bridgehead proton H_4 appeared at δ 2.46 and the cyclopropane ring protons H_2 and H_6 gave an unresolved singlet at δ 2.21. Irradiation of H_3 revealed a 1.3-Hz coupling with proton H_{5a}. The characteristic ^{19}F AB multiplet of the geminal vinyl fluorines was absent and a narrow triplet ($J_{FF} \cong 4$ Hz) was observed at ϕ 42.0 for the fluorines adjacent to bromine. The absence of a C=CF_2 double bond stretching frequency at 1760–1777 cm^{-1}, which was observed for 1 and 3–5, and the characteristic[8] ir bands observed at 828, 833, and 867 cm^{-1} further confirmed the nortricyclene structure.

The 100-MHz spectrum of dibromide 3 is shown in Figure 2. Irradiation of the upfield protons H_{3x}, H_{3n} at δ 2.63 and 2.70 collapsed the H_2 triplet (J = 6.5 Hz) at δ 4.04 to a broad singlet. Irradiation of the allylic proton H_1 at δ

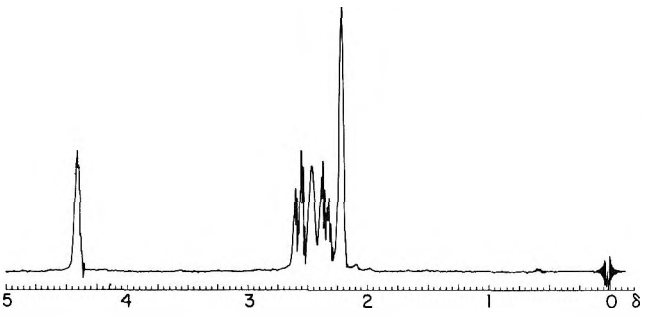


Figure 1. Nmr spectrum (100 MHz) of 1-(bromodifluoromethyl)-3-bromo-7,7-difluorotricyclo[2.2.1.0^{2,6}]heptane (2).

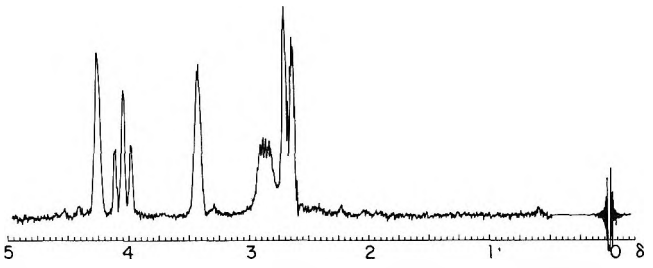


Figure 2. Nmr Spectrum (100 MHz) of 2,7-dibromo-5,5-difluoro-6-(difluoromethylene)norbornane (3).

3.43 did not perturb the H_2 or H_{3x}, H_{3n} resonances. The proton adjacent to bromine at δ 4.04 therefore is endo and vicinal to H_1 and not H_4. The higher field methine proton H_4 exhibited a complex multiplet resulting from 4–5 Hz proton and fluorine couplings. Proton H_7 exhibited no appreciable coupling and appeared as an unresolved singlet at δ 4.26. A strong ir band at 1767 cm^{-1} confirmed the retained difluoromethylene functionality.

The assignment of structure 4 was more complicated, since isomers 2 and 4 could not be efficiently separated by glpc (see Experimental Section). The 2:1 mixture of 2:4 was examined (Figure 3). Careful integration of the downfield δ 4.4 multiplet indicated that one proton adjacent to bromine in 4 overlaps with H_3 in 2. A second proton geminal to bromine appeared at δ 4.14, while the bridgehead protons appeared at δ 2.88 and 3.21. At 220 MHz the downfield δ 4.4 proton could not be resolved. Double irradiation of the δ 4.4 and 4.14 multiplets sharpened the δ 3.21 multiplet while the δ 2.88 multiplet was unaffected. This establishes coupling between the allylic proton H_4 and an exo proton. Proton H_2 at δ 4.14 is an apparent doublet of triplets which resulted from 3.4 Hz H_2H_3, ~2 Hz H_2H_7, and ~2 Hz H_2F_6 couplings. Proton H_2 is therefore endo and the magnitude of H_2H_3 coupling is consistent with a trans orientation of the vicinal protons.[2,9-12] These results agree with structure 4 and not with the trans isomer having an exo proton vicinal to H_1. The difluoromethylene moiety was confirmed by ^{19}F nmr and ir (1775 cm^{-1}, C=CF_2).

Dibromide 5 gave a characteristic[2] AB multiplet with J = 6.9 Hz for cis-oriented protons H_2,H_3 (Figure 4). A long-range $H_{2,3}H_{7a}$ coupling of 2 Hz established the cis-endo stereochemistry of H_2,H_3. The retained exocyclic double bond was established by ^{19}F nmr and ir (1760 cm^{-1}, C=CF_2)

Discussion

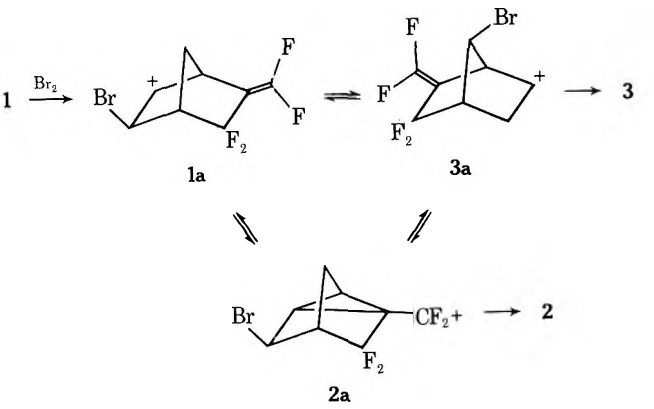
The reactivity of 1 toward ionic bromination when compared with other fluorinated norbornenes[2] and the dominant homoallylic participation of the exocyclic fluorinated double bond are support for the stability of α-fluorinated electron-deficient carbon. The proposed reaction intermediates are shown in Scheme I.[13]

Table I
Chemical Shifts[a] for Dibromides in Carbon Tetrachloride

Nucleus	2	3	4	5
H_1		3.43	2.88	2.96
H_2	2.21[b]	4.04	4.14	
H_{3n}	4.41	2.70		(4.35, 4.56)[c]
H_{3x}		2.63	~4.4[d]	
H_4	2.46	2.85	3.21	3.29
H_{5n}, H_{5x}	2.35, 2.57			
H_6	2.21[b]			
H_{7n}, H_{7x}		4.26	2.0–2.2[d]	1.96, 1.37
F_{5x}, F_{5n}		(98.1, 106.7)		
F_{6x}, F_{6n}			(95.5, 114.2)	(98.2, 113.8)
F_{7x}, F_{7n}	(115.8, 120.8)			
F_8	42.0	(78.8, 79.8)	(79.5, 81.7)	(79.5, 80.8)

[a] All proton chemical shifts are reported in parts per million (δ) relative to internal tetramethylsilane. All fluorine chemical shifts are in parts per million (φ) relative to fluorotrichloromethane (F-11) internal standard. All values refer to the high-field side of F-11. [b] H_2, H_6 not resolved. [c] Values in parentheses indicate respective resonances unassigned. [d] Not determined accurately owing to interferences.

Scheme I



Preferential attack of electrophile occurs on the endocyclic double bond at the 2 position followed by charge delocalization through homoallylic (2a) or σ participation (3a). Initial attack at the 3 position would generate positive charge γ to the geminal fluorines, which is known to be unfavorable.[2] Furthermore, initial attack on the exocyclic double bond is unlikely owing to the known unreactivity of related fluoro olefins to electrophilic addition.[14,15] Such attack followed by synchronous homoallylic participation would again unfavorably position positive charge γ to the geminal fluorines. Therefore, major product 2 arises from preferred intermediate 2a.

The effects of fluorine substitution on carbonium ion stabilities is a recent topic of interest.[16-21] Stabilization is possible through p-π overlap of the fluorine 2p lone-pair electrons into the vacant carbon p orbital, whereas the electronegativity of fluorine relative to hydrogen serves to destabilize positive charge on carbon. The stabilizing influence of fluorine substitution has been demonstrated theoretically[16,17] and experimentally.[18-22] Postulation of 2a as the preferred intermediate is therefore reasonable. The regiospecific addition to 1 is also noteworthy. Several

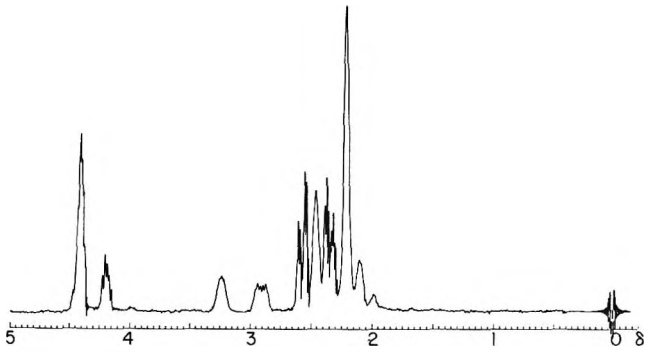


Figure 3. Nmr spectrum (100 Mz) of **2** and *exo*-2-bromo-*endo*-3-bromo-5-(difluoromethylene)-6,6-difluoronorbornane (**4**) (2:1 mixture).

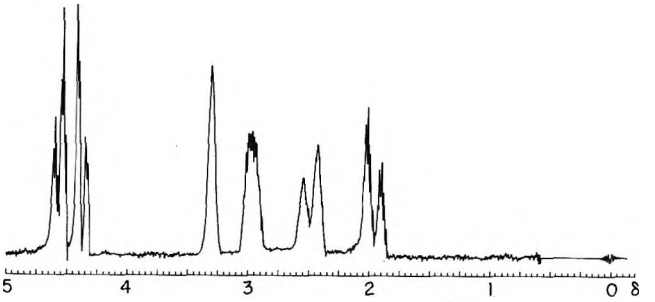
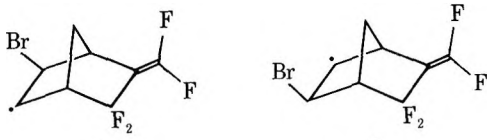


Figure 4. Nmr spectrum (100 MHz) of *exo-cis*-2,3-dibromo-5-(difluoromethylene)-6,6-difluoronorbornane (**5**).

examples of electrophilic additions to fluoro olefins that proceed in accordance with the double-bond polarity are known.[14,15] However, strongly polarized olefins *e.g.*, 1,1-difluoroethylene,[23] are required for unequivocal electrophilic addition, and regiospecific addition is guaranteed in these instances, which, *a priori*, is not the case for **1**.[24]

These results contrast with the free-radical addition. Free-radical attack occurs initially on the internal double bond of **1** from the exo direction to give **8** or **9**. Subsequent attack by a chain-propagating bromine molecule on **8** occurs from the exo side to give **5**. Such stereochemical control by endo fluorine substituents has been demonstrated.[1-3] Attack on **9** gives **4**, and rearrangement prior to bromine attack leads to **2**. The nearly equivalent amounts of (**2** + **4**) and **5** formed suggests that there is no preference for the formation of radical **9** or subsequent homoallylic participation.[25,26]



8 **9**

Experimental Section

All melting and boiling points are uncorrected. The gas chromatography work was performed as before[2] with a 6 ft × 0.375 in. 20% QF-1 fluorosilicone on 60/80 Chromosorb P column. The ^1H and ^{19}F nmr spectra and decoupling experiments followed previous procedures.[2,27] Olefin **1** was available from a previous study.[2] The free-radical and ionic reaction experimental procedures have been described in detail.[2,27]

Ionic Bromination. A solution of 1.78 g (10 mmol) of **1** in 9 ml of methylene dichloride was brominated under ionic conditions with 1.60 g (10 mmol) of bromine in 1 ml of methylene dichloride. Work-up afforded a quantitative yield of a mixture of 79% 1-(bromodifluoromethyl)-3-bromo-7,7-difluorotricyclo[2,2.1.$0^{2,6}$]heptane (**2**) and 21% 2,7-dibromo-5,5-difluoro-6-(difluoromethylene)norbornane (**3**) by glpc (150°). Collection of the 9.4- (**2**) and 11.7-min (**3**) peaks *via* preparative glpc gave pure **2**, an oil, and **3**, mp 55–57°. A cold pentane wash gave an analytical sample of **3**, mp 58.5–60°.

Anal. Calcd for $C_8H_6Br_2F_4$: C, 28.43; H, 1.79; Br, 47.29. Found (**2**): C, 28.69; H, 1.87; Br, 47.20; (**3**): C, 28.41; H, 1.70.

The reaction was scaled up fivefold and distillation of the product mixture afforded 14.3 g of product, by 73–76° (4 mm). The cut with bp 73° (4 mm) was pure **2**; the 75–76° cut contained ~46% **3**.

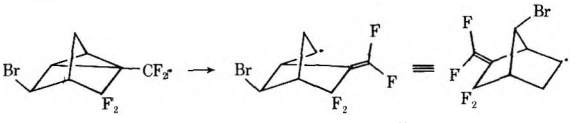
Free-Radical Bromination. Bromination of 10 mmol of **1** with 10 mmol of bromine under free-radical conditions gave a quantitative yield of crude dibromides. Glpc (150°) revealed three peaks with respective retention times of 9.4, ~9.8, and 11.8 min. The 9.4- and 9.8-min peak products (56%) were collected together, and the 11.8-min peak product (44%) was collected separately. Examination of the first collection by ^1H and ^{19}F nmr and ir indicated a mixture of 68% **2** and 32% **4**. The 11.8-min retention time material, mp 46–49°, was a mixture of 92% **5** and 8% **3** by ^{19}F and ^1H nmr. Several washings with cold pentane gave pure **5**, mp 51–53°.

Anal. Found (**2** + **4**): C; 28.71; H, 1.80; (**5**): C; 28.64; H, 1.78.

Registry No.—**1**, 39037-72-4; **2**, 50357-81-8; **3**, 50357-82-9; **4**, 50357-83-0; **5**, 50357-84-1.

References and Notes

(1) Previous paper in this series: B. E. Smart, *J. Org. Chem.*, **38**, 2039 (1973).
(2) B. E. Smart, *J. Org. Chem.*, **38**, 2027 (1973).
(3) B. E. Smart, *J. Org. Chem.*, **38**, 2035 (1973).
(4) E. S. Huyser and G. Echegaray, *J. Org. Chem.*, **27**, 429 (1962).
(5) C. K. Alden and D. I. Davies, *J. Chem. Soc. C*, **1017** (1967).
(6) See J. W. Wilt in "Free Radicals," Vol. I, J. K. Kochi, Ed., Wiley, New York, N. Y., 1973, pp 466–480, for a discussion of homoallylic radical rearrangements.
(7) S. J. Cristol, T. W. Russell, and D. I. Davies, *J. Org. Chem.*, **30**, 207 (1965).
(8) G. E. Pollard, *Spectrochim. Acta*, **18**, 837 (1962).
(9) P. Laszlo and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **86**, 1171 (1964).
(10) . Subramanian, M. T. Emerson, and N. A. LeBel, *J. Org. Chem.*, **30**, 2624 (1965).
(11) C. L. Osborne, T. V. Van Auken, and D. J. Trecker, *J. Amer. Chem. Soc.*, **90**, 5806 (1968).
(12) A. G. Ludwick and J. C. Martin, *J. Org. Chem.*, **34**, 4108 (1969).
(13) The intermediates are shown as equilibrating classical species for convenience only. Representation by nonclassical entities, especially for the fluorinated system, is a moot point.
(14) W. A. Sheppard and C. M. Sharts, "Organic Fluorine Chemistry," W. A. Benjamin, New York, N. Y., 1969.
(15) B. L. Dyatkin, E. P. Mochalina, and I. L. Knunyants in "Fluorine Chemistry Reviews," Vol. 3, P. Tarrant, Ed., Marcel Dekker, New York, N. Y., 1969.
(16) N. C. Baird and R. K. Dalta, *Can. J. Chem.*, **49**, 3708 (1971).
(17) L. D. Kispert, *et al.*, *J. Amer. Chem. Soc.*, **94**, 5979 (1972).
(18) G. A. Olah, M. B. Comisarow, and C. A. Cupas, *J. Amer. Chem. Soc.*, **88**, 362 (1966).
(19) G. A. Olah, R. D. Chambers, and M. B. Comisarow, *J. Amer. Chem. Soc.*, **89**, 1268 (1967).
(20) G. A. Olah, Y. K. Mo, and Y. Halpern, *J. Amer. Chem. Soc.*, **94**, 3551 (1972).
(21) T. B. McMahon, *et al.*, *J. Amer. Chem. Soc.*, **94**, 8934 (1972).
(22) P. E. Peterson, R. J. Bopp, and M. M. Ajo, *J. Amer. Chem. Soc.*, **92**, 2834 (1970).
(23) R. N. Hazeldine and J. E. Osborne, *J. Chem. Soc.*, *61* (1956).
(24) These results do not necessarily support the contention[16-21] that fluorine stabilizes a carbonium ion relative to hydrogen. Ionic bromination of 5-methylene-2-norbornene also gave *ca.* 80% homoconjugate addition: B. E. Smart, unpublished results. A kinetic study on unfluorinated, monofluorinated, and difluorinated compounds is required to demonstrate whether fluorine stabilization is operative in the rate-determining step. However, the ionic bromination results do indicate the preference for the α-fluorinated electron-deficient structure **2a** over **1a**, **3a**, and other possible intermediates.
(25) In contrast, ca. 80% of the products (including 36–50% homoconjugate addition) from the free-radical addition of thiophenol to 5-methylene-2-norbornene results from initial attack at the 2 position; see ref 7.
(26) The assumption that **3** is not a free-radical reaction product but a result of the superimposed ionic reaction demands further comment. Rearrangement of radical **9** to **10** followed by ring opening to **11** is a possibility. Subsequent attack on **11** is anticipated to afford a mixture of exo (**3**) and predominantly endo products. However, no endo 2,7-dibromide was observed. For a discussion of steric control from syn 7 substituents see ref 6 and D. I. Davies in "Essays on Free-Radical Chemistry," Special Publication No. 24, The Chemical Society, Burlington House, London, 1970.



10 **11**

(27) B. E. Smart, *J. Org. Chem.*, **38**, 2366 (1973).

Mercury in Organic Chemistry. III.[1] The Anti-Markovnikov Esterification of Terminal Alkenes

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Received October 5, 1973

The direct anti-Markovnikov esterification of monosubstituted alkenes can be achieved in excellent yields under very mild reaction conditions using a hydroboration–mercuration–iodination sequence. Hydroboration with "borane" and subsequent mercuration with a variety of mercuric carboxylates gives excellent yields of the corresponding primary alkylmercuric carboxylates. *In situ* iodination generates alkyl iodides which under the reaction conditions are rapidly transformed into primary esters. This procedure does not permit the synthesis of esters derived from very strong carboxylic acids or more highly substituted alkenes.

Although the addition of carboxylic acids to alkenes proceeds readily in accordance with Markovnikov's rule (eq 1),[2] there presently appear to be no convenient, direct

$$RCH{=}CH_2 \longrightarrow RCH(O_2CR')CH_3 \quad (1)$$

synthetic methods available for the anti-Markovnikov esterification of alkenes (eq 2). We wish to report that

$$RCH{=}CH_2 \longrightarrow RCH_2CH_2O_2CR' \quad (2)$$

monosubstituted olefins can be directly converted under very mild reaction conditions to the corresponding primary esters in excellent yield by a sequence involving hydroboration–mercuration–iodination.

Results and Discussion

We recently reported a convenient method for the conversion of terminal alkenes into primary alkylmercuric salts *via* hydroboration–mercuration (eq 3, 4).[3] At the

$$3RCH{=}CH_2 + BH_3 \longrightarrow (RCH_2CH_2)_3B \quad (3)$$

$$(RCH_2CH_2)_3B + 3Hg(OAc)_2 \longrightarrow 3RCH_2CH_2HgOAc + B(OAc)_3 \quad (4)$$

same time, Tufariello and Hovey reported that *in situ* bromination of these organomercurials provides a convenient method for the anti-Markovnikov hydrobromination of alkenes (eq 5).[4] We have observed, however, that the *in*

$$RCH{=}CH_2 \xrightarrow{1/3BH_3} \xrightarrow{Hg(OAc)_2} \xrightarrow{Br_2} RCH_2CH_2Br \quad (5)$$

situ iodination of these same organomercurials does *not* afford the corresponding alkyl iodides, but provides excellent yields of the primary alkyl acetates instead! In view of this surprising result we have examined the reaction more closely and wish now to report the details of that study.

The reaction conditions necessary for the conversion of monosubstituted olefins into esters are extremely mild. Both the hydroboration reaction and the subsequent mercuration of the resultant primary trialkylboranes are very facile reactions requiring only minutes at room temperature.[3] The addition of iodine directly to the reaction mixture results in the rapid decolorization of the iodine and the formation of the corresponding primary esters in excellent yield. For example, treatment of a tetrahydrofuran (THF) solution of tri-*n*-butylborane[5] with 3 equiv of mercuric acetate and iodine results in an 81% yield of *n*-butyl acetate and 3% of *n*-butyl iodide. The alkyl iodide completely disappears if a 5–10% excess of mercuric acetate is used. Substitution of diglyme for THF results in a more rapid decolorization of iodine and a 93% yield of pure *n*-butyl acetate. The use of diglyme seems to lead to uniformly higher yields. Using diglyme as described above, we have been able to convert a number of different monosubstituted alkenes into esters in excellent yields. Furthermore, the reaction is not limited to the synthesis of acetates alone. Indeed, mercuric *n*-butyrate and mercuric benzoate also give excellent yields of the corresponding esters. Some representative conversions are summarized in Table I.

Several limitations to this reaction have been observed. Although mercuric acetate, mercuric *n*-butyrate, and mercuric benzoate give excellent yields of esters, mercuric trifluoroacetate gives only very poor yields. Thus, esters of very strong acids may not be accommodated by this reaction sequence. Furthermore, although all monosubstituted alkenes, including 3,3-dimethyl-1-butene, give excellent yields under our reaction conditions, disubstituted terminal alkenes such as isobutylene give only very poor yields and are generally contaminated with large amounts of the corresponding iodide. Finally, trialkylboranes derived from internal olefins do not readily react with mercuric carboxylates.[6] Thus, this procedure appears limited to the synthesis of esters derived from weaker carboxylic acids and monosubstituted olefins.

In view of the tremendous difference in the products of bromination and iodination of the same organomercurials under essentially identical reaction conditions, we have taken a closer look at both of these reactions. It is well known that the halogenation of organomercurials gives the corresponding alkyl halides.[7] This we have confirmed in the case of *n*-butylmercuric acetate. However, *in situ* bromination of the *n*-butylmercuric acetate obtained under our reaction conditions leads to *n*-butyl bromide contaminated with about 10% of *n*-butyl acetate. This result, plus the fact that minor amounts of iodide were evident in our reactions when only stoichiometric amounts of mercuric acetate were used, strongly suggested to us that we must first be forming the alkyl iodide, which was rapidly transformed into the ester. In fact, immediate glpc analysis of the reaction mixture obtained from treatment of tri-*n*-butylborane with mercuric acetate and iodine indicated significant amounts of *n*-butyl iodide which rapidly disappeared.

It is obvious that the other product of the mercuration reaction, namely the boron tricarboxylate, is playing a major role in this reaction. This was confirmed by the following experiments. After the mercuration of tri-*n*-butylborane, addition of methanol (24 hr) and subsequent iodination gave only a 7% yield of *n*-butyl acetate and a 63% yield of *n*-butyl iodide. The methanol presumably removes the boron triacetate (eq 6). Furthermore, the hy-

$$B(O_2CCH_3)_3 + 3HOCH_3 \longrightarrow B(OCH_3)_3 + 3HO_2CCH_3 \quad (6)$$

droboration–mercuration–iodination of 1-decene using dicyclohexylborane gives only about a 20% yield of *n*-decyl

Table I
The Anti-Markovnikov Esterification of Alkenes

$$RCH{=}CH_2 \xrightarrow{^1/_3BH_3} \xrightarrow{Hg(O_2R')_2} \xrightarrow{I_2} RCH_2CH_2O_2CR'$$

Registry no.	Alkene[a]	Registry no.	Mercuric carboxylate	Ester	Yield,[b] %
74-85-1	Ethylene	1600-27-7	Mercuric acetate	Ethyl acetate	92
		13257-51-7	Mercuric trifluoroacetate	Ethyl trifluoroacetate	17
		19348-32-4	Mercuric butyrate	Ethyl butyrate	97 (88)
		583-15-3	Mercuric benzoate	Ethyl benzoate	86
106-98-9	1-Butene		Mercuric acetate	*n*-Butyl acetate	93 (84)
			Mercuric butyrate	*n*-Butyl butyrate	84
115-11-7	Isobutylene		Mercuric acetate	Isobutyl acetate	30[c]
563-45-1	3-Methyl-1-butene		Mercuric acetate	Isoamyl acetate	88
558-37-2	3,3-Dimethyl-1-butene		Mercuric acetate	3,3-Dimethyl-1-butyl acetate	73
872-05-9	1-Decene		Mercuric acetate	*n*-Decyl acetate	89

[a] Reference 5. [b] Glpc yield (isolated yield). [c] Contains approximately 20% isobutyl iodide.

acetate and 70–80% of *n*-decyl iodide (eq 7). Thus, dicyclohexylboron acetate is evidently also ineffective in con-

$$n\text{-}C_8H_{17}CH{=}CH_2 \xrightarrow{HB(\bigcirc)_2} \xrightarrow{Hg(OAc)_2} \xrightarrow{I_2} n\text{-}C_{10}H_{21}I \quad (7)$$

verting the organomercurial into the ester upon iodination.

The following mechanism seems most consistent with these observations (eq 8–12).

$$3RCH{=}CH_2 + BH_3 \longrightarrow (RCH_2CH_2)_3B \quad (8)$$

$$(RCH_2CH_2)_3B + 3Hg(O_2CR')_2 \longrightarrow RCH_2CH_2HgO_2CR' + B(O_2CR')_3 \quad (9)$$

$$RCH_2CH_2HgO_2CR' + I_2 \longrightarrow RCH_2CH_2I + IHgO_2CR' \quad (10)$$

$$IHgO_2CR' + B(O_2CR')_3 \longrightarrow IHgB(O_2CR')_4 \quad (11)$$

$$IHgB(O_2CR')_4 + RCH_2CH_2I \longrightarrow RCH_2CH_2O_2CR' + HgI_2 + B(O_2CR')_3 \quad (12)$$

Equations 8–10 are all well-known reactions. The presence of the boron tricarboxylate presumably formed in the mercuration step (eq 9) has been shown to be vital to the overall conversion of organomercurial to ester. We suggest that this compound reacts with the iodomercuric carboxylate present from the iodination step (eq 10) to form a species, iodomercuric boron tetracarboxylate (eq 11), capable of displacing the iodide of the alkyl iodide by a carboxylate group (eq 12). The boron tricarboxylate actually serves as a catalyst in this reaction, since it is regenerated in the displacement step (eq 12).

The following observations lend support to this mechanism. The addition of lithium iodide to the organomercurial prior to iodination results in high yields of alkyl iodide, not acetate.[8] Presumably the alkylmercuric iodide is formed. Upon iodination one then obtains mercuric iodide incapable of abstracting another iodide from the alkyl iodide (eq 13, 14). Furthermore, treatment of tri-*n*-butylborane with only 1 equiv of mercuric acetate results in the rapid formation of di-*n*-butylmercury.[9] Iodination of this reaction mixture gives a 98% yield of *n*-butyl iodide and no *n*-butyl acetate (eq 15). At no time is any mercuric acetate derivative present upon iodination. Only mercuric iodide can be formed by the iodination of di-*n*-butylmercury.

$$RCH_2CH_2HgO_2CR' + LiI \longrightarrow RCH_2CH_2HgI + LiO_2CR' \quad (13)$$

$$RCH_2CH_2HgI + I_2 \longrightarrow RCH_2CH_2I + HgI_2 \quad (14)$$

$$(n\text{-}C_4H_9)_3B + Hg(OAc)_2 + 2I_2 \longrightarrow 2n\text{-}C_4H_9I + HgI_2 + n\text{-}C_4H_9B(OAc)_2 \quad (15)$$

We have also attempted to reproduce the reactions outlined in eq 11 and 12. Mercuric acetate is relatively insoluble in THF. Addition of 1 equiv of mercuric iodide results in a clear solution, suggesting the formation of iodomercuric acetate. Treatment with *n*-butyl iodide for 24 hr at room temperature gave only a 9% yield of *n*-butyl acetate, but addition of 10% of boron triacetate (prepared from "borane" and acetic acid) gave a 55% yield of ester. Similarly, mercuric acetate does not react in 24 hr with *n*-butyl iodide at room temperature, but gives an 88% yield of *n*-butyl acetate in a little over 1 hr in the presence of 10% boron triacetate (eq 16).[10] On the other hand, isobutyl iodide gives only a very poor yield of isobutyl acetate under these same conditions, thus explaining our earlier poor results with isobutylene. Mercuric trifluoroacetate also yields very little of the corresponding ester. *n*-Butyl bromide fails to react at all under identical conditions. This result explains the vast difference in products in the bromination and iodination reaction sequences. We are currently exploring the scope of these alkyl halide esterification reactions and will report on this work shortly.

$$CH_3CH_2CH_2CH_2I + Hg(OAc)_2 \xrightarrow{B(OAc)_3} CH_3CH_2CH_2CH_2OAc + IHgOAc \quad (16)$$

Thus, the many unusual observations made during the course of this investigation on the hydroboration–mercuration–iodination of alkenes are all consistent with the mechanism outlined above. In view of the many reactions actually involved in this reaction sequence, it is indeed amazing that such excellent yields of esters can be obtained. Each step from alkene to organoborane, organomercurial, alkyl iodide, and finally ester must be proceeding in near quantitative yield.

Experimental Section

Materials. Most materials, solvents, and chemicals used have been described previously.[3] Triethylborane and tri-*n*-butylborane were used directly as obtained from Callery Chemical Co. The preparations of mercuric *n*-butyrate, benzoate, and trifluoroacetate have been described previously.[6] Mercuric benzoate is best dried over phosphorus pentoxide under a high vacuum for several days.

Hydroboration–Mercuration–Iodination of Representative Alkenes. Although the hydroboration–mercuration of all alkenes using both "borane" and dicyclohexylborane has been described previously,[3] the following synthesis of *n*-butyl acetate is illustrative. A dry 300-ml flask equipped with septum inlet, pressure-equalizing addition funnel, and magnetic stirrer was flushed with nitrogen and maintained under a static pressure of gas. To 100 ml of 0.33 *M* tri-*n*-butylborane (8.13 ml = 33.3 mmol) in diglyme was added at 0° 35.06 g (110 mmol) of mercuric acetate while backflushing with nitrogen. After stirring for 10 min at 0°, 55 ml (110 mmol) of a solution of 2 *M* iodine in diglyme was slowly added. The resulting solution was stirred overnight at room temperature.

Addition of ether, decolorization of excess iodine with aqueous sodium thiosulfate, washing with 5 × 100 ml of 5 *M* potassium iodide or 3 *M* sodium thiosulfate (to remove mercuric iodide) and 2 × 100 ml of saturated sodium bicarbonate, decolorization with activated carbon, and drying over anhydrous sodium sulfate gave a solution which upon distillation yielded 9.82 g (84%) of *n*-butyl acetate.

All yields determined by glpc analysis were run in a similar fashion on a 10-mmol scale using a suitable hydrocarbon internal standard. The exact experimental procedures used for hydroboration–mercuration are those reported earlier.[3] THF is readily removed under vacuum and replaced by dry diglyme. In those reactions in which diglyme interferes with the distillation of the desired ester, THF is recommended as a reaction solvent, although slightly lower yields are generally obtained.

All organoboranes prepared from monosubstituted alkenes by hydroboration in THF possess 6% of *sec*-alkylboron groups which will not react.[3] Thus 10% less mercuric acetate and iodine were used and all yields were based on available primary alkylboron groups.

The Boron Triacetate Catalyzed Conversion of *n*-Butyl Iodide to Acetate. Ten milliliters of 0.1 *M* boron triacetate was prepared by addition of 0.42 ml (1 mmol) of 2.4 *M* "borane" in THF to 9.4 ml of THF containing 0.18 g (3.0 mmol) of acetic acid at −78°. After removal of the cold bath, this solution was stirred for 3 hr at room temperature. To this solution was added 1.84 g (10 mmol) of *n*-butyl iodide, the appropriate amount of mercuric acetate (5 or 10 mmol) and/or mercuric iodide (5 mmol), and 0.8 ml of nonane as an internal standard. Glpc analysis indicated the extent of reaction.

Acknowledgment. The author gratefully acknowledges the donors of the Petroleum Research Fund, administered by the American Chemical Society, for their generous support of this research. The capable assistance of Mr. Gary Molander and Mr. Stephan McLain is also deeply appreciated.

References and Notes

(1) Part II: R. C. Larock, *J. Organometal. Chem.*, in press.
(2) J. Guenzet and M. Camps, *Tetrahedron Lett.*, 2647 (1972), and references cited therein.
(3) R. C. Larock and H. C. Brown, *J. Amer. Chem. Soc.*, **92**, 2467 (1970).
(4) J. J. Tufariello and M. M. Hovey, *J. Chem. Soc. D*, 372 (1970); *J. Amer. Chem. Soc.*, **92**, 3221 (1970).
(5) Pure triethylborane and tri-*n*-butylborane were used directly as obtained commercially. All other organoboranes were prepared *via* hydroboration of the appropriate alkene and thus sometimes contain minor amounts (up to 6%) of secondary alkyl groups which will not react.
(6) R. C. Larock and H. C. Brown, *J. Organometal. Chem.*, **26**, 35 (1971).
(7) F. R. Jensen and B. Rickborn, "Electrophilic Substitution of Organomercurials," McGraw-Hill, New York, N. Y., 1968.
(8) J. J. Tufariello, private communication.
(9) J. D. Buhler and H. C. Brown, *J. Organometal. Chem.*, **40**, 265 (1972).
(10) Further details on this interesting reaction will be reported shortly.

Polarographic and Spectrophohotometric Evaluation of Acid Dissociation Constants of Some Substituted Ethyl Benzoylacetates

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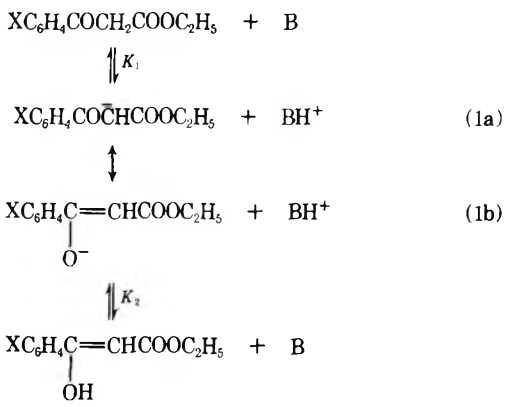
Received June 25, 1973

The overall dissociation constants K_Σ of ethyl benzoylacetate and *p*-methoxy, -methyl, -chloro, and -cyano derivatives were evaluated spectrophotometrically and polarographically, and [enol]/[keto] ratios were measured by titration with bromine. Values of the dissociation constants of the keto (K_1) and enol (K_2) forms were isolated; like polarographic half-wave potentials, they were shown to be linear functions of Hammett substituent constants $\sigma_{p\text{-}X}$.

In alkaline solutions of β-keto esters, the keto and enol forms dissociate to give a common conjugate base, the carbanion enolate (eq 1). When spectrophotometry is used



for the study of such an equilibrium, the only condition which must be fulfilled is that the equilibrium must be established before the spectrum is recorded. However, with methods such as bromination, which involve a chemical interaction of either the keto form or the enol, it is essential that the establishment of the keto–enol equilibrium be slow in comparison with the competing reaction. Information on the rate of establishment of this equilibrium, which is of interest with respect to the general reactivity of the carbonyl compound, can be obtained by polarography. Using accepted criteria,[1] it is possible to show whether the limiting current is governed by diffusion or by the rate of chemical reaction. If, for a system at equilibrium, the limiting current of one species is diffusion controlled, the rate of establishment of the equilibrium must be much lower than the rate of the mass transport by diffusion. This has been found to be true for unsubstituted ethyl benzoylacetate.[2]

It was of interest to investigate phenyl-substituted benzoylacetates to follow the substituent effects on the acid–base and keto–enol equilibria and to show whether the presence of substituents affects the relatively slow rate of establishment of equilibrium 1.

In view of the nature of system 1, it seemed preferable to attempt first separation of the two acid dissociation constants K_1 and K_2 from experimental data rather than to try to express the substituent effects on the [enol]/[keto] ratio.

Values of K_1 and K_2 are usually not directly accessible to measurement, but they can be calculated from two kinds of measurable quantities: The first of these is the value of the overall acid–base dissociation constant K_Σ, defined by the expression K_Σ = [carbanion enolate] [H^+]/([keto form] + [enol form]). The value of K_Σ is re-

Table I
Spectral Properties of Substituted Benzoylacetates (10% Aqueous Ethanol)

Substituent	Keto form						Anion					
	π → π*		B		n → π*		π → π*		B		a → π*	
	λ, nm	ε	λ, nm	ε	λ, nm	ε	λ, nm	ε	λ, nm	ε	λ, nm	ε
p-CH_3	<200	$>1.5 \times 10^4$	262	1.46×10^4	~290	$<2 \times 10^2$	<210	$>1 \times 10^4$	239	$\sim 6 \times 10^3$	304	1.4×10^4
H	<200	$>1.8 \times 10^4$	250	1.28×10^4	~286	$\sim 8 \times 10^2$	<210	$>8 \times 10^3$	232	$\sim 7 \times 10^3$	303	1.3×10^4
p-Cl	<190	$>1 \times 10^4$	260	1.45×10^4	~280	$<1 \times 10^2$	<200	$>1 \times 10^4$	237	$\sim 7 \times 10^3$	305	1.3×10^4
p-CN	<200	$>2 \times 10^4$	251	2×10^4	~320[a]	$\sim 6 \times 10^2$	<200	$>2 \times 10^4$	240	$>1.9 \times 10^4$	325	1×10^4
p-OCH_3	<200	$>1.3 \times 10^4$	283	1.5×10^4	~290	$<1 \times 10^2$	<200	$>1.3 \times 10^4$	248	$\sim 6 \times 10^3$	305	1.7×10^4

[a] Broad band, envelope of three or more peaks.

Table II
Acid Dissociation Constants and Half-Wave Potentials of Substituted Benzoylacetates

Registry no.	Substituent	σ	Spectral data[a] pK$_\Sigma$	λ_{max} (nmr)	Polarographic data[b] pK$_\Sigma$*	$E^1/_2$, V vs. sce pH 8.45	pH 10.0
2888-83-6	*p*-OCH_3	−0.27	10.81	240	10.8	−1.46	−1.54
27835-00-3	*p*-CH_3	−0.17	10.51	305	10.5	−1.41	−1.47
94-02-0	H	0	10.35	305	10.35	−1.37	−1.43
2881-63-2	*p*-Cl	0.23	9.86	305	9.9	−1.31	−1.38
49744-93-6	*p*-CN	0.66	9.00	305	9.1		

[a] 1×10^{-4} *M* solutions containing 10% ethanol. [b] 2×10^{-4} *M* solutions containing 10% ethanol.

Figure 1. Dependence of absorption spectra of 1×10^{-4} *M* *p*-methylbenzoyl acetate on pH. Buffers used: (1) borate, pH 9.1; (2) borate, pH 10.1; (3) phosphate, pH 11.1; (4) phosphate, pH 11.4.

lated to the dissociation constants K_1 and K_2 by the equation $K_\Sigma = K_1K_2/(K_1 + K_2)$. The other accessible value is the ratio [enol form]/[keto form], which is equal to the ratio of K_1/K_2.

It may be pointed out that, contrary to some traditional belief, the [enol]/[keto] ratio is pH independent. As the pH increases,[3] the sum of concentrations [enol] + [keto] decreases. Simultaneously the concentration of the carbanion enolate increases, and the ratio of the sum of the [enol] + [keto] to the concentration of the anion changes. A plot of the concentration of any of these three forms (enol, keto, or carbanion enolate) against pH has the shape of a simple dissociation curve with an inflexion point at pH = pK_Σ.

The [enol]/[keto] ratio is most conveniently evaluated at a pH value low enough to render the concentration of the ambident anion negligible and maximize the concentrations of the keto and enol forms.

From the values of K_Σ and the ratio [enol]/[keto], it is possible[4] to calculate the value of K_1 by means of the expression $K_1 = K_\Sigma(1 + [\text{enol}]/[\text{keto}])$, then to calculate that of K_2 from K_1 and the expression $K_2 = K_1([\text{keto}]/[\text{enol}])$. If in aqueous solutions the keto form strongly predominates, so that [enol] << [keto], then the measured value of K_Σ is practically equal to K_1.

To apply this treatment to substituted ethyl benzoylacetates, it was first necessary to determine corresponding values of K_Σ. Both spectrophotometric and polarographic measurements were used for this purpose. Titration with bromine was used to evaluate the ratio [enol]/[keto], taking advantage of the fact that the keto–enol equilibrium is slowly established.

Results and Discussion

At pH < 8 ethyl benzoylacetates show an intensive $\pi \rightarrow \pi^*$ absorption band at about 200 nm and a very weak $n \rightarrow \pi^*$ band at 290–320 nm. A third, intensive band corresponding to the benzenoid absorption of the C_6H_5CO grouping was observed at 250–280 nm. In alkaline media the carbanion enolate $XC_6H_4COCHCOOC_2H_5^- \leftrightarrow XC_6H_4C(O^-) = CHCOOC_2H_5$ shows an intensive $\pi \rightarrow \pi^*$ absorption band at short wavelengths, a medium-intensity benzenoid band at 230–250 nm, and an intensive band at 305–325 nm which is characteristic for carbanion enolates. Spectral data are summarized in Table I.

Spectra recorded at different pH values show an isosbestic point (Figure 1) provided that they are obtained within 5 min after mixing of the stock solution with the buffer. At higher pH values the spectra change during the

Table III
Separation of Dissociation Constants of the Keto (K_1) and Enol (K_2) Forms of Substituted Benzoylacetates

Substituent	σ	$K \times 10^{-11}$	% enol	[enol][a]/[keto]	$K_2^b \times 10^{-9}$	$K_1^c \times 10^{-10}$
p-OCH_3	−0.27	0.158	15.6	0.18	0.104	0.187
p-CH_3	−0.17	0.316	15.9	0.19	0.198	0.376
H	0	0.447	12.3	0.14	0.364	0.310
p-Cl	0.23	1.31	13.2	0.15	1.00	1.50
p-CN	0.66	8.90	14.3	0.17	6.12	10.4

[a] [Enol]/[keto] = K_1/K_2. [b] $K_2 = K_\Sigma(1 + [\text{enol}]/[\text{keto}])/([\text{enol}]/[\text{keto}])$. [c] $K_1 = K_2[\text{enol}]/[\text{keto}]$.

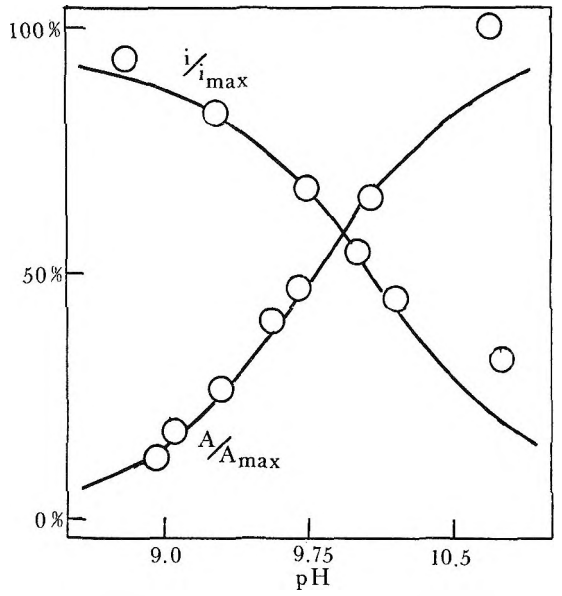


Figure 2. Dependence of absorbance at 320 nm ($100\,A/A_{max}$) and polarographic limiting currents ($100\,i/i_{max}$) of p-chlorobenzoyl acetate on pH. The value for i_{max} was measured at pH 8, that for A_{max} at pH 11. Experimental points, theoretical curves.

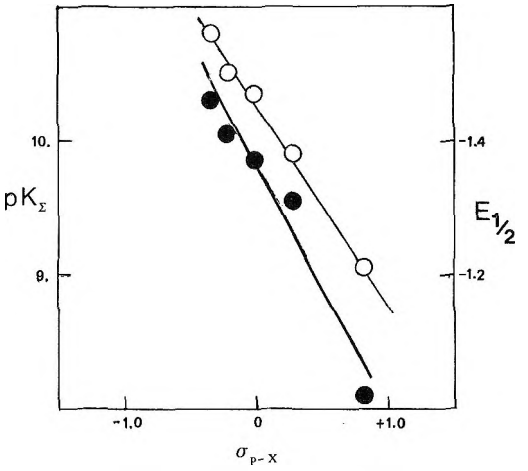


Figure 3. Dependences of the overall acid dissociation constant (pK_Σ) and half-wave potential ($E_{1/2}$) on Hammett substituent constants σ_X. pK_Σ values, circles; $E_{1/2}$ (*vs.* sce), full points.

first hour because of hydrolysis, which was particularly important in the case of the p-cyano derivative.

The absorbance of a freshly prepared solution measured at the wavelength of the absorption maximum of either the carbanion enolate or the benzenoid band of the keto form plotted against pH shows a dependence in the shape of a dissociation curve of a monobasic acid (in Figure 2 the deviation at pH 10.75 is due to hydrolysis). Values of pK_Σ determined from such curves are given in Table II.

Polarographic current-voltage curves, obtained with dropping mercury electrode, show one two-electron cathodic wave at pH ~ 8 which corresponds to the reduction of the unprotonated carbonyl group.[2] At pH > 8, a plot of the height of this wave against pH has shape of a dissociation curve decreasing with increasing pH, which corresponds to a monobasic acid (Figure 2). At pH 11, where the current i is less than 15% as large as at pH ~ 8, the wave height is directly proportional to the square root of the height of the mercury column, which indicates that the current is diffusion controlled. Hence the limiting currents are a linear function of the bulk concentration of the keto form over the entire pH range studied. Conditions are thus fulfilled for the use of the wave height measurement for determination of pK_Σ values.[5]

The values of pK_Σ obtained from the pH dependence of polarographic and spectrophotometric data were in very good agreement (Table II).

The facts that polarographic limiting currents were diffusion controlled and that the polarographic and spectrophotometric values coincide indicate that the keto form is comparatively slowly regenerated from the carbanion enolate when the equilibrium between them is perturbed by the electroreduction of the former. More specifically, it can be deduced[6] that the second-order rate constant for the protonation of the carbanion enolate on carbon must be smaller than about 4×10^9 l. mol^{-1} sec^{-1} for the p-cyanobenzoyl acetate or smaller than about 7×10^{10} l.mol^{-1} sec^{-1} for p-methoxybenzoyl acetate.

Polarographic curves of these compounds show an adsorption prewave, which is separated from the main wave only at pH < 5. At higher pH values, in the pH region where height of the main wave decreases, the adsorption process could be detected only through its effect on the shape of the instantaneous current-time curves recorded at potentials near the foot of the wave. The portion of the wave which is governed by adsorption is less dependent on pH than the diffusion-controlled portion at more negative potentials. This effect contributed to deviations of experimental points from the theoretical shape of the dissociation curve at higher pH values (*e.g.*, at pH 10.75, Figure 2).

Whereas limiting currents of most of the waves were parallel with the potential axis even in the pH range where the wave height was observed to decrease, a deformation (a trough) was observed on the limiting current of ethyl p-cyanobenzoylacetate. This deformation has been attributed to adsorption. Since the wave remains diffusion controlled in its unaffected portion, the origin of this process must be different from the surface phenomena accompanying kinetic currents.[7]

The values of pK_Σ obtained either spectrophotometrically or polarographically for para-substituted ethyl benzoylacetates are a linear function of Hammett substituent constants $\sigma_{p\text{-}X}$ (Figure 3) and the reaction constant ρ is 1.84 (r = 0.992). Attempts to correlate the values of pK_Σ with $\sigma^+_{p\text{-}X}$ were much less satisfactory. Comparison of the values of the reaction constant for the bases $ArCOCH^-$ and $ArCOO^-$ for which ρ = 1.0 by definition indicates that the carbanion enolate is more susceptible to

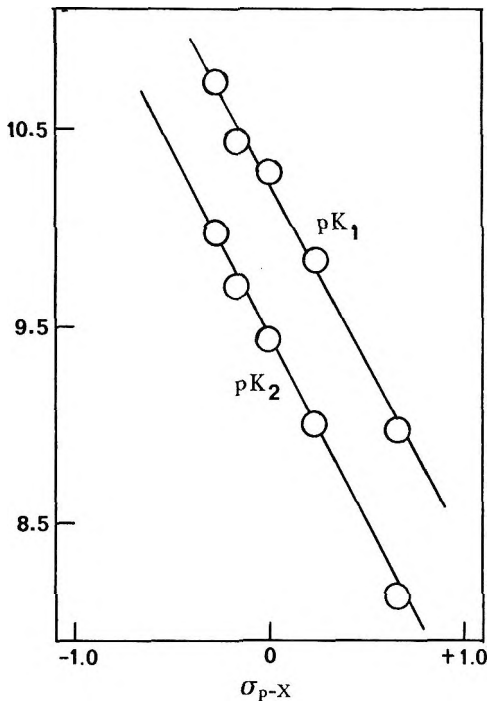


Figure 4. Dependence of the dissociation constant of the keto form (pK_1) and the enol form (pK_2) on Hammett substituent constants σ_X.

the transmission of substituent effects than the carboxylate ion by a factor of about 1.5.

Polarographic half-wave potentials of all benzoylacetates investigated in this study are shifted by about 45–50 mV/pH to more negative potentials with increasing pH. The linear plots were practically parallel at pH < pK_Σ, showing that the value of αn_a remains approximately constant within the reaction series. At higher pH values the half-wave potentials of the *p*-methoxy and *p*-methyl derivatives became pH independent. The intersection of the two linear portions, at pH 10.35 for *p*-OCH_3 and at pH 10.25 for *p*-CH_3, respectively, were observed at somewhat smaller pH values than corresponds to pK_Σ. For the other derivatives, the adsorption prewaves that were present at pH > pK made the measured values of half-wave potentials less accurate and reliable at higher pH values.

For a study of the substituent effects, the half-wave potentials measured at any pH value below 10 were suitable, because the plots of half-wave potentials against pH were parallel in this pH region. The half-wave potentials are a linear function[8] of Hammett substituent constants $\sigma_{p\text{-}X}$ (Figure 3). The susceptibility of the molecule to substituent effects (ρ_π = 0.29 V; r = 0.983) is of the order of magnitude which would be predicted[8] (ρ_π ~0.3 V) from the ρ_π–E_0 relationship for a system where the unsubstituted parent compound is reduced at about −1.4 V *vs.* sce.

Unlike the pK_Σ values and half-wave potentials, the ratio [enol]/[keto] does not seem to show any noticeable correlation with substituent constants $\sigma_{p\text{-}X}$ (Table III). This may be due to the small variations of these ratios with substituents. The enol concentrations found in solutions containing 10% ethanol are somewhat higher than the value reported[9] for aqueous solutions. This is in agreement with the prediction of the linear free energy relationship expressing solvent effects on such equilibria.[10] Nevertheless, when the dissociation constants (Figure 4) of the keto form (K_1) and enol form (K_2) are evaluated separately as described in the introduction, the values of pK_1 (r = 0.996) and pK_2 (r = 0.998) show an excellent correlation with substituent constants $\sigma_{p\text{-}X}$. Identical values of the reaction constant (ρ = 1.84) were determined for the two reaction series.

This indicates that the introduction of a substituent exerts its predominant effect on the electron density distribution on the carbanion enolate rather than on that of either on the keto or the enol form. Comparison of the individual contributions indicates that changes in the value of the dissociation constant of the keto form are predominantly due to the changes in the value of K_Σ and are almost unaffected by the relatively small changes in the value of the [enol]/[keto] ratio.

On comparing the results presented here with the fractions of the keto form reported[11] in neat substituted ethyl benzoylacetates, it can be concluded that the larger variations observed in neat compounds than in solutions are probably chiefly due to the effect of the change in solvent rather than to the substituent effect in the solute. A neat compound should be regarded as a solution of the given compound in the same compound as solvent. The role of a strong solvent effect might explain why the correlation of the log ([enol]/[keto]) was reported[11] to be better with σ_X^+ than with σ_X. Our results for dilute solutions of β-keto esters can be compared with those for dilute solutions of β-diketones.[12] Although variations in the ratios [enol]/[keto] are relatively small also for substituted benzoylacetones, the differences, *e.g.*, between the unsubstituted parent compound (34% enol form) and the *p*-chloro derivative (35.5%), are comparable with those observed for benzoylacetates (Table III). As values of K_Σ are not available for benzoylacetones, it is difficult to distinguish the origin of the individual contributions as expressed by the values of dissociation constants K_1 and K_2. Nevertheless, from the reported linear dependence of log ([enol]/[keto]) on σ (even though r is only 0.952), it is possible to assume that the variation in [enol]/[keto] ratios of β-diketones is more affected by introducing a meta or para substituent than we have found it to be for β-keto esters.

Experimental Section

Synthesis. The procedure of Rathke[13,14] has been found to be superior to Claisen condensation[15] for preparation of ethyl benzoylacetates substituted on the phenyl ring.

General Procedure. In a dry 250-ml round-bottom flask equipped with a magnetic stirrer and a mercury bubbler, 14.1 g of *N*-isopropylcyclohexylamide was added dropwise under N_2 to 30 g of a 1 *M* solution of *n*-butyllithium in hexane. After 10 min, the hexane was removed by reduced pressure and 50 ml of tetrahydrofuran was added to the residue.

After cooling in a Dry Ice–acetone bath, 4.4 g (50 mmol) of ethyl acetate was added dropwise over 5 min, followed after 10 min by 50 mmol of the substituted benzoyl chloride. After another 10 min, 30 ml of 20% HCl was quickly added to quench the reaction.

After warming to room temperature and adding enough water to dissolve the LiCl formed, the tetrahydrofuran was separated and the remaining aqueous phase was washed with ether. The combined tetrahydrofuran–ether mixture was dried and evaporated off. The residue was dissolved in 50 ml of absolute ethanol, and a saturated solution of $Cu(OAc)_2$ was added until no more precipitate formed. After filtering and washing the solid with ethanol, enough 10% acetic acid to dissolve the precipitate was added along with 50 ml of ether. The organic layer was separated off, washed with H_2O and with saturated $NaHCO_3$, and then removed by evaporation.

The residue was recrystallized from petroleum ether (bp 30–60°)–ether if solid, or distilled under reduced pressure if liquid. All compounds gave physical and spectral properties in agreement with the reported values.

The yields follow: *p*-Cl (10%), *p*-CH_3 (40%), *p*-CN (90%), *p*-OCH_3 (50%). Ethyl *p*-cyanobenzoylacetate, previously unreported, formed yellow crystals, mp 63–64° (uncorrected).

Spectra. Electronic spectra of 1 × 10^{-4} *M* aqueous solutions of ethyl benzoylacetates, containing 10% ethanol and simple borate or phosphate buffers, were recorded in a 10-mm quartz cell using

a Unicam SP800 spectrophotometer. The spectra were recorded within 2 min after preparation of the solution. The absorbance was obtained by comparison with a blank containing the particular buffer and 10% ethanol alone.

Polarography. Polarographic i-E curves were recorded in solutions placed in a Kalousek-type cell with separated reference calomel electrode, using a dropping mercury electrode with $t_1 = 3.4$ sec (at 0.0 V) and $m = 2.1$ mg/sec, by means of a Sargent-Welch Mark XVI polarograph.

Nine milliliters of a simple borate or carbonate buffer was transferred into the cell and deaerated by a stream of nitrogen for 2 min; then 1 ml of a 2×10^{-3} M stock solution of the corresponding ethyl benzoylacetate in ethanol was added. After deaeration for another 45 sec the polarographic curve was recorded. All buffer solutions were checked for impurities.

Keto-Enol Titrations. In the modified Meyer titration,[16] 50 ml of 2×10^{-3} M benzoylacetate in 10% ethanol was chilled and treated with 10 ml of a solution of bromine in 10% ethanol, followed immediately by 10 ml of a 10% solution of β-naphthol. After 2 min, 50 ml of 0.1 N potassium iodide solution was added, and the mixture was warmed up to room temperature and titrated with standard thiosulfate solution. End points tended to fade after a few minutes.

References and Notes

(1) (a) L. Meites, "Polarographic Techniques," 2nd ed, Wiley, New York, N. Y., 1965, p 132; (b) J. Heyrovský and P. Zuman, "Practical Polarography," Academic Press, London, 1968, p 32.
(2) G. Nisli, D. Barnes, and P. Zuman, *J. Chem. Soc. B*, 764 (1970).
(3) D. Barnes and P. Zuman, *Talanta*, **16**, 975 (1969).
(4) G. Schwarzenbach and E. Felder, *Helv. Chim. Acta*, **27**, 1701 (1944).
(5) P. Zuman in "Progress in Polarography," Vol. 3, P. Zuman, L. Meites, and I. M. Kolthoff, Ed., Wiley, New York, N. Y., 1972, p 73.
(6) G. Nisli, D. Barnes, and P. Zuman, *J. Chem. Soc. B*, 778 (1970).
(7) S. G. Majranovskij, "Catalytic and Kinetic Waves in Polarography," Plenum Press, New York, N. Y., 1968, p 194.
(8) P. Zuman, "Substituent Effects in Organic Polarography," Plenum Press, New York, N. Y., 1967.
(9) (a) K. H. Meyer, *Ber.*, **45**, 2843 (1912); (b) *ibid.*, **47**, 826 (1914).
(10) P. Zuman, unpublished.
(11) R. Gelin, S. Gelin, and C. H. Zambartas, *C. R. Acad. Sci., Ser. C*, **270**, 832 (1970).
(12) M. Bergon and J. P. Calmon, *C. R. Acad. Sci., Ser. C*, **273**, 181 (1971).
(13) M. W. Rathke and J. Deitch, *Tetrahedron Lett.*, 2953 (1971).
(14) M. W. Rathke and A. Lindert, *J. Amer. Chem. Soc.*, **93**, 2318 (1971).
(15) V. H. Wallingford, A. H. Homeyer, and D. M. Jones, *J. Amer. Chem. Soc.*, **63**, 2252 (1941).
(16) C. H. Ward, *J. Chem. Educ.*, **39**, 95 (1962).

Notes

Medium Effects in the Acid-Catalyzed Hydrolysis of Phenylacetohydroxamic Acid in Aqueous Sulfolane

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Received July 23, 1973

Tetramethylene sulfone (sulfolane) is a typical dipolar aprotic solvent. Inspection of the data of Tommila and coworkers[1] on aqueous sulfolane mixtures reveals a rather special relationship, namely, that these mixtures approximate regular solutions[2] in which the entropy of mixing is nearly that of ideal mixtures. This result is unexpected for mixtures of polar substances such as sulfolane and water and might lead to interesting solvent effects upon reactivity. In addition there appear to be no studies of acid-catalyzed hydrolyses in these media. Consequently, a study of the effect of aqueous sulfolane mixtures on an acid-catalyzed hydrolysis reaction has been carried out.

The kinetics of acid-catalyzed hydrolysis of phenylacetohydroxamic acid in various aqueous sulfolane mixtures has been studied and the results are listed in Table I.

The accepted mechanism[3-5] for acid-catalyzed hydrolysis of hydroxamic acids is represented by eq 1 and 2.

$$\mathrm{RCONHOH} + \mathrm{H^+} \overset{K}{\rightleftharpoons} \mathrm{R\overset{+}{C}(OH)NHOH} \quad (1)$$

$$\mathrm{R\overset{+}{C}(OH)NHOH} + \mathrm{H_2O} \xrightarrow{k_2} \mathrm{RCO_2H} + \mathrm{H_3\overset{+}{N}OH} \quad (2)$$

Under pseudo-first-order conditions (excess catalytic acid and water) the observed first-order rate constant, k, is given by eq 3 for the above mechanism where K is an

$$k = k_2 K[\mathrm{H^+}][\mathrm{H_2O}]^n \quad (3)$$

equilibrium constant and k_2 is a rate constant. The order of reaction with respect to catalytic acid has been established previously[3-5] for the conditions employed in this study. Since sulfolane is a very weak base,[6] the hydrated proton is the catalytic acid under the conditions employed. The order with respect to water, n, will be one for the above mechanism unless there is a *difference* between the number of water molecules hydrogen bonded in the transition state and in the initial state. As the concentration of water is varied (with pseudo-first-order conditions maintained) in the presence of a nonreactive cosolvent, the rate changes as a result of general solvent effects as well as a result of differing water concentrations, as shown in eq 3.

If the solvent effect is only a dielectric constant effect, then a graph of $\log k/[\mathrm{H_2O}]^n$ *vs.* the reciprocal of the dielectric constant would yield a straight line. This relationship was tested for the data at 50.5 and 70.3° for $n = 0$, 1, and 2. Dielectric constants for 50 and 70° were obtained by interpolation of the extensive data of Tommila and coworkers.[1] Curves resulted in all cases with the same trends obtained for the data at 50.5° (ionic strength 0.240 M) and at 70.3° (ionic strength 0.0479 M). Two ionic strengths were investigated, since in principle the ionic strength as well as the dielectric effect influence the reaction rates, although in practice the ionic strength effect is very small for this type of reaction and rate constants need not be extrapolated to zero ionic strength to test for dielectric constant correlations.[7] Reynaud[8] has determined pK_a values for some carboxylic acids and pK (BH^+) values for some amines in aqueous sulfolane. Graphs of his values *vs.* the reciprocal of the dielectric constant yield essentially straight-line relationships.

A possible relationship between the observed pseudo-first-order constant, k, and the mole fraction of sulfolane, N_s, in the solvent is given in eq 4 and 5 where n, a, and b are

$$\log \frac{k}{[\mathrm{H_2O}]^n} = aN_s + b \quad (4)$$

or

$$\log k = n \log[\mathrm{H_2O}] + aN_s + b \quad (5)$$

Table I
Kinetic Data for Hydrolysis of Phenylacetohydroxamic Acid in Aqueous Sulfolane

Wt % sulfolane	Mole fraction of sulfolane	[Water], *M*	[HCl], *N*	Temp, °C	$10^5 k$,[a] sec^{-1}
0	0	55.51	0.240	50.5	4.12
32.58	0.0675	39.98	0.240	50.5	4.58
52.50	0.142	29.55	0.240	50.5	5.63
70.20	0.261	19.33	0.240	50.5	8.13
95.80	0.774	2.90	0.240	50.5	23.2
0	0	55.51	0.0479	70.3	4.45
34.92	0.0744	38.46	0.0479	70.3	5.03
49.09	0.126	31.56	0.0479	70.3	5.83
67.89	0.241	20.80	0.0479	70.3	8.02
88.57	0.537	7.785	0.0479	70.3	19.8

[a] Average pseudo-first-order rate constant.

constants. A least-squares multiple regression analysis of the data at 70.3° in Table I yields a value of 0.82 for *n*, the order with respect to water. The coefficient of multiple regression for eq 5 is 1.000 to three significant figures. Figure 1 shows a graph of this data for log $k/[H_2O]$ *vs.* mole fraction sulfolane where *n* is taken to be 1. An excellent linear relationship results. This represents a range of 0–88.6 wt % sulfolane (0–0.54 mol fraction sulfolane). A graph of log $k/[H_2O]$ *vs.* mole fraction sulfolane for the data at 50.5° (0–95.8 wt %, 0–0.77 mol fraction sulfolane) is linear but not as exact as Figure 1.

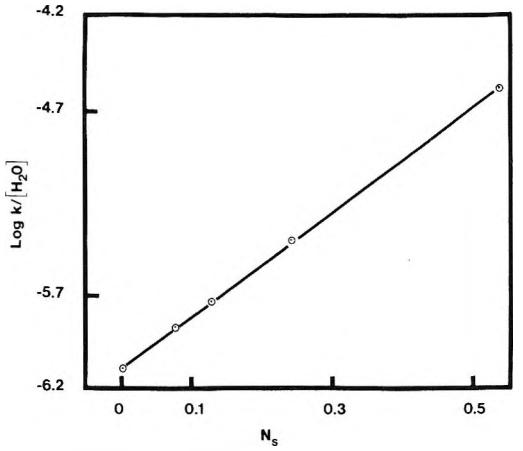

Figure 1. Log $k/[H_2O]$ as a function of mole fraction of sulfolane for hydrolysis of phenylacetohydroxamic acid in aqueous sulfolane mixtures 0.0479 *N* with respect to HCl at 70.3°.

Equation 4 is a linear free-energy relationship. Koppel and Palm[9] have discussed in detail linear free-energy relationships in solvent effects. A linear relationship between log *k* and the mole fraction of one component of a binary solvent system is predicted under certain conditions, namely, that the nonspecific and specific solvent–solute interactions of each solvent component are invariable (including the absence of shifts in solvation equilibria) throughout the range of solvent composition involved. Koppel and Palm[9] consider two types of nonspecific solvent effects, dielectric effects and polarizability interactions. Since a linear relationship between log $k/[H_2O]$ and the reciprocal of the dielectric constant does not exist for this system (see above) and since the reciprocal of the dielectric constant is not linear in mole fraction sulfolane, dielectric effects can be discounted in the system reported herein.

It is noteworthy that linear relationships between log *k* and mole fraction sulfolane are not evident in the alkaline hydrolysis of dimethylacetylacetone[10] or in the alkaline hydrolysis of benzoate esters[11] in aqueous sulfolane.

Experimental Section

Phenylacetohydroxamic acid has been described previously.[5] Sulfolane was distilled at low pressure from sodium hydroxide pellets, $n^{30}D$ 1.4816 (lit.[12] 1.4820). All solutions were prepared with double-distilled water with concentrations referred to ambient temperature. The kinetic measurements were made and the rate constants were calculated as described before.[5] Initial concentration of phenylacetohydroxamic acid for rate measurements at 50.5° was 0.0120 *M* and for those at 70.3° was 0.00600 *M*. Average deviation from the mean for average rate constants in Table I is less than 1.5%.

Registry No.—Phenylacetohydroxamic acid, 5330-97-2.

References and Notes

(1) E. Tommila, E. Lindell, M. Virtalaine, and R. Laakso, *Suom. Kemistilehti B*, **42**, 95 (1969).
(2) J. H. Hildebrand and R. L. Scott, "Regular Solutions," Prentice-Hall, Englewood Cliffs, N. J., 1962.
(3) D. C. Berndt and R. L. Fuller, *J. Org. Chem.*, **31**, 3312 (1966).
(4) A. J. Buglass, K. Hudson, and J. G. Tillett, *J. Chem. Soc. B*, 123 (1971).
(5) D. C. Berndt and J. K. Sharp, *J. Org. Chem.*, **38**, 396 (1973).
(6) S. K. Hall and E. A. Robinson, *Can. J. Chem.*, **42**, 1113 (1964).
(7) E. S. Amis, "Solvent Effects on Reaction Rates and Mechanisms," Academic Press, New York, N. Y., 1966, p 33.
(8) R. Reynaud, *Bull. Soc. Chim. Fr.*, 4597 (1967).
(9) I. A. Koppel and V. A. Palm, "Advances in Linear Free Energy Relationships," N. B. Chapman and J. Shorter, Ed., Plenum Press, New York, N. Y., 1972, Chapter 5.
(10) J. P. Calmon and J. L. Canavy, *J. Chem. Soc., Perkin Trans. 2*, 972 (1972).
(11) E. Tommila and J. Martinmaa, *Suom. Kemistilehti B*, **40**, 216 (1967).
(12) J. W. Vaughn and C. F. Hawkins, *J. Chem. Eng. Data*, **9**, 140 (1964).

Proximity Effects. Correlation of Ortho-Substituted Benzohydroxamic Acid Reactivities[1]

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Received October 2, 1973

The role of ortho substituents in chemical reactivity is complicated by several factors which may contribute to the reactivity effect of these substituents.[2,3] Empirical correlation schemes are useful for systematizing the data and for comparison of effects in related systems which will lead to further understanding of reactivity parameters and reaction mechanisms. The Pavelich–Taft equation (eq 1)

$$\log k/k_o = \rho^*\sigma^* + \delta E_s \qquad (1)$$

is based upon reactions of esters and was developed for analysis of systems in which steric effects are expected to be present.[2,3]

Table I
Hydrolysis Rates of 2-Substituted Benzohydroxamic Acids in 0.605 *M* Hydrochloric Acid at 90.0°

Registry no.	2 Substituent	$10^5 k$[a]	−Log k	−Log k (calcd)[b]
31791-97-6	Methoxy	21.5	3.668	3.669
50357-86-3	Ethoxy	16.4	3.785	3.772
17512-73-1	Methyl	2.53	4.597	4.611
17512-69-5	Chloro	1.82	4.740	4.796
50357-88-5	Bromo	1.00	5.000	4.941

[a] Average pseudo-first-order rate constant, sec^{-1}. [b] Calculated from eq 4.

In eq 1, σ^* is the polar contribution and E_s the steric contribution of the substituent to relative reactivity. ρ^* and δ are proportionality constants which indicate the susceptibility of the reaction system to the substituent effects measured by the σ^* and E_s parameters, respectively. Equation 1 has been successfully applied to various aliphatic and ortho-substituted benzene systems (with ρ^* *or* δ equal to zero in some instances) and has been the subject of a recent review.[2]

The acid-catalyzed hydrolyses of aliphatic amides[4] and ortho-substituted benzamides[5] are well correlated by the E_s parameter alone; *i.e.*, polar effects are zero or nearly so in these systems. Reactivities in the acid-catalyzed hydrolysis of a series of aliphatic hydroxamic acids were recently determined and are not correlated by E_s alone.[6] Equation 1 provides a fair correlation between these reactivities and σ^* and E_s with ρ^* and δ of comparable magnitude but of opposite sign. Consequently, polar effects are not zero in the acidic hydrolysis of aliphatic hydroxamic acids[6] in contrast to the amide hydrolyses.

Equation 1 should be applicable to the hydrolysis of acyl compounds following the bimolecular mechanism[2,3] which is the accepted mechanism for the hydrolysis of amides[7] and hydroxamic[6,8,9] acids (eq 2 and 3) at moderate acidity.

$$RCONHOH + H^+ \rightleftharpoons R\overset{+}{C}(OH)NHOH \quad (2)$$

$$R\overset{+}{C}(OH)NHOH + H_2O \longrightarrow RCO_2H + H_3\overset{+}{N}OH \quad (3)$$

This paper reports a study of the acid-catalyzed hydrolysis of a series of ortho-substituted benzohydroxamic acids at moderate acidity. The results are in Table I. Included are log k values calculated from eq 4 where k is a pseudo-first-order rate constant directly proportional to the catalytic acid concentration under these conditions.[6,8,9]

$$\log k = -0.868\sigma_o^* + 0.759E_s - 4.611 \quad (4)$$

The parameters of eq 4 were calculated by the method of least squares.[10] The ortho methyl group is the reference substituent with the ortho polar substituent constant, σ_o^*, scale[3] adjusted accordingly (range −0.22 to +0.38). E_s values (range 0–0.99) for ortho substituents[3] with methyl as the reference substituent are applied in eq 4. The correlation coefficient[10] is 0.998. The F test[10] for statistical significance indicates that the correlation by eq 4 is significant at the 1% level, a very satisfactory result. Figure 1 illustrates the correlation graphically.

The correlation by eq 4 extends the range of usefulness of eq 1 as well as indicating that eq 1 is applicable to hydroxamic acid reactivities and that the substituent effects studied in this system are adequately represented by the σ_o^* and E_s parameters. Since $\rho^*\sigma_o^*$ and δE_s measure the contribution of polar and steric effects, respectively, these quantities may be used to compare polar and steric effects of the substituents *relative* to methyl. Examination of these quantities reveals that the polar effect is greater

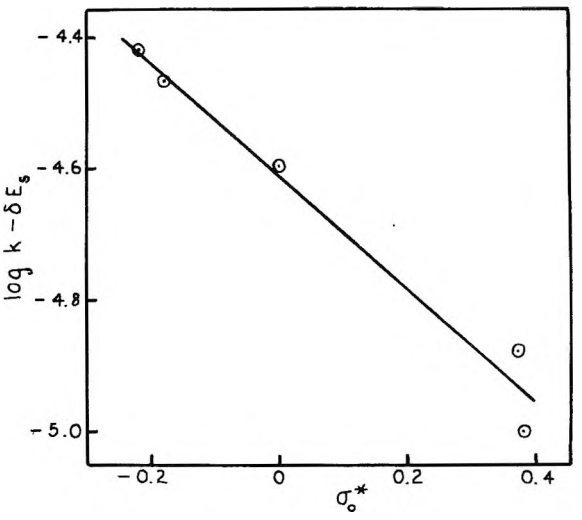

Figure 1. Experimental log k corrected for steric effects, δE_s, plotted as a function of σ_o^*. The line is the least-squares line (eq 4).

than the steric effect for chloro and bromo while the reverse is true for the methoxy and ethoxy substituents *relative* to methyl. This result is in contrast to the acid-catalyzed hydrolysis of amides,[4,5] in which only steric effects as measured by E_s are significant.

The rate constants in Table I are overall rate constants, *i.e.*, a composite for steps 2 and 3; consequently, ρ^* and δ are for the overall process. Since $\rho^* < 0$ in eq 4, electron-donating groups accelerate the rate compared to that of the reference compound, 2-methylbenzohydroxamic acid. This is consistent with the greater electronegativity of hydroxyl compared to hydrogen in changing from amides to hydroxamic acids, provided that the polar effect on the protonation step (eq 2) is greater than the polar effect for nucleophilic attack by water on the protonated intermediate (eq 3). The positive value of δ means that the rate is decelerated as E_s becomes smaller; smaller E_s values presumably correspond to increasing effective steric bulk,[2,3] although a resonance contribution is probably present.[2] In any event, the substituent effects in the present system parallel those in the system which defines σ_o^* and E_s. Analogous results with respect to polar and steric effects were observed in the acid-catalyzed hydrolysis of aliphatic hydroxamic acids.[6]

Experimental Section

All hydroxamic acids exhibited positive ferric chloride tests. All analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

2-Chloro- and 2-methylbenzohydroxamic acids were prepared from the corresponding substituted benzoyl chlorides according to the method of Jones and Hurd.[11] 2-Chlorobenzohydroxamic acid, crystallized from toluene, had mp 159.5–160.1 (lit.[12] mp 158–159°). 2-Methylbenzohydroxamic acid, crystallized from ethyl acetate, had mp 130.5–131°. *Anal.* Calcd for $C_8H_9NO_2$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.82; H, 6.14; N, 9.18.

2-Bromo-, 2-methoxy-, and 2-ethoxybenzohydroxamic acids were prepared from the correspondingly substituted methyl benzoates by adaptations of the "Organic Syntheses" procedure[13] and crystallized from 3:7 (v/v) ethanol–water. 2-Bromobenzohydroxamic acid had mp 177.5–178.5° (lit.[12] mp 178–180°). 2-Methoxybenzohydroxamic acid had mp 124–126°. *Anal.* Calcd for $C_8H_9NO_3$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.65; H, 5.28; N, 8.44. 2-Ethoxybenzohydroxamic acid had mp 124–125.5°. *Anal.* Calcd for $C_9H_{11}NO_3$: C, 59.65; H, 6.13; N, 7.73. Found: C, 59.76; H, 6.29; N, 7.66.

The 0.605 *M* hydrochloric acid was prepared from double-distilled water and standardized by titration. The kinetic measurements were made by the spectrophotometric method reported previously[8] employing a Beckman DU spectrophotometer set at 520 nm. Pseudo-first-order rate constants were obtained from the

slope of the appropriate graph[8] with the numerical values computed by least squares.

The rate constants in Table I are the average of three to four runs for each compound. Average deviation from the mean is less than 4.5%. Temperature control was ±0.05°. Initial concentration of hydroxamic acids in the kinetics runs was 0.012 *M*.

Acknowledgment. The authors wish to thank J. R. McDowell for the preparation of two hydroxamic acids.

References and Notes

(1) Abstracted from the M.A. theses of I. E. W., Western Michigan University, 1973.
(2) J. Shorter in "Advances in Linear Free Energy Relationships," J. Shorter and N. B. Chapman, Ed., Plenum Press, New York, N. Y., 1972, Chapter 2.
(3) R. W. Taft, Jr., "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y. 1956, Chapter 13.
(4) P. D. Bolton and G. L. Jackson, *Aust. J. Chem.*, **24**, 471 (1971).
(5) R. W. Taft, Jr., *J. Amer. Chem. Soc.*, **75**, 4538 (1953).
(6) D. C. Berndt and J. K. Sharp, *J. Org. Chem.*, **38**, 396 (1973).
(7) C. O'Connor, *Quart. Rev., Chem. Soc.*, **24**, 553 (1970).
(8) D. C. Berndt and R. L. Fuller, *J. Org. Chem.*, **31**, 3312 (1966).
(9) A. J. Buglass, K. Hudson, and J. G. Tillett, *J. Chem. Soc. B*, 123 (1971).
(10) D. A. Leabo, "Basic Statistics," 4th ed, Richard D. Irwin, Inc., Homewood, Ill., 1972, Chapter 16.
(11) L. W. Jones and C. D. Hurd, *J. Amer. Chem. Soc.*, **43**, 2447 (1921).
(12) K. Buraczewski, E. Czerwinska, Z. Eckstein, E. Grochowski, R. Kowalik, and J. Plenkiewicz, *Bull. Acad. Pol. Sci., Ser. Sci. Chim.*, **12**, 773 (1964).
(13) C. R. Hauser and W. B. Renfrow, Jr., "Organic Syntheses," Collect. Vol. II, E. H. Blatt, Ed., Wiley, New York, N. Y., 1943, p 67.

Skipped Diynes. IV. Diacetylenic Ketone Reactions[1]

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Received June 5, 1973

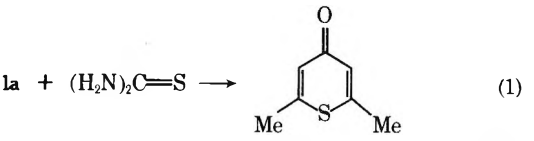
Ketones with geminal triple bonds (1) are vulnerable to attack at several sites. As is the case with the more common monoethynyl ketones, additions of nucleophiles,[2-10] electrophiles,[11,12] dienes,[2] and dipolarophiles[13] to 1 have been observed. These were particularly interesting to us when both ethynyl groups became involved in conversions to families such as cyclopentenones, thiolenones, (5-triazolyl)isoxazoles, (pyrazolyl)pyrazoles, etc.[2,7] To expand this still relatively unfamiliar area, we investigated the chemistry of 1 with emphasis on **1a**.

$(RC{\equiv}C)_2C{=}O$

1a, R = CH_3
b, R = C_6H_5

Those reactions of **1a** which proceed as expected will simply be mentioned, while those with new features will be described.[2,3,6] Thus, with primary or secondary amines, **1a** yields isolable monoadducts which may be cyclized to pyridones; with hydrazines and **1a**, the monoadduct may not always be isolable but the cyclization can usually be made to take place; with thiols, **1a** yields symmetrical diadducts; with tetracyclone, **1a** forms a Diels–Alder monoadduct.

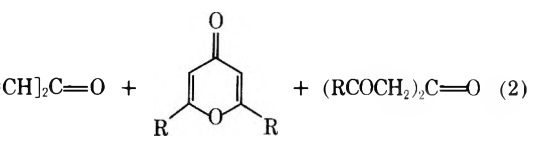
The reaction of diethynyl ketones with thiourea and substituted thioureas occurs readily but often unpredictably. Penta-1,4-diyn-3-one is reported to react with *N,N'*-diphenylthiourea to give an adduct of unspecified structure.[5] Compound **1b** reacted with both thiourea and *N,N'*-diphenylthiourea to give the same dihydrothiophene derivative,[2] but **1a** reacted with thiourea to give 2,6-dimethyl-4*H*-thiopyran-4-one as the only isolable product (eq 1).



(1)

Our reaction conditions are quite different from the formally similar addition of hydrogen sulfide to **1b**, which proceeds in a bomb at 180° to give an analogous thiopyranone.[11]

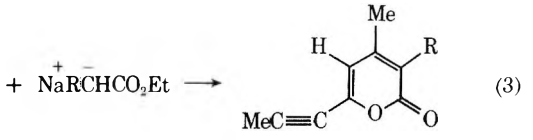
While not defined in every detail, the course of the additions of alcohols or water to 1 has been clarified. With **1b** Russian workers have recently shown that a monoalkoxy adduct of 1 as well as the products of eq 2 may be formed.[4] In the presence of acid the γ-pyrone is generally the major product.[12]



(2)

When **1a** was treated with sodium ethoxide in ethanol, the only isolable product was 2,6-diethoxyhepta-2,5-dien-4-one, but with sodium methoxide in methanol, a 3:2 mixture of 2,6-dimethyl-4-pyrone and 2,6-dimethoxyhepta-2,5-dien-4-one was produced. The pyrone presumably arises from the slow acid-catalyzed hydrolysis of the bis(enol) ether to 2,4,6-heptanetrione, which then spontaneously condenses under the reaction conditions to give the pyrone. Indeed, **1a** yields 2,6-dimethyl-4-pyrone upon treatment with aqueous acid.[12]

Additions of Grignard reagents to the carbonyl group are possible, but additions of other carbon nucleophiles to 1 have varying success.[2,9] In the case of **1a** these additions are usually foiled by its sensitivity to the strongly basic conditions usually employed in such reactions. This problem was circumvented by employing inverse addition of the anions of diethyl malonate and ethyl cyanoacetate in solution to a cold solution of **1a**.



(3)

R = CO_2Et, CN

The mode of attack and the resulting products are typical of monoethynyl ketones.[2] Under similar reaction conditions, **1b** reacts with carbon nucleophiles to give exclusively cyclopentenones.[2]

Experimental Section

For general details see ref 1, 2, and 14. **1a** had mp 80–81° (lit.[6a] mp 78–80°); ir (CCl_4) 2260, 2230, 1630 cm^{-1}; nmr (CCl_4) δ 2.05 (s, 6 H). **1b** had mp 65° (lit.[2] mp 64–66°); ir (CCl_4) 2240, 2180, 1605 cm^{-1}.

3-Propynyl-5-methylpyrazole. To a solution of **1a** (0.5 g) in 10 ml of methanol at 0°, hydrazine hydrate (1 ml) was added dropwise. Work-up followed by chromatography (twice) on silica gel with ether–chloroform (2:1, v/v) gave a yellow solid: mp 93.5–94.5°; ir ($CHCl_3$) 3490 (NH), 2230 (C≡C), 1580, 1465, 1410 cm^{-1}; nmr ($CDCl_3$) δ 2.0 (s, 3 H), 2.4 (s, 3 H), 6.0 (s, 1 H), 12.1 (broad, 1 H).

Anal. Calcd for $C_7H_8N_2$: C, 69.97; H, 6.76. Found: C, 69.86; H, 6.75.

2,4-Dinitrophenylhydrazone of 1a, as orange needles from ethyl acetate, had mp 201–203°; ir (KBr) 3220 (NH), 2220 (C≡C), 1618 cm^{-1} (C=N); nmr ($CDCl_3$) δ 2.1 (s, 3 H), 2.3 (s, 3 H), 8.6 (m, 3 H), 12.0 (broad, 1 H).

Anal. Calcd for $C_{13}H_{10}N_4O_4$: C, 54.54; H, 3.57. Found: C, 54.55; H, 3.05.

1-(2,4-Dinitrophenyl)-3-propynyl-5-methylpyrazole. A solu-

tion of sodium methoxide (0.2 g) in methanol (20 ml) and the above DNP (0.25 g) was heated to boiling. Water (10 ml) precipitated a solid which was recrystallized twice from absolute ethanol to give silky yellow needles (0.2 g): mp 137–139°; ir (KBr) 2230, 1610, 1550 cm^{-1}; nmr ($CDCl_3$) δ 2.0 (s, 3 H), 2.2 (s, 3 H), 6.4 (s, 1 H), 8.12 (m, 3 H).

Anal. Calcd for $C_{13}H_{10}N_4O_4$: C, 54.54; H, 3.57. Found: C, 54.33; H, 3.36.

2-(o-Carboxyanilino)-hept-2-en-5-yn-4-one. A solution of **1a** (0.5 g) and anthranilic acid (0.64 g) in absolute ethanol was refluxed for 1 hr. Work-up and recrystallization from chloroform gave a yellow solid whose melting point could not be determined since ring closure to the pyridone occurred on slow heating: ir (KBr) 2240, 2280 (C≡C), 1700 (CO_2H), 1610 (C=O), 1570 cm^{-1} (C=C); nmr (DMSO) δ 2.0 (s, 6 H), 5.5 (s, 1 H), 7.6 (m, 4 H), 8.3 (s, 1 H), 12.9 (broad, 1 H).

Anal. Calcd for $C_{14}H_{13}NO_3$: C, 69.13; H, 5.39. Found: C, 68.77; H, 5.23.

***N*-(o-Carboxyphenyl)-2,6-dimethyl-4-pyridone.** 2-(o-Carboxyanilino)-hept-2-en-5-yn-4-one (0.5 g) was suspended in xylene (50 ml) and refluxed for 4 hr. Filtration of the cooled reaction mixture gave white crystals (0.5 g) from methanol: mp 360° dec; ir (KBr) 3100 (OH), 1690 (CO_2H), 1650 cm^{-1} (C=O); nmr (H_2SO_4, external TMS) δ 2.8 (s), 7.7 (s), 8.6 (m): neut equiv 244 ± 2.

Anal. Calcd for $C_{14}H_{13}NO_3$: C, 69.13; H, 5.39. Found: C, 69.09; H, 5.30.

***N*-(m-Carboxyphenyl)-2,6-dimethyl-4-pyridone.** Dipropynyl ketone (0.25 g) and *m*-aminobenzoic acid (0.34 g) were dissolved in absolute ethanol and heated at *ca.* 65° for 20 min. Removal of the solvent gave a nearly quantitative yield of the adduct, 2-(*m*-carboxyanilino)hept-2-en-5-yn-4-one: mp 143–145°; ir (KBr) 2260, 2230 (C≡C), 1690 (CO_2H), 1620 (C=O), 1570 cm^{-1} (C=C). This adduct (0.5 g) was heated as a suspension in refluxing xylene (30 ml) for 6 hr. Filtration of the cooled reaction mixture gave a gray solid: mp 333° dec from methanol; ir (KBr) 3100 (OH), 1710 (CO_2H), 1640 cm^{-1} (C=O); nmr (H_2SO_4, external TMS) δ 2.9 (s), 7.8 (s), 8.5 (m), 9.0 (m); neut equiv 242 ± 2.

Anal. Calcd for $C_{14}H_{13}NO_3$: C, 69.13; H, 5.39. Found: C, 69.13; H, 5.23.

2-(3,4-Xylidino)-hept-2-en-5-yn-4-one. A solution of **1a** (0.4 g) and 3,4-xylidine (0.48 g) in 30 ml of absolute ethanol was boiled on a steam bath for 5 min. On cooling in ice, 0.95 g of a solid was deposited. Two recrystallizations from ethanol (Norit) gave yellow needles (0.6 g): mp 107.5–108.5°; ir (KBr) 2280, 2240 (C≡C), 1595 (C=O), 1540 cm^{-1} (C=C); nmr ($CDCl_3$) δ 1.95 (s, 6 H), 2.25 (s, 6 H), 5.3 (s, 1 H), 7.0 (m, 3 H), 12.4 (broad, 1 H).

Anal. Calcd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54. Found: C, 79.36; H, 7.25.

***N*-(3,4-Dimethylphenyl)-2,6-dimethyl-4-pyridone.** 2-(3,4-Xylidino)-hept-2-en-5-yn-4-one (0.3 g) in 20 ml of xylene was refluxed for 19 hr and the resulting solution was cooled and poured into ligroin at 0°. This yielded 0.3 g of a white-gray solid: mp 199–200°; ir (KBr) 1645 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.95 (s, 6 H), 2.35 (s, 6 H), 6.2 (s, 2 H), 7.1 (m, 3 H).

Anal. Calcd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54. Found: C, 79.18; H, 7.25.

2,6-Bis(o-aminobenzenethio)hepta-2,5-dien-4-one. Dipropynyl ketone (0.25 g) and o-aminobenzenethiol (0.65 g) were dissolved in 20 ml of methanol. To this solution was added dropwise with stirring 1 ml of a saturated solution of sodium methoxide in methanol. Within seconds, a light yellow solid precipitated out. The solid was collected and recrystallized twice from absolute ethanol to give 0.4 g of yellow needles which melted at 154–160°, presumably because of cis–trans isomerization: ir ($CHCl_3$) 3500, 3400 (NH), 1615 (C=O), 1560 cm^{-1} (C=C); nmr ($CDCl_3$) δ 1.9 (d, 6 H), 4.05 (broad, 4 H), 6.3 (q, 2 H), 6.75 (m, 4 H), 7.25 (m, 4 H).

Anal. Calcd for $C_{19}H_{20}N_2S_2O$: C, 64.0; H, 5.66. Found: C, 63.84; H, 5.71.

2,6-Bis(*p*-tolylthio)hepta-2,5-dien-4-one. This compound, which isomerizes on heating to 130°, was prepared in the same manner as above: mp 188–189°; ir ($CHCl_3$) 1625 (C=O), 1560 cm^{-1} (C=C); nmr ($CDCl_3$) δ 1.9 (d, 6 H), 2.4 (s, 6 H), 6.25 (q, 2 H), 7.25 (m, 8 H).

Anal. Calcd for $C_{21}H_{22}S_2O$: C, 71.14; H, 6.26. Found: C, 71.13; H, 6.12.

2,6-Bis(*p*-chlorobenzenethio)hepta-2,5-dien-4-one. This compound, which isomerizes on heating to 130°, was prepared in the same manner as above: mp 187–188°; ir ($CHCl_3$) 1630 (C=O), 1560 cm^{-1} (C=C); nmr ($CDCl_3$) δ 1.9 (d, 6 H), 6.35 (q, 2 H), 7.45 (m, 8 H).

Anal. Calcd for $C_{19}H_{16}Cl_2S_2O$: C, 57.72; H, 4.08. Found: C, 57.57; H, 4.01.

2,6-Diethoxyhepta-2,5-dien-4-one. To a freshly prepared solution of sodium ethoxide (0.4 g of sodium metal in 20 ml of absolute ethanol) was added dropwise a solution of **1a** (0.75 g) in 15 ml of absolute ethanol. The resulting solution was refluxed for 8 hr and then poured into ice water. Vigorous stirring of this mixture produced a precipitate which was then filtered off and recrystallized from chloroform–ligroin. Two further recrystallizations from isopropyl alcohol–water gave white needles: mp 91–93°; ir ($CHCl_3$) 1665 (C=O), 1585 (C=C), 1068 cm^{-1} (C=CO); nmr ($CDCl_3$) δ 1.35 (t, 3 H), 2.3 (s, 6 H), 3.85 (q, 4 H), 5.4 (s, 2 H).

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.65; H, 9.15. Found: C, 66.99; H, 9.34.

2,6-Dimethoxyhepta-2,5-dien-4-one and 2,6-Dimethyl-4-pyrone. A solution of **1a** (0.5 g) in 30 ml of freshly prepared methanolic sodium methoxide (0.2 g of Na) was refluxed for 24 hr and then poured into water. Ether extraction gave a yellow oil which proved to be an inseparable mixture of dienone and pyrone. The dienone had nmr ($CDCl_3$) δ 2.35 (s, 6 H), 3.65 (s, 6 H), 5.14 (s, 2 H); the pyrone[12] had nmr ($CDCl_3$) δ 2.25 (s, 6 H), 6.06 (s, 2 H).

2,6-Dimethyl-4*H*-thiapyran-4-one. A solution of **1a** (0.5 g) and thiourea (0.35 g) in 15 ml of dry DMF was allowed to stand at room temperature for 14 hr. The reaction mixture was then poured into ice water and extracted with chloroform. Work-up yielded a reddish-brown semisolid, which after two sublimations at 75° (0.3 mm) gave a solid: mp 104° (lit.[15] mp 104°); ir (CCl_4) 1625 (C=O), 1595 cm^{-1} (C=C); nmr ($CDCl_3$) δ 2.35 (s, 6 H), 6.7 (s, 2 H).

4-Methylhepta-2,5-diyn-4-ol. A freshly prepared solution of methylmagnesium iodide (10 mmol, 1.58 g, prepared from 0.25 g of magnesium metal and 1.34 g of iodomethane) in ether was added dropwise to a solution of **1a** (1.0 g, 10 mmol) in ether at 0°. The resulting yellow-brown suspension was then refluxed for 30 min and poured into an excess of cold, saturated ammonium chloride solution. Work-up gave white needles (0.3 g): mp 37–38° from ligroin–carbon tetrachloride (lit.[9,10] mp 35°); ir (CCl_4) 3675 (free OH), 3435 (H-bonded OH), 2275 (C≡C), 1230, 1325 cm^{-1} (CO); nmr (CCl_4) δ 1.62 (s, 3 H), 1.83 (s, 6 H), 3.08 (broad, 1 H).

3-Cyano-4-methyl-6-propynyl-2*H*-pyran-2-one. A solution of freshly prepared sodioethyl cyanoacetate [ethyl cyanoacetate (0.54 g) and excess sodium hydride (50% dispersion in oil, washed with pentane before use)] in benzene–DMF (1:1) was added dropwise to a solution of **1a** (0.5 g) in dry benzene (10 ml) at 5°. The dark red solution was stirred at 25° for 90 min, poured into ice-cold 2% acetic acid, and extracted with chloroform (3 × 100 ml). The extracts were washed in turn with water, saturated sodium bicarbonate, and saturated salt solution and finally filtered through anhydrous sodium sulfate. Removal of the chloroform yielded a viscous, dark red oil which was chromatographed on silica gel with chloroform as the eluting solvent. The middle fractions gave a reddish solid, which on recrystallization from ligroin–chloroform and sublimation at 95° (0.5 mm) yielded a yellow solid: mp 137–138°; ir ($CHCl_3$) 2265, 2250 (C≡N, C≡C), 1745 (C=O), 1615, 1540 (C=C), 1120 (=CO), 640 cm^{-1} (cis C=C); nmr ($CDCl_3$) δ 2.2 (s, 3 H), 2.45 (s, 3 H), 6.65 (s, 1 H).

Anal. Calcd for $C_{10}H_7NO_2$: C, 69.36; H, 4.08. Found: C, 69.12; H, 4.12.

3-Carboethoxy-4-methyl-6-propynyl-2*H*-pyran-2-one. A freshly prepared solution of diethylsodio malonate [0.8 g of diethyl malonate and 0.3 g of sodium hydride dispersion (50% in oil, washed with pentane before use)] in dry benzene was added dropwise to a solution of **1a** (0.5 g) in benzene at 5° under a nitrogen atmosphere. When the addition was completed, the mixture was stirred at 5° for 30 min and then poured into cold 2% acetic acid. Work-up yielded a red oil which was chromatographed on silica gel with ligroin–ethyl acetate (2:1) as the eluting solvent. The late fractions yielded the pure pyranone as a yellow oil: ir (CCl_4) 2225 (C≡C), 1745 (C=O), 1630 (C=C), 1265 cm^{-1} (CO); nmr ($CDCl_3$) δ 1.37 (t, 3 H), 2.07 (s, 3 H), 2.2 (s, 3 H), 4.38 (q, 2 H), 6.2 (s, 1 H); mass spectrum *m/e* (rel intensity) 220 (P^+, 70), 192 (100), 175 (70), 164 (70), 148 (50), 120 (50).

1-(2-Methyl-3,4,5,6-tetraphenylphenyl)-but-2-yn-1-one. Dipropynyl ketone (1.0 g) and tetracyclone (3.85 g) were refluxed in o-dichlorobenzene under nitrogen for 24 hr. The reaction mixture was then poured into 100 ml of hexane, cooled to −80° for 5 min, and then allowed to stand at 0° for 1 hr. The solid (2 g) which deposited was recrystallized from hexane–dichloromethane to give 1.0 g of an off-white solid: mp 234–235°; ir (KBr) 2200 (C≡C), 1650 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.78 (s, 3 H), 2.16 (s, 3 H), 6.78 (d, 10 H), 7.07 (s, 10 H); uv (99.5% ethanol) λ_{max} 280 nm (ϵ

7300), 236 (33,200).

Anal. Calcd for $C_{35}H_{26}O$: C, 90.87; H, 5.67. Found: C, 90.79; H, 5.94.

1-(Pentaphenylphenyl)-3-phenylprop-2-yn-1-one. Diphenyl ethynyl ketone (1.15 g) and tetracyclone (1.9 g) were refluxed in *o*-dichlorobenzene under nitrogen for 24 hr. The resulting brown-red solution was cooled to 25°, poured into cold hexane (100 ml), and kept at 0° for 2 hr. The brown solid which precipitated was recrystallized several times from dichloromethane–methanol to give 1.0 g of an off-white solid: mp 279–281°; ir (KBr) 2210 (C≡C), 1645 cm^{-1} (C=O); nmr ($CDCl_3$) δ 6.86, 7.1, 7.25 (m, 10 H); uv (ethanol) λ_{max} 310 nm (ε 12,400), 280 (20,500), 240 (51,700), 226 (49,000); mol wt (osmometric in benzene) 585 (calcd, 587).

Anal. Calcd for $C_{45}H_{30}O$: C, 92.12; H, 5.15. Found: C, 91.95; H, 5.14.

Registry No.—**1a**, 34793-66-3; **1a** 2,4-DNP, 50278-05-2; **1b**, 15814-30-9; 3-propynyl-5-methylpyrazole, 50278-07-4; hydrazine hydrate, 10217-52-4; 2,4-dinitrophenyl)-3-propynyl-5-methylpyrazole, 50278-08-5; 2-(*o*-carboxyanilino)hept-2-en-5-yn-4-one, 50278-09-6; anthranilic acid, 118-92-3; *N*-(*o*-carboxyphenyl)-2,6-dimethyl-4-pyridone, 50278-10-9; *m*-aminobenzolic acid, 99-05-8; *N*-(*m*-carboxyphenyl)-2,6-dimethyl-4-pyridone, 50278-11-0; 2-(*m*-carboxyanilino)hept-2-en-5-yn-4-one, 50278-12-1; 2-(3,4-xylidino)-hept-2-en-5-yn-4-one, 50278-13-2; 3,4-xylidine, 95-64-7; *N*-(3,4-dimethylphenyl)-2,6-dimethylpyridone, 50278-14-3; 2,6-bis(*o*-aminobenzenethio)hepta-2,5-dien-4-one, 50278-15-4; *o*-aminobenzenethiol, 137-07-5; 2,6-bis(*p*-tolylthio)hepta-2,5-dien-4-one, 50278-16-5; *p*-toluenethiol, 106-45-6; 2,6-bis(*p*-chlorobenzenethio)hepta-2,5-dien-4-one, 50278-17-6; *p*-chlorobenzenethiol, 106-54-6; 2,6-diethoxy-2,5-dien-4-one, 50278-18-7; 2,6-dimethoxy-2,5-dien-4-one, 50278-19-8; 2,6-dimethyl-4-pyrone, 1004-36-0; 2,6-dimethyl-4*H*-thiapyran-4-one, 1073-80-9; 4-methylhepta-2,5-diyn-4-ol, 32156-89-1; iodomethane, 74-88-4; thiourea, 62-56-6; sodioethyl cyanoacetate, 18852-51-2; 3-cyano-4-methyl-6-propynyl-2*H*-pyran-2-one, 50278-24-5; diethylsodio malonate, 996-82-7; 3-carboethoxy-4-methyl-6-propynyl-2*H*-pyran-2-one, 50278-26-7; *o*-dichlorobenzene, 95-50-1; 1-(2-methyl-3,4,5,6-tetraphenyl)but-2-yn-1-one, 50278-27-8; 1-(pentaphenylphenyl)-3-phenylprop-2-yn-1-one, 50278-28-9; tetracyclone, 479-33-4.

References and Notes

(1) Abstracted from the Ph.D. thesis of K. G. M., Illinois Institute of Technology, 1973.
(2) T. Metler, A. Uchida, and S. I. Miller, *Tetrahedron*, **24**, 4285 (1968), and references cited therein. This paper may be regarded as the third of this series.
(3) H. Reimlinger and J. Vandewalle, *Justus Liebigs Ann. Chem.*, **720**, 117 (1968).
(4) L. I. Vereschagin, N. V. Sushkova, and L. P. Vologdina, *Zh. Org. Khim.*, **8**, 1376 (1972).
(5) F. Wille and R. Strasser, *Chem. Ber.*, **94**, 1606 (1961).
(6) (a) C. K. Liang, *Bull. Soc. Chim. Fr.*, 33 (1933); (b) J. Chauvelier, *ibid.*, 734 (1954).
(7) Y. Tanaka, S. Velen, and S. I. Miller, *Tetrahedron*, **29**, 3271 (1973).
(8) T. Bohm-Gossl, W. Hunsmann, L. Rohrschneider, W. M. Schneider, and W. Ziegenbein, *Chem. Ber.*, **96**, 2504 (1963).
(9) G. Iotsitch and V. Lebedev, *J. Russ. Phys. Chem. Soc.*, 42, 1494 (1910).
(10) J. Chauvelier, C. *R. Acad. Sci., Ser. C*, **212**, 793 (1941).
(11) F. Gaudemar-Bardone, *Ann. Chim. (Paris)*, **13**, 52 (1958).
(12) J. Chauvelier, C. *R. Acad. Sci., Ser. C*, **226**, 927 (1948).
(13) H. Reimlinger, J. Vandewalle, and A. van Overstraeten, *Justus Liebigs Ann. Chem.*, 720, 124 (1968).
(14) K. G. Migliorese, Y. Tanaka, and S. I. Miller, *J. Org. Chem.*, **39**, 0000 (1974).
(15) F. Arndt, E. Aron, C. Martius, and R. Schwartz, *Rev. Fac. Sci. Istanbul.* **66**, 413 (1948); *Chem. Abstr.*, **42**, 4178 (1948).

The Photochemistry of (−)-*trans*-Verbenone Epoxide

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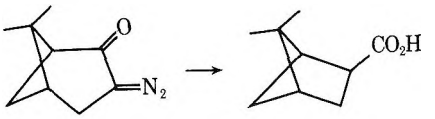
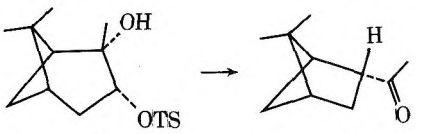
Received August 24, 1973

In pursuance of our interest in the development of methods for the synthesis of compounds of the bicyclo[2.1.1]hexane series,[1,2] we have turned our attention to the ring contraction of bicyclo[3.1.1]heptanes.

Two methods have been developed previously based on this model, one of which involved the photochemical ring contraction of the diazo ketone **1**,[3] while the other utilized the base-catalyzed rearrangement of *cis*-pinene glycol monotosylate (**2**).[4,5]



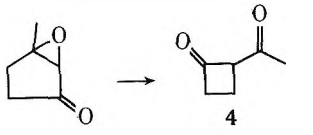
1



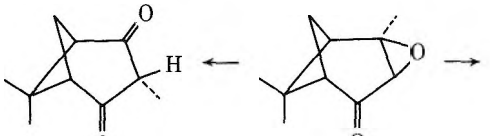
2

A reaction which has received relatively little attention as a ring contraction method is the photochemical rearrangement of α,β-epoxy ketones. Extensive studies of this reaction in steroid systems have shown that β-diketones can be generated in good yields, where product formation occurs by stereospecific shift of a β substituent to the α position.[6] Generally, yields are better in those systems which form readily enolizable β-diketones, as nonenolic diketones are relatively susceptible to further photochemical reaction by photocleavage processes.[7]

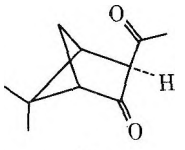
The possibility that the photochemical rearrangement of α,β-epoxy ketones might be useful for the generation of the strained bicyclo[2.1.1]hexanone ring system was supported by the reasonably efficient ring contraction of the epoxy ketone **3** to the cyclobutanone **4**.[8] Verbenone epoxide (**5**) appeared to be a convenient compound to examine as a test of the hypothesis, especially with regard to competition between transfer of the methyl group to give compound **6** and ring contraction to give **7**.



3 **4**



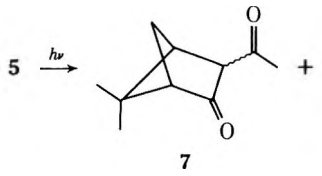
6 **5**



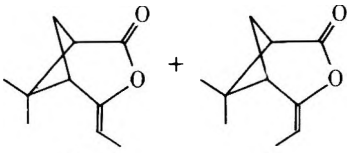
7

Results

Irradiation of a solution of (−)-**5**[9] (*ca.* 0.01 *M*) in pentane or benzene with a 450-W medium-pressure mercury arc lamp for 12 hr produced a mixture of starting material and three volatile products in 50% yield. Analysis by gas chromatography showed that starting material comprised 56% of the mixture. Isolation of the products by preparative glc and analysis by spectroscopic methods allowed the identification of the enol lactone **8** (30%), its isomer **9** (2%), and an inseparable 3:1 mixture of the ring-contracted diketones **7** (12%). The enol lactone **8**, mp 46–47°,



7

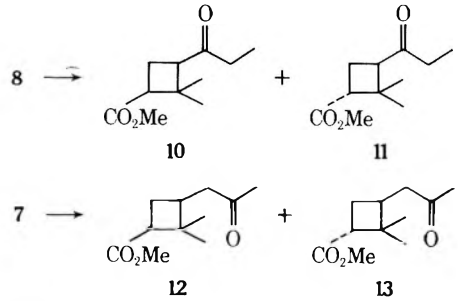


8 9

showed infrared bands at 5.61 and 5.89 μ, and nmr signals at τ 8.34 and 5.47. The latter signals, which appear as a doublet and a quartet, can be atributed to the protons of the methyl group on the double bond and to the olefinic proton, respectively. The isomeric enol lactone **9** showed similar data. The assignment of configuration to **8** and **9** is based on the chemical shifts of the olefinic protons. Using the additive increment values determined by Matter, *et al.*,[10] the chemical shifts for the olefinic protons in **8** and **9** were calculated to be τ 5.16 and 4.93, respectively. The observed values of τ 5.47 and 4.79 for the major and minor products are in relatively good agreement with these values.

The mixture of isomers **7** showed two maxima in the carbonyl region of the infrared spectrum at 5.68 and 5.86 μ. These values are in good agreement with those expected for the isolated carbonyl groups in the bicyclo[2.1.1]hexanone[2] and acetyl moieties, respectively. That no extensive enolization of the two carbonyl groups in **7** occurs is reasonable in view of the difficulty of introduction of a double bond into the bicyclohexane framework.[11] The presence of a mixture of epimers in **7** was indicated by the nmr spectrum, which showed, among other signals, two singlets at τ 9.03 and 9.29 with relative weights of 3:1, respectively. These are assigned to the endo methyl groups in the two isomers, but we could not find a sufficient precedent to assist in the specific assignment to the two isomers.[12] All attempts to separate the two diketones by glc methods were unsuccessful.

Further evidence for the structures of compounds **7**–**9** was obtained as follows. Treatment of the enol lactone **8**, isolated by preparative glc and contaminated with about 25% of verbenone epoxide, with sodium methoxide in anhydrous methanol produced the keto esters **10** and **11** in



10 11 12 13

good yield in a ratio of approximately 2:1. The verbenone epoxide was recovered unchanged, and its unreactivity under these conditions was confirmed by a control experiment. Treatment of the mixture of isomers **7** under similar conditions produced the keto esters **12** and **13** in a ratio of 7:3. Since the keto esters are formed under equilibrating conditions, it is expected that the pseudo-diequatorial cis isomers should predominate, and the ratios of products observed in these reactions are closely similar to those obtained in similar systems. For example, the equilibrium mixture of methyl *cis*- and *trans*-pinonate is reported to contain 75% of the cis isomer.[13] The nmr spectra of the isomeric keto esters are also in good agreement with their assignments. Subramanian and Krishna Rao have established the effects of substituents in 2,2-dimethyl 1,3-disubstituted cyclobutanes on the chemical shifts of the quaternary methyl groups.[13] Application of the rules derivable from their data to the keto esters **10**–**13** shows that in each instance the cis diequatorial isomer is formed in major amount. A detailed presentation of the spectroscopic data for all isolated compounds is given in the Experimental Section.

Table I

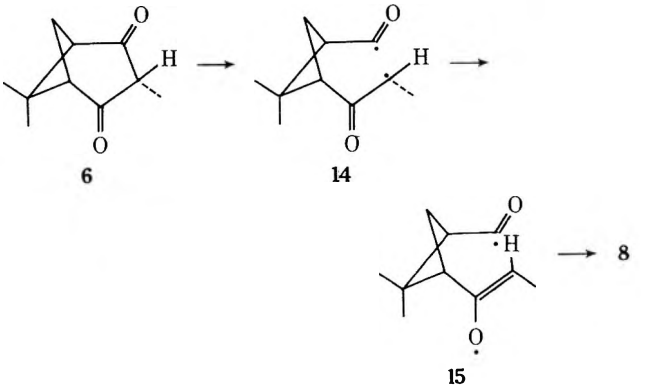
Solvent	Concn, *M*	Time, hr	Yield,[a] %	5	8	9	7
Benzene[b,c]	4.5×10^{-2}	12	50	56	30	2	12
Benzene[b,c,e]	1.6×10^{-2}	12	78	16	71	6	7
Acetonitrile[b,d,e]	4.8×10^{-2}	100	70	19	46	4	31
Acetonitrile[d,f]	3.1×10^{-2}	72	80	83			17

[a] Distilled volatile product. Relative proportions of individual products were determined by area measurement of glc peaks. [b] 450-W mercury lamp, Hanovia 679-A36. [c] Vycor. [d] Pyrex. [e] 4 equiv of 1,3-pentadiene added. [f] 300-nm lamps in Rayonet reactor.

In an effort to detect the transient formation of the diketone **6** which would result from methyl transfer, the irradiation of verbenone epoxide was carried out in the presence of a 3-molar excess of 1,3-pentadiene. Previous work on similar systems has shown that conversion of nonenolic β-diketones to enol lactones proceeds by way of the n–π^* triplet state and can be quenched by 1,3-pentadiene.[7] However, we could obtain no evidence for the formation of **6** under these conditions, although it was found that the formation of products **7**–**9** took place more cleanly and rapidly. Furthermore, when the light was filtered with a Pyrex sleeve, the rate of disappearance of verbenone epoxide dropped considerably, but the relative yield of the ring-contraction products increased. Finally, when the irradiation was performed with a bank of lamps emitting at 300 nm, only the ring-contracted diketones were formed, although very slowly. The results are presented in Table I.

Discussion

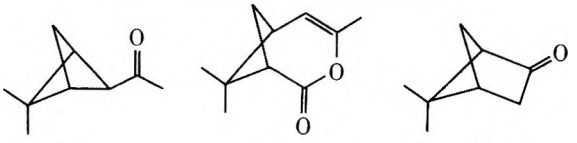
No direct evidence could be obtained for the formation of the β-diketone **6** during the course of the irradiations. The inability to quench the formation of the enol lactones with 1,3-pentadiene shows that, if **6** is indeed an intermediate in this process, it either does not rearrange by way of a triplet excited state or the reaction is very rapid with respect to the quenching process.[14] However, support for the presence of a symmetrical intermediate such as **6** was provided by the lack of optical rotation of **8**. Assuming that **6** is an intermediate, its photocleavage would generate the diradical **14**. Rotation of the methyl group at the



6 14 15

radical site of 14 during conversion to diradical 15 should occur in such a way as to minimize interaction with the bulky *gem*-dimethyl substituted bridge, leading to the trans stereochemistry as depicted. Closure would then generate 8 as the initial product in agreement with the stereochemical conclusion reached on the basis of the nmr spectra.

The apparent photostability of 7 under these conditions is surprising, since nonenolic β-diketones such as these are generally observed to be much more reactive than their enolic counterparts. Also, since transfer of the substituent has been shown to be stereospecific in rigid systems,[6] only the trans isomer would be expected to form in the rearrangement. One possible process by which epimerization could occur would involve photocleavage of the C_2–C_3 bond of 7 followed by rotation of the C_3–C_4 bond and recombination. This process gains some support from the observation that the base peak in the high-resolution mass spectrum of the mixture of diketones results from loss of carbon monoxide, which can be most easily rationalized by formation of the bicyclo[1.1.1]pentane derivative 16. In fact, a monoketone with molecular ion corresponding to that of 16 was isolated in trace amount from one irradiation run, but too little material was obtained to determine its structure. No compound with structure 17, the product which would result from a process analogous to the rearrangement of 6, was observed in any of these experiments. The lack of formation of the bicyclohexanone 18 during methoxide treatment of 7 is easily rationalized by the lack of stabilization of the enolate anion in the strained ring system, by the same argument as that applied to the interpretation of the infrared spectra of these compounds.



16 17 18

Experimental Section[16]

In a typical irradiation, a solution of 0.965 g of verbenone epoxide, $[\alpha]D$ − 114°, in 130 ml of pentane was irradiated through Vycor glassware with a 450-W medium-pressure mercury arc lamp for 12 hr. The solution was flushed with argon for 0.5 hr before irradiation and maintained under argon for the duration of the reaction. Removal of solvent and bulb-to-bulb distillation of the residue gave 0.465 g, bp (bath) 65–75° (1.2 mm). Gc analysis on the SE-30 column showed the presence of a leading shoulder under the verbenone epoxide peak and two resolved peaks, the latter two being formed in about 30 and 2%, respectively. On the BDS column only two peaks appeared in the ratio of 88:12. Verbenone epoxide under these conditions exhibits no decomposition. Collection of the three peaks by preparative gc gave samples for analysis.

Peak 1 (SE-30) was a mixture of verbenone epoxide and 7.

Peak 2 (SE-30) was 8 (30%), isolated as a solid. Sublimation gave material with mp 46–47°, $[\alpha]D$ ~0°, ir 3.27, 5.61, 5.89, and 9.61 μ, and a molecular ion at m/e 166. The nmr spectrum showed signals at τ 9.05 (3 H, s), 8.67 (3 H, s), 8.34 (3 H, d, J = 6.8 Hz), 8.30 (1 H, d, J = 10 Hz), 7.2–7.4 (2 H, m), 5.47 (1 H, q, J = 6.8 Hz), and 7.48 (1 H, q, J = 5.2 Hz). *Anal.* Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.20; H, 8.40.

Peak 3 (SE-30) was 9 (2%), a liquid: ir 5.63, 5.90, and 9.50 μ; molecular ion at m/e 166.1005 (calcd for $C_{10}H_{14}O_2$, 166.0994); and nmr signals at τ 9.03 (3 H, s), 8.59 (3 H, s), 8.41 (3 H, d, J = 7 Hz), 8.27 (1 H, d, J = 9.6 Hz), 7.37 (1 H, dd, J = 9.6, 5.8 Hz), 7.22 (1 H, t, J = 5.8 Hz), 6.88 (1 H, t, J = 5.8 Hz), and 4.78 (1 H, q, J = 7 Hz).

Peak 1 (BDS) was a mixture of verbenone epoxide and 8.

Peak 2 (BDS) was 7 (12%), a liquid: ir 5.68 and 5.86 μ; molecular ion at m/e 166.0989 ($C_{10}H_{14}O_2$); and nmr signals at τ 9.29 and 9.03 (3 H, 2 s, ratio 1:3), 8.72 (1 H, d, J = 9 Hz), 8.59 (3 H, s), 8.45 (1 H, d, J = 8 Hz), 7.68 and 7.63 (3 H, 2 s, ratio 3:1), 7.43 (3 H, m), 6.88 and 6.58 (1 H, s and d, J = 5 Hz, ratio 1:3).

Sodium Methoxide Cleavage of 8. To a solution of *ca.* 0.2 g of sodium in 2 ml of dry methanol was added 0.100 g of 8, which had been isolated by preparative gc and which was contaminated with about 20% of verbenone epoxide. The solution was brought to reflux for 2 hr, cooled, diluted with ether, washed with saturated $NaHCO_3$ solution, and dried over $MgSO_4$. Removal of solvent gave 0.072 g of oil, which was shown by gc analysis on the BDS column to be composed of three materials in the ratio of 21:25:54. The minor constituent was identified as verbenone epoxide. The 25% constituent (11) showed ir bands at 5.76 and 5.85 μ, a molecular ion at m/e 198.1275 (calcd for $C_{11}H_{18}O_3$, 198.1256), and nmr signals at τ 8.95 (3 H, t, J = 7.2 Hz), 8.92 (3 H, s), 8.79 (3 H, s), 7.68 (2, H, q, J = 7.2 Hz), 7.23 (1 H, dd, J = 6.0, 8.5 Hz), 6.90 (1 H, dd, J = 6.7, 8.5 Hz), and 6.31 (3 H, s). The major constituent (10) showed ir bands at 5.75 and 5.85 μ, a molecular ion at m/e 198.1240 ($C_{11}H_{18}O_3$), and nmr signals at τ 9.14 (3 H, s), 8.96 (3 H, t, J = 7 Hz), 8.59 (3 H, s), 7.0–8.25 (6 H), and 6.34 (3 H, s).

Sodium Methoxide Cleavage of 7. To a solution of *ca.* 0.2 g of sodium in 1 ml of methanol was added 37.4 mg of a mixture of isomers of 7 isolated by preparative glc. After reflux for 2 hr, the solution was cooled, diluted with ether, and washed with saturated $NaHCO_3$ solution. After drying over $MgSO_4$, the solvent was carefully evaporated to give 28.6 mg of yellow oil. Gc analysis on the BDS column showed the presence of two peaks in a ratio of 7:3, both of which were isolated by preparative gc. The minor constituent (13) showed ir bands at 5.78 and 5.83 μ, a molecular ion at m/e 198.1231 ($C_{11}H_{18}O_3$), and nmr signals at τ 8.95 (3 H, s), 8.92 (3 H, s), 8.35 (1 H, m), 7.88 (3 H, s), 7.49 (2 H, m), 7.2–7.7 (3 H), and 6.34 (3 H, s). The major constituent (12) showed ir bands at 5.77 and 5.84 μ, a molecular ion at m/e 198.1263 ($C_{11}H_{18}O_3$), and nmr signals at τ 9.12 (3 H, s), 8.78 (3 H, s), 7.90 (3 H, s), 7.6–8.2 (3 H), 7.57 (2 H, d, J = 2 Hz), 7.26 (1 H, dd, J = 10 and 7.8 Hz), and 6.38 (3 H, s).

Registry No.—(±)-5, 33967-70-3; 7 (epimer A), 49830-06-0; 7 (epimer B), 49830-07-1; 8, 49830-08-2; 9, 49830-09-3; 10, 49830-10-6; 11, 49830-11-7; 12, 49830-12-8; 13, 49830-13-9.

References and Notes

(1) T. W. Gibson and W. F. Erman, *J. Org. Chem.*, **37**, 1148 (1972).
(2) T. W. Gibson, *J. Org. Chem.*, **37**, 700 (1972).
(3) J. Meinwald and P. G. Gassman, *J. Amer. Chem. Soc.*, **82**, 2857 (1960).
(4) T. Suga, T. Hirata, T. Shishibori, and T. Matsuura, *Tetrahedron Lett.*, 5553 (1968).
(5) R. G. Carlson and J. K. Pierce, *Tetrahedron Lett.*, 6213 (1972).
(6) H. Wehrli, C. Lehmann, T. Iizuka, K. Schaffner, and O. Jeger, *Helv. Chim. Acta*, **50**, 2403 (1967); J.-P. Pete and M.-L. Viriot-Villaume, *Bull Soc. Chim. Fr.*, 3699 (1971); O. Jeger and K. Schaffner, *Pure Appl. Chem.*, **21**, 247 (1970).
(7) H. Nozaki, Z. Yamaguti, T. Okada, R. Noyori, and M. Kawanisi, *Tetrahedron*, **23**, 3993 (1967); D. Bellus, *Advan. Photochem.*, **8**, 149 (1971).
(8) C. S. Markos and W. Reusch, *J. Amer. Chem. Soc.*, **89**, 3363 (1967).
(9) E. Klein and G. Ohloff, *Tetrahedron*, **19**, 1091 (1963).
(10) V. E. Matter, C. Pascual, E. Pretsch, A. Pross, W. Simon, and S. Sternhell, *Tetrahedron*, **25**, 691 (1969).
(11) K. B. Wiberg and R. W. Ubersax, *J. Org. Chem.*, **37**, 3827 (1972).
(12) Presumably, the chemical shift of the endo methyl group in 5,5-dimethylbicyclo[2.1.1]hexanone could be used to settle this problem, but, unfortunately, the nmr spectrum of this substance does not appear to have been determined.[3]
(13) L. R. Subramanian and G. S. Krishna Rao, *Tetrahedron*, **25**, 1749 (1969).
(14) The intermediacy of the triplet state in the photoreactions of β-diketones may not be well established, since the work cited to support this hypothesis was carried out in neat 1,3-pentadiene solution.[7] It is known that at high quencher concentration it is possible to quench the singlet state of some systems.[15]
(15) A. A. Lamola in "Technique of Organic Chemistry," Vol. XIV, A. Weissberger, Ed., Interscience, New York, N. Y., 1969, p 104.
(16) Melting points were determined on a micro hot stage and are corrected; boiling points are uncorrected. Infrared spectra were recorded on Perkin-Elmer 257 and 137 spectrophotometers as neat films. Nuclear magnetic resonance spectra were obtained on a Varian Associates HA-100 spectrometer using TMS as an internal reference in $CDCl_3$. Nmr data are recorded in this order: chemical shift (integration, multiplicity where s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and coupling constant in hertz). High-resolution mass spectra were determined with an Atlas SM-1 spectrometer in which exact masses were obtained from element maps. Glc analyses were carried out on a Varian Aerograph Model 202B Instrument using thermal conductivity detectors. Columns used were 5 ft × 0.25 in. stainless steel packed with 15% butanediol succinate (BDS) or 15% SE-30 silicone oil on HMDS-treated 60–80 mesh Chromosorb W support. Microanalyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich.

Synthesis of the Bicyclo[4.3.1]decan-10-one System by Cycloalkylation of Specific Cyclohexanone Enolates with Reactive 1,4-Dichlorides

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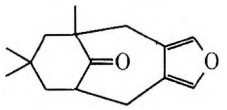
Received September 25, 1973

In an approach to the total synthesis of the hydroazulenic sesquiterpene velleral,[1] we set out to find a method of preparing compound **1**. Ketones with the bicyclo[4.3.1]decan-10-one skeleton have been synthesized from cycloheptanones[2] and by a cycloalkylation reaction of a propyl-2-tetralone with a 1,2-bis(chloromethyl)benzene using sodium hydride as base.[3] However, an attempt by us to prepare compound **4** by a similar base-induced cycloalkylation of 2-methylcyclohexanone yielded a complex mixture. In the present case the relative kinetic acidities of the α-methine and α-methylene protons can presumably account for the failure of the method, since spiro compounds could be formed if the first alkylation step does not take place at the methine carbon atom.



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We now wish to report a new method of reasonably general applicability which gives fair to excellent yields of the four bicyclic ketones shown in Scheme I. We considered the possibility of forming the specific enolate **2a** by the convenient procedure used by House, Gall, and Olmstead[4] for the preparation of 2,2-dialkylated ketones. These authors reported that the lithium *tert*-butoxide formed in the reaction caused some dialkylation. However, the lithium *tert*-butoxide can very suitably function as the base required in the second step of a cycloalkylation sequence using a reactive 1,4-dihalide as alkylating agent.

Reactions with **7** yielding **8** and **9** gave lower yields, partly owing to reaction of 2 mol of enolate with 1 mol of dichloride (by-product vpc–mass spectrum: M^+ 276, $C_{18}H_{22}O_2$). The preparation of **7** includes a hydrogenation of but-2-yne-1,4-diol to *cis*-but-2-ene-1,4-diol. It may be noted that this can be done excellently with a method (Pd on $BaSO_4$ in pyridine) indicated without experimental details by Fieser and Fieser[5] (though not mentioned in a recent review article[6]).

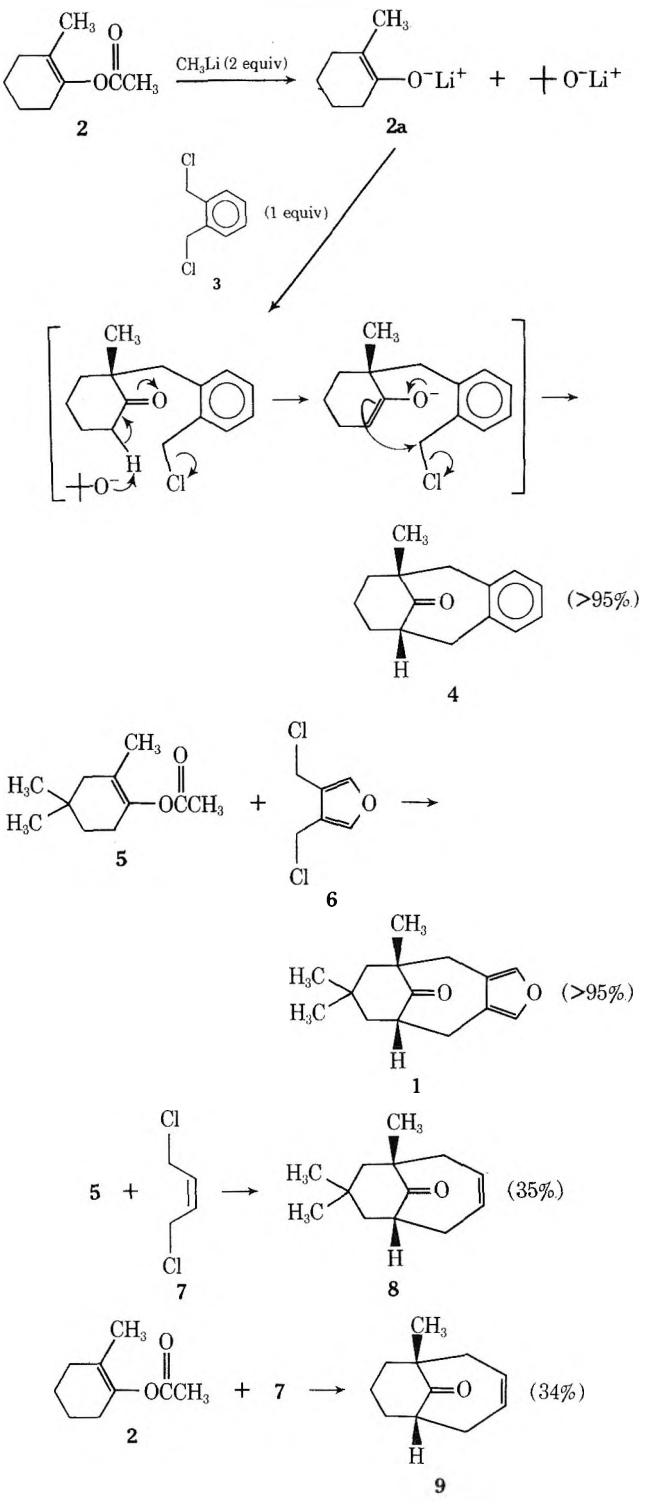
Ketones such as **8** and **9** can be suitable synthetic precursors for stereospecific preparations, for instance of *cis*-2,6-dialkylcyclohexanones, which are otherwise difficult to prepare free of the trans isomer and for syntheses of nine-membered ring compounds.[3] The present cycloalkylation method may be less suitable for some acyclic ketones because of the difficulty of obtaining the proper trisubstituted enol acetate.[4]

Experimental Section

Vpc was carried out on a 1.5 m × 3.1 mm XE-60 column (2% on Chromosorb G, 100–120 mesh) at 130–180°. Melting points are uncorrected. Nmr spectra were recorded on a Varian T-60 instrument and mass spectra on a LKB 1100 instrument (70 eV). Ir spectra refer to liquid films unless otherwise stated.

1-Acetoxy-2-methylcyclohexene (**2**) was prepared according to House, *et al.*,[4] 4,4-dimethylcyclohexanone according to Conia and Le Craz,[7] and 3,4-bis(chloromethyl)furan (**6**) and *cis*-1,4-dichlorobut-2-ene[8] (**7**) (from *cis*-but-2-ene-1,4-diol) according to Novitskii, *et al.*[9]

Scheme I



2-Methoxycarbonyl-4,4-dimethylcyclohexanone was prepared following a method of Corey, Mitra, and Uda:[10] yield 93%; bp 46.5–47° (0.2 mm); $n^{22}D$ 1.4819; ir 1752, 1720 (C=O of keto form), 1660, 1622 cm^{-1} (C=O and C=C of enol form); nmr ($CDCl_3$) δ 3.77 (s, 3), 2.26 (t, 2, J = 7 Hz), 2.02 (s, 2), 1.42 (t, 2, J = 7 Hz), 0.97 (s, 6).

Anal. Calcd for $C_{16}H_{20}N_4O_6$ (dinitrophenylhydrazone): C, 52.7; H, 5.5; N, 15.4. Found: C, 52.7; H, 5.5; N, 15.2.

The dinitrophenylhydrazone had mp 154–156° (EtOAc–EtOH–H_2O).

2-Methoxycarbonyl-2,4,4-trimethylcyclohexanone was prepared by the general procedure of Ritchie and Taylor:[11] yield 83%; bp 56–57° (0.3 mm); $n^{23}D$ 1.4585; ir 1730, 1745 (C=O), 1395, 1375 cm^{-1} (*gem*-CH_3); nmr ($CDCl_3$) δ 3.74 (s, 3), 1.27 (s, 3), 1.08 (s, 3), 1.00 (s, 3).

Anal. Calcd for $C_{17}H_{22}N_4O_6$ (dinitrophenylhydrazone): C, 54.0; H, 5.9; N, 14.8. Found: C, 53.9; H, 5.8; N, 14.7.

The dinitrophenylhydrazone had mp 152–154° (EtOAc–EtOH–H_2O).

2,4,4-Trimethylcyclohexanone[12] was prepared by the general procedure of Ritchie and Taylor:[11] yield 79%; bp 76–77° (15 mm); $n^{22}D$ 1.4481; ir 1718 (C=O), 1390, 1370 cm^{-1} (*gem*-CH_3); nmr ($CDCl_3$) δ 1.23 (s, 3), 1.01 (s, 6), 0.95 (d, 3, J = 7 Hz).

The dinitrophenylhydrazone had mp 150–151° (ethanol) (lit.[12] mp 149–150°).

1-Acetoxy-2,4,4-trimethylcyclohexene (5) was prepared following the general procedure of House, *et al.*:[4] yield 90%; bp 92.5–93.5° (15 mm); $n^{22}D$ 1.4514; ir 1760 (C=O), 1715 (C=C), 1390, 1370 cm^{-1} (*gem*-CH_3); nmr ($CDCl_3$) δ 2.12 (s, 3), 0.98 (s, 6).

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.5; H, 10.0. Found: C, 72.4; H, 9.9.

1,2-Bis(chloromethyl)benzene[13] **(3).** Phthalyl alcohol (6.9 g, 0.05 mol) and triphenylphosphine (27.0 g, 0.103 mol) were refluxed in 200 ml of dry carbon tetrachloride for 22 hr.[14] The reaction mixture was cooled to 0° and poured into petroleum ether (400 ml, bp 40–60°) to complete the precipitation of triphenylphosphine oxide. Filtration, evaporation, and distillation gave pure 1,2-bis(chloromethyl)benzene: yield 5.2 g (61%); bp 55–56° (0.3 mm); mp 55–56° (lit.[11] mp 54–55°); nmr ($CDCl_3$) δ 7.34 (s, 4), 4.74 (s, 4).

***cis*-But-2-ene-1,4-diol**[15] was prepared by hydrogenation of but-2-yne-1,4-diol (20.0 g) in 300 ml of pyridine (5% Pd on $BaSO_4$, 1.0 g)[5] in 88% yield.

General Cycloalkylation Procedure. Methyllithium in ether (21 mmol) was added to 50 ml of dimethoxyethane (DME) and the bulk of the ether was removed under reduced pressure. The enol acetate (10 mmol) in 5 ml of DME was added dropwise to the methyllithium solution containing a white precipitate (0°, slow N_2 stream, magnetic stirring). After 15 min the reaction mixture was heated to 60° to dissolve the lithium *tert*-butoxide. The dichloride (10 mmol) in 5 ml of DME was added in one lot. After *ca.* 5 min the reaction was complete (vpc and nmr; prolonged reaction time did not affect the yield significantly) and the reaction mixture was poured into an ice-cooled mixture of 5% sodium bicarbonate solution (100 ml) and pentane (50 ml). The water phase was extracted with pentane (2 × 50 ml), the combined pentane extracts were dried (Na_2SO_4), and the solvent was evaporated to yield the crude reaction product.

1,8,8-Trimethylfuro[3,4-*c*]bicyclo[4.3.1]decan-10-one (1) was prepared from **5** and **6**. The crude reaction product (yield >95%) was practically pure **1** (nmr, ir). Sublimation *in vacuo* gave an analytical sample: mp 108–110°; ir (KBr) 3125, 3100 (furan), 1697 (C=O), 1393, 1378 (*gem*-CH_3), 878 cm^{-1} (furan); nmr ($CDCl_3$) δ 7.30 (s, 2), 1.27 (s, 3), 0.98 (s, 3), 0.92 (s, 3); mass spectrum m/e 232 (M^+).

Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.6; H, 8.7. Found: C, 77.5; H, 8.7.

1-Methyl-3,4-benzobicyclo[4.3.1]decan-10-one (4) was prepared from **2** and **3**. The crude reaction product (yield >95%) was almost pure **4** (nmr). Distillation gave a colorless oil which crystallized on cooling: yield 65%; bp 110–112° (0.4 mm); mp 64–65.5°; $n^{21}D$ 1.5555; ir 3030 (aromatic CH), 1708 (C=O), 750 cm^{-1}; nmr ($CDCl_3$) δ 7.06 (s, 4), 1.08 (s, 3); mass spectrum m/e 214 (M^+).

Anal. Calcd for $C_{15}H_{18}O$: C, 84.1; H, 8.5 Found: C, 84.1; H, 8.5.

1,8,8-Trimethylbicyclo[4.3.1]dec-3-en-10-one (8) was prepared from **5** and **7**. The crude reaction product was chromatographed on silica (50 g) with methylene chloride as eluent to give **8** in 35% yield: $n^{25}D$ 1.4913; ir 1706 cm^{-1} (C=O); nmr ($CDCl_3$) δ 5.93–5.70 (m, 2), 3.10–2.55 (m, 1, J = 4.4 Hz), 1.20 (s, 3), 0.93 (s, 3), 0.87 (s, 3); mass spectrum m/e 192 (M^+).

Anal. Calcd for $C_{13}H_{20}O$: C, 81.2; H, 10.5. Found: C, 80.9; H, 10.3.

1-Methylbicyclo[4.3.1]dec-3-en-10-one (9) was prepared from **2** and **7**. The crude reaction product was chromatographed on silica (50 g) with methylene chloride as eluent to give **9** in 34% yeild: bp 59–60° (0.4 mm); $n^{26}D$ 1.4998; ir 1710 cm^{-1} (C=O); nmr ($CDCl_3$) δ 5.92–5.67 (m, 2), 1.11 (s, 3); mass spectrum m/e 164 (M^+).

Anal. Calcd for $C_{17}H_{20}N_4O_4$ (dinitrophenylhydrazone): C, 59.3; H, 5.9; N, 16.3. Found: C, 59.6; H, 5.8; N, 16.2.

The dinitrophenylhydrazone had mp 177–179° (EtOAc–EtOH–H_2O).

Acknowledgments. We thank Professor Börje Wickberg for stimulating discussions and Dr. Brian Thomas for helpful linguistic criticism. This work was supported in part by the Swedish Natural Science Research Council.

Registry No.—**1**, 50388-42-6; **2**, 1196-73-2; **3**, 612-12-4; **4**, 50388-44-8; **5**, 50388-45-9; **6**, 6372-18-5; **7**, 1476-11-5; **8**, 50388-48-2; **9**, 50388-49-3; **9** 2,4-dinitrophenylhydrazone, 50388-50-6; 2-methoxycarbonyl-4,4-dimethylcyclohexanone, 50388-51-7; 2-methoxycarbonyl-4,4-dimethylcyclohexanone 2,4-dinitrophenylhydrazone, 50388-52-8; 2-methoxycarbonyl-2,4,4-trimethylcyclohexanone, 50388-53-9; 2-methoxycarbonyl-2,4,4-trimethylcyclohexanone 2,4-dinitrophenylhydrazone, 50388-54-0; 2,4,4-trimethylcyclohexanone, 2230-70-8; phthalyl alcohol, 612-14-6; *cis*-but-2-ene-1,4-diol, 6117-80-2; but-2-yne-1,4-diol, 110-65-6.

References and Notes

(1) G. Magnusson, S. Thorén, and T. Drakenberg, *Tetrahedron*, **29**, 1621 (1973).
(2) J. A. Marshall and J. J. Partridge, *Tetrahedron*, **25**, 2159 (1969).
(3) G. Stork, J. M. Tabak, and J. F. Blount, *J. Amer. Chem. Soc.*, **94**, 4735 (1972).
(4) H. O. House, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, **36**, 2361 (1971).
(5) W. P. Schneider in L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Vol. 1, Wiley, New York, N. Y., 1967, p 566.
(6) E. N. Marvell and T. Li, *Synthesis*, 457 (1973).
(7) J. M. Conia and A. Le Craz, *Bull. Soc. Chim. Fr.*, 1937 (1960).
(8) L. H. Amundsen, R. H. Mayer, L. S. Pitts, and L. A. Malentacchi, *J. Amer. Chem. Soc.*, **73**, 2118 (1951).
(9) K. Yu. Novitskii, Yu, K. Yur'ev, V. N. Zhingareva, and E. F. Egorova, *Dokl. Akad. Nauk SSSR*, **148**, 856 (1963).
(10) E. J. Corey, R. B. Mitra, and H. Uda, *J. Amer. Chem. Soc.*, **86**, 485 (1964).
(11) E. Ritchie and W. C. Taylor, *Aust. J. Chem.*, **17**, 281 (1964).
(12) W. Reusch and R. LeMahieu, *J. Amer. Chem. Soc.*, **86**, 3068 (1964).
(13) M. Kulka, *Can. J. Res.*, **23**, 106 (1945).
(14) I. M. Downie, J. B. Holmes, and J. B. Lee, *Chem. Ind. (London)*, 900 (1966).
(15) A. W. Johnson, *J. Chem. Soc.*, 1014 (1946).

Addition of Chlorine to 1,3-Butadiene with Antimony Pentachloride

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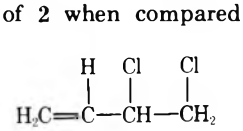
Received September 14, 1973

The reaction of $SbCl_5$ with simple olefins was reported recently.[1] The reaction yielded vicinal dichloroalkanes by a cis addition, as evidenced by the formation of *cis*-1,2-dichlorocyclohexane from cyclohexene, presumably by a concerted pathway.

We report here on the reaction of $SbCl_5$ and 1,3-butadiene (BDN) to produce dichlorobutene (DCB) isomers. This reaction is strongly stereoselective toward the formation of **2** when compared to the reaction of molecular



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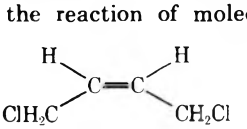

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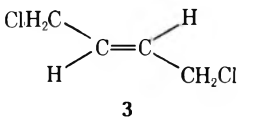

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chlorine and butadiene under similar conditions. The latter reaction has been studied previously,[2] and data indicate only trace quantities of **2**. These data have been confirmed by our work, using conditions and apparatus com-

Table I
$SbCl_5$ + BDN Reactions[a]

Run No.	Solvent	Reaction temp, °C Low	Reaction temp, °C High	DCB isomers,[b] % 1	DCB isomers,[b] % 2	DCB isomers,[b] % 3	Remarks
1	CH_2Cl_2	−26	−5	38.3	23.5	38.2	Mole fraction BDN = 0.5 ($SbCl_5$ added neat).
2	CH_2Cl_2	−19	−10	23.8	40.9	35.3	Run as in footnote *a* except shielded from ambient light in lab.
3	CH_2Cl_2	−19	−13	26.3	37.9	35.8	Run as in footnote *a*.
4	CH_2Cl_2	−22	−12	25.6	23.6	50.8	Reverse addition mode. BDN added to $SbCl_5$ solution.
5	CH_2Cl_2	−26	−13	35.1	40.1	24.8	Concentration of both reactants was about $^1/_2$ that in footnote *a*.
6	CCl_4	−8	−1	33.0	33.5	33.5	Temperature was higher to avoid freezing CCl_4. Run as in footnote *a*.
7	$CHCl_3$	−20	−11	38.4	26.5	35.1	Run as in footnote *a*.

[a] General reaction conditions were 0.1 mol of BDN + 0.5 mol of solvent (mole fraction BDN = 0.17) with a solution of 50% by volume $SbCl_5$ in same solvent added dropwise until 0.02 mol of $SbCl_5$ had been added. Equipment was not shielded from ambient light in lab. System was under dry N_2 and essentially anhydrous. [b] Area per cent by gc normalized to DCB. Results were reported at 20% theoretical BDN conversion. Samples taken at lower conversions during each experiment did not show significant variation.

Table II
Cl_2 + BDN Reaction in CH_2Cl_2[a]

Mole ratio of Cl_2/BDN	Reaction temp, °C Low	Reaction temp, °C High	DCB isomers,[b] % 1	DCB isomers,[b] % 2	DCB isomers,[b] % 3
0.085	−21	−12	54.3	0.4	45.3
0.17	−20	−15	53.5	0.7	45.8
0.22	−20	−12	53.8	0.8	45.4

[a] General reaction conditions were 0.1 mol of BDN + 0.5 mol of CH_2Cl_2, with Cl_2 bubbled into solution in stepwise fashion and snap samples taken with gc syringe. [b] For comparison, vapor-phase reaction of BDN + Cl_2 at about 150° produces approximately 36% of **1**, 17% of **2**, and 47% of **3**. See also P. M. Colling, *Diss. Abstr.*, **24**, 3977 (1964).

Table III
Cl_2 + BDN Reaction in Various Solvents

Solvent	DCB isomers,[a] % 1	DCB isomers,[a] % 2	DCB isomers,[a] % 3
$CHCl_3$	61.0	0.7	38.3
CCl_4	42.4	0.7	56.9
CH_3OH	61.6	0.0	38.4
CH_3CN	50.7	0.0	49.3
$CHCl_2CHCl_2$	57.1		42.9
CH_3CCl_3	48.2	0.6	51.2
dl-$CH_2ClCHClCHClCH_2Cl$	47.0	0.8	52.2

[a] General reaction conditions same as in Table II, footnote *a*.

parable to those used for study of the $SbCl_5$ reaction.[3] Earlier work has shown that liquid-phase reaction of Cl_2 and butadiene in a wide variety of solvents has no significant effect on the relative amount of **2** produced.[4]

Data for the current study are presented in Tables I–V. In view of equilibrium data, product isomer ratios appear to be kinetically controlled. A possible intermediate for the formation of **2** is suggested in Figure 1. Conductivity data imply that $SbCl_5$ does not have significant ionic character in the solvents employed (*i.e.*, $SbCl_4^+$ and $SbCl_6^-$ are insignificant). Monomeric $SbCl_5$, as a trigonal bipyramid, could interact with cisoid butadiene and result in transfer of two chlorine atoms to the diene in which the addition occurs antarafacially, *e.g.*, trans to the butadiene molecular plane. The orbital symmetry of the intermediate for the antarafacial 1,4 addition to butadiene (*i.e.*, participation of the highest occupied molecular orbital in butadiene) is similar to the orbital symmetry for a concerted suprafacial, or cis 1,2 addition to cyclohexene. Suprafacial 1,4 addition would be symmetry forbidden. In-

Table IV
Dichlorobutene Isomer Equilibrium Data

Compd	Equil at 60°, %	Equil at 105°, %
1	17	24
2	6	8
3	77	68

Table V
Conductivity of $SbCl_5$ Solutions (μmhos)

	Solvent	Soln, 50% by volume
CH_2Cl_2	1.10	1.25
CCl_4	0.00	0.10
$CHCl_3$		0.10

volvement of various combinations of axial and equatorial bonds of $SbCl_5$ may be invoked to obtain reasonably good intermediate stereochemistry, employing a very simple approximation using covalent radii[5] (Figure 2). For example, axial–equatorial participation may be reasonable for a concerted suprafacial 1,2 addition to form **1**, equatorial–equatorial for a concerted antarafacial 1,4 addition to cisoid butadiene to form **2**, and axial–axial for formation of **3**.

To substantiate this mechanism $SbCl_5$ was treated with *trans,trans*-2,4-hexadiene. The addition of molecular chlorine to this diene has been studied in detail[6] and closely resembles the addition of molecular chlorine to butadiene. However, repeated attempts to add chlorine to the hexadiene by means of $SbCl_5$ led to complete formation of polymeric substances.

Dependency of isomer ratio on the solvent employed, order of reactant mixing, and reactant concentration was observed. All solvents tested showed an overwhelming preference for **2** compared to the Cl_2 and butadiene reaction. CH_2Cl_2 gave the highest selectivity under the same reaction conditions. Order of reactant mixing appears important, since reversing the addition mode (*i.e.*, addition of butadiene to $SbCl_5$ solution) while maintaining other reaction conditions essentially the same reduced the concentration of **2** by almost a factor of 2 while showing an increase in **3** (run 4). It is believed that this change in isomer ratio is not due to preferential overchlorination of the dichlorobutene isomers. The increase of **3** may be caused by its formation by an intermolecular mechanism which would be favored in the presence of excess $SbCl_5$ encountered in the reverse addition mode.

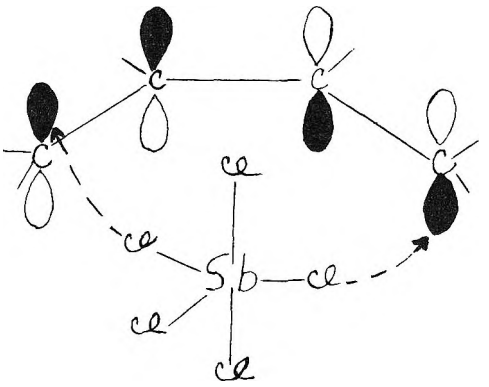

Figure 1. Intermediate for the formation of *cis*-1,4-dichlorobutene-2.

Two experiments point to reactant concentration as possible factor in isomer selectivity. The experiment in which the butadiene concentration was relatively high (mole fraction = 0.5) and $SbCl_5$ was added neat indicated relatively low **2**. Another experiment in which the concentration of both reactants were reduced by a factor of 2 relative to normal conditions in Table I had no significant effect on **2**, but the relative amount of **1** increased at the expense of **3**. In both cases, where chlorination occurred in the presence of relatively high concentrations of $SbCl_5$ (*i.e.*, neat $SbCl_5$ addition and reverse mixing of reactants), the isomer selectivity toward **2** was reduced.

The reaction mixture is stable toward isomerization. A sample remained at ambient lab conditions for 4 days with no significant change in the dichlorobutene isomer ratio. The presence of ambient light in the lab had no significant effect. The existence of the dichlorobutene isomers in the reaction mixture was determined by gc retention times relative to known isomer mixtures and verified semiquantitatively by nmr [multiplets at 3.6 and 4.0 ppm characteristic of terminal and allylic CH_2Cl groups in **1** and (**2** + **3**), respectively]. Experiments were performed to demonstrate that alteration of the dichlorobutene isomer ratio does not occur either in the gc or by prolonged exposure to $SbCl_3$, a likely reaction product. The reaction product from one of the chlorinations in CH_2Cl_2 was mixed at the 50% level with a solution of known dichlorobutene isomer ratio and analyzed by gc with no significant difference observed. This virtually eliminated the possibility of isomerization catalysis by an unidentified reaction product. Solutions of known isomer ratio were dissolved in $SbCl_3$ + CH_2Cl_2 solutions in proportions comparable to those encountered in the chlorination experiments, allowed to stand at room temperature for several hours, and analyzed by gc. No significant change in isomer ratio was observed.

Experimental Section

Solvents employed were of Spectrograde quality. CH_2Cl_2 was supplied by Fischer Scientific Co., $CHCl_3$ and CCl_4 by Matheson Coleman and Bell, as was 1,3-butadiene, instrument grade lecture bottle. $SbCl_5$ was supplied by Alpha Inorganic.

Karl Fischer reagent titration, employed to measure the amount of water in 1,3-butadiene and solvents, yielded the following: butadiene, <10 ppm; CH_2Cl_2, 39 ppm; CCl_4, 27 ppm; and $CHCl_3$, 330 ppm. Gc analysis was as follows: butadiene, 99.97%; CH_2Cl_2, 99.9%; CCl_4, 98.8%; and $CHCl_3$, 99.0% purity. The reaction system was maintained anhydrous by purging and blanketing with nitrogen having a water content of less than 0.001% by weight.

Conductivity data (Table V) clearly indicate that $SbCl_5$ was essentially anhydrous.

The dichlorobutene isomer equilibrium data[7] (Table IV) were obtained from the following starting mixtures: **1**, 0%; **2**, 5%; **3**, 95%; and from **1**, 95%; **2** and **3** combined 1%; impurities, mainly dichlorobutanes, 4%.

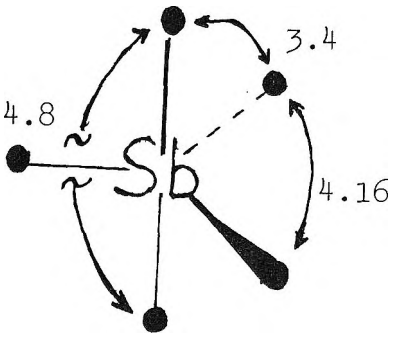

Figure 2. Approximate molecular dimensions of $SbCl_5$.

Registry No.—Chlorine, 7782-50-5; 1,3-butadiene, 106-99-0; antimony pentachloride, 7647-18-9; *cis*-1,4-dichlorobutene-2, 1476-11-5.

References and Notes

(1) S. Uemura, O. Sasaki, and M. Okano, *Chem. Commun.*, 1064 (1971).
(2) M. L. Poutsma, *J. Org. Chem.*, **31**, 4167 (1966), and references cited therein.
(3) R. P. Vignes, unpublished data (see Table II).
(4) R. P. Vignes, unpublished data (see Table III).
(5) F. A. Cotton and G. Wilkinson, "Advanced Inorganic Chemistry," 3rd ed, Wiley, New York, N. Y., 1972.
(6) M. S. Edmondson, *Diss. Abstr.*, 3914 (1971).
(7) D. D. Wild, private communication.

Solvolysis of Xanthenyl and Fluorenyl Ion Pairs in 1,2-Dimethoxyethane

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Received September 6, 1973

An ostensibly routine attempt to prepare the xanthenylmethylamine derivative **4** from the corresponding amide **1** by hydride reduction in hot 1,2-dimethoxyethane (DME) led instead to an 83% yield of 9,9-dimethylxanthene (**2**),

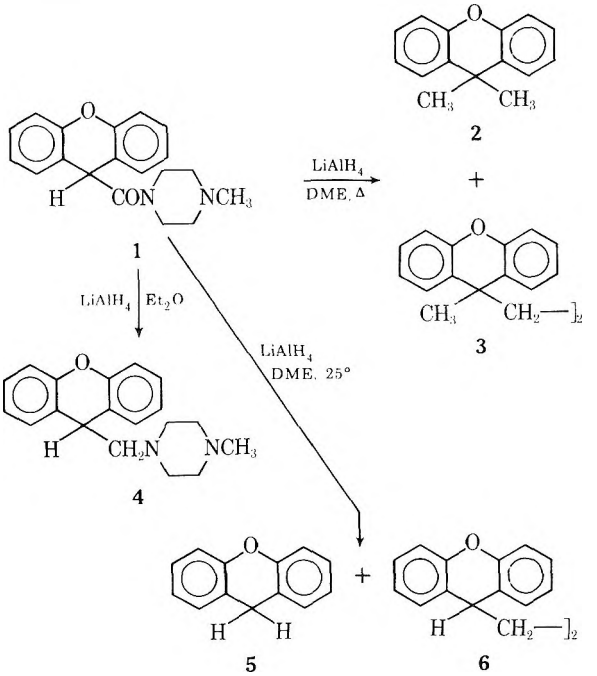
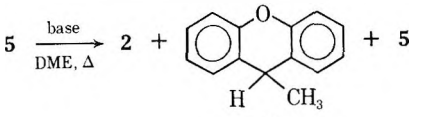


Table I
Reactions of Xanthene with DME + Base[a]



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Base	Mol ratio base:5	Product composition, %[b] 2	7	5
$LiAlH_4$	2:1	>90	0	<10
$LiAlH_4$	1:1	54	30	16
n-BuLi	1:1	26	36	38
n-BuLi	3:1	30	40	30
NaH	2:1	9	13	78

[a] All reaction mixtures (0.01 mol of **5**) were stirred and heated under reflux for 20 hr. [b] Yields of total product were 90–95%.

identical with material prepared[1] by a more conventional method. In contrast, when ethyl ether was used as solvent a nearly quantitative yield of the expected product **4** was obtained. Because a solvent effect of this kind had not been noted previously, a more detailed study was undertaken.[2]

Further investigation of the reaction in hot DME led to the additional isolation of a minor amount (17%) of the di(methylxanthenyl)ethane derivative **3**. With $LiAlD_4$ instead of $LiAlH_4$ neither deuterated nor nondeuterated **3** could be detected. However, 60% of the dimethylxanthene had one (and only one) methyl group completely deuterated. In cold (25°) DME with $LiAlH_4$, neither **2** nor **3** could be detected. Rather, the unmethylated xanthene **5** and the unmethylated dixanthylethane **6** were the only products formed in appreciable quantity. Therefore, attention was turned to the reactions of xanthene itself with various strong bases in hot DME. Results are summarized in Table I.

With xanthene as the starting material neither of the two dimeric compounds (**3**, **6**) could be detected (tlc, nmr) in the reaction mixture. The only observable products (in addition to unreacted xanthene) were monomethylxanthene **7** and dimethylxanthene **2**.

To test the generality of the reaction, fluorene also was treated with $LiAlH_4$ in hot DME. Under conditions that were optimum for dimethylation of xanthene (2:1 mol ratio), fluorene was monomethylated to the extent of only 20%, and barely dimethylated at all (~5%).

In all of the reactions leading to methylated products, the reaction mixtures initially developed deep red colors characteristic of the xanthenyl (or fluorenyl) carbanion. The color (sometimes with green fluorescence) usually persisted throughout the reaction, but was discharged on work-up.

Discussion

Four items of evidence suggest that the ethylene group in **3** and **6** originates from a reductive dimerization of the amide **1** and not from the ethylene moiety of DME. (1) The dimers are formed only from **1** and not from xanthene (**5**). (2) Dimer **6** is formed from amide **1** even at room temperature. Under these conditions no *obvious* solvent participation in the form of methylation is observed. (3) No 9-(β-methoxyethyl)xanthene is detectable in any of the reactions even though this would be a more likely product than **6** if the ethylene moiety in **6** were indeed derived from the solvent. (4) Although **3** (either deuterated or nondeuterated) was not formed from **1** with $LiAlD_4$ in hot DME, the production of major amounts of trideuterated **2** under these conditions clearly shows that carbonyl reduction does indeed compete with the fragmentation process leading to xanthene (**5**).

Several conclusions are indicated by the data of Table I. The variation in product composition with change in cation strongly suggests the involvement of ion pairs. Furthermore, methylation is best promoted by the cations most able to coordinate with an oxygen atom of DME (*i.e.*, $LiAl^{n+} > Li^+ > Na^+$). The complex cations derived from $LiAlH_4$ assist most efficiently in the removal of the oxygen atom from a solvent methyl group as it is being attacked by the xanthenyl anion. Also, a relatively high order of nucleophilic reactivity seems to be required in the carbanion. The oxygen atom in xanthene destabilizes the corresponding carbanion relative to the fluorenyl anion with the result that, under comparable conditions, the xanthenyl anion is solvolyzed in DME to a much greater extent.

Finally, in view of the well-known[4] tendency of the fluorenyl anion (and presumably xanthenyl also) to form solvent-separated ion pairs in DME, it is tempting to suggest that such species are intimately involved in these solvolyses. They provide, *in the ground state*, the precise ternary system necessary for the "push-pull" mechanism suggested above.[5]

Experimental Section[7]

9,9-Dimethylxanthene (2) from 1-Methyl-4-xanthen-9-ylcarbonylpiperazine (1). To a stirred suspension of $LiAlH_4$ (9.8 g, 0.26 mol) in DME (250 ml) was added dropwise a warm (35–45°) solution of **1** (40.3 g, 0.13 mol)[8] in DME (200 ml). The resulting deep-red solution was stirred and heated under reflux for 18 hr, during which time the color changed to a dark fluorescent green. To the cooled, stirred reaction mixture was added dropwise, successively, 30 ml of H_2O, 30 ml of 50% aqueous NaOH, and 30 ml of H_2O. The mixture was then stirred and heated under reflux for 0.5 hr and the hot DME solution was decanted from the gelatinous precipitate, which was washed with ether several times by decantation. The combined solutions were concentrated to dryness by distillation and the *neutral* residue (25.8 g) was distilled under reduced pressure to give 22.6 g (83%) of **2**: bp 114–115° (0.6 mm); $n^{25}D$ 1.5954; ir ($CHCl_3$) 890, 1580, and 1605 cm^{-1}; nmr ($CDCl_3$) δ 1.57 (s, 6, CH_3), 7.05 (m, 6, ArH), and 7.43 ppm (m, 2, ArH) [lit.[1] ir ($CHCl_3$) 878, 1575, and 1600 cm^{-1}; nmr ($CDCl_3$) δ 1.57 (s, 6), 7.02 (m, 6), and 7.47 ppm (m, 2)].

Anal. Calcd for $C_{15}H_{14}O$: C, 85.68; H, 6.71; O, 7.61. Found: C, 85.99; H, 6.65; O, 7.80.

1-Methyl-4-xanthen-9-ylmethylpiperazine (4) from 1. When diethyl ether (250 ml) was substituted for DME in the foregoing procedure using 0.03 mol of **1** and heating under reflux for 48 hr, no red color developed, and a quantitative yield of crude basic product, mp 75–78°, was obtained. Recrystallization from hexane gave pure **4** (83% yield), mp 80–81°.

Anal. Calcd for $C_{19}H_{22}N_2O$: C, 77.51; H, 7.53; N, 9.52. Found: C, 77.46; H, 7.65; N, 9.46.

Dihydrochloride of **4** had mp 241–242° (from ethanol).

Anal. Calcd for $C_{19}H_{24}Cl_2N_2O$: C, 62.13; H, 6.58; N, 7.62. Found: C, 61.91; H, 6.58; N, 7.83.

1,2-Di(9-methylxanthen-9-yl)ethane (3). To a stirred suspension of $LiAlH_4$ (0.8 g, 0.02 mol) in DME (20 ml), under an atmosphere of N_2, solid **1** (3.08 g, 0.01 mol) was added in one portion. More DME (10 ml) was added and the red solution was stirred and heated under reflux for 22 hr. The reaction mixture was worked up in the usual way, but the neutral product (2.14 g) was not distilled. Rather it was kept in a vacuum oven overnight at 60°, during which time colorless prisms crystallized from the liquid dimethylxanthene (**2**) that constituted the bulk of the total product (1.95 g) as indicated both by tlc and nmr. The crystals were collected at the filter, washed with 95% ethanol, and recrystallized from benzene to give 0.35 g (17%) of pure **3**: mp 163–165°; ir ($CDCl_3$) 1040 (w), 1110 (w), 1270 (s), 1330 (s), 1450 (s), 1470 (s), 1495 (s), 1590 (m), and 1615 cm^{-1} (w); nmr ($CDCl_3$) δ 1.32 (s, 6, CH_3), 1.52 (s, 4, CH_2), and 7.08 ppm (m, 16, ArH); high-resolution *m/e* of molecular ion, 418.1930 (calcd for $C_{30}H_{26}O_2$, 418.1933).

Anal. Calcd for $C_{30}H_{26}O_2$: C, 86.09; H, 6.26. Found: C, 86.34; H, 6.33.

Xanthene (5) and 1,2-Dixanthen-9-ylethane (6) from 1. The foregoing procedure was repeated except that the reactants were combined at ice-bath temperature and then stirred at room temperature for 24 hr. The crude product was separated into a glassy basic (0.20 g) and a semisolid neutral (1.44 g) fraction. Trituration of the neutral fraction with pentane followed by successive recrystallizations from cyclohexane (10 ml) and 2-butanone (3 ml) gave 0.10 g of pure **6**: mp 209–211°; ir ($CHCl_3$) 900 (m), 1100 (w), 1125 (w), 1260 (s), 1315 (m), 1465 (s), 1485 (s), 1585 (m), and 1605 cm^{-1} (w); nmr ($CDCl_3$) δ 1.53 (m, 4, CH_2), 3.80 (m, 2, CH), and 7.00 ppm (m, 16, ArH); high-resolution m/e of molecular ion, 390.1603 (calcd for $C_{28}H_{22}O_2$, 390.1620).

Anal. Calcd for $C_{28}H_{22}O_2$: C, 86.12; H, 5.68. Found: C, 86.17; H, 5.81.

Combined residues (1.2 g) obtained from all mother liquors were dissolved in hot cyclohexane and chromatographed on a silica gel column (15 × 380 mm) using cyclohexane (500 ml) for elution. Concentration of the eluate to dryness in a rotary evaporator gave 0.30 g of white powder, mp 98–99°, identical (mixture melting point, ir, and nmr) with xanthene (**5**).

Reaction of the Amide 1 with $LiAlD_4$. When **1** was treated with $LiAlD_4$ in place of $LiAlH_4$ in hot DME exactly as described above for the preparation of **3**, there was obtained 1.93 g (92%) of a crude liquid product from which no solid deposited on standing. The nmr spectrum showed the presence of a single methyl species (δ 1.57 ppm) corresponding to **2** (no other peaks outside the aromatic region). However, the ratio of aromatic to methyl protons was roughly 2:1 instead of the 4:3 ratio required for pure **2**, suggesting the presence of deuterated material. (Treatment of a sample with excess *n*-BuLi in DME did not give a deep red color, thus eliminating 9,9-dideuterioxanthene as a possible component.) The nmr spectrum of a distilled sample of the product (>90% distillable) was nearly identical with that of the crude material. The pertinent mass spectrum follows: m/e (rel intensity) 213 (12), 210 (8), 198 (40), 195 (100). Of these four peaks only m/e 210 and 195 appeared in the mass spectrum of pure **2**. Thus, the nmr and mass spectra are uniquely consistent for a mixture composed of 40% **2** and 60% of the analog containing one completely deuterated methyl group.

Reaction of Xanthene with $LiAlH_4$ in DME. A 1.82-g (0.01 mol) sample of xanthene (**5**) was treated with $LiAlH_4$ (0.80 g, 0.02 mol) in hot DME in the usual way (20 hr under reflux). Work-up of the deep red reaction mixture gave 1.79 g (86% yield based on **2**) of light yellow oil consisting of >90% of dimethylxanthene **2** (by nmr). No peaks corresponding to **3** or **6** were observable in the nmr spectrum. The only sign of an impurity in the spectrum was a slight integral at 3.97 ppm corresponding to the presence of no more than 5–10% of starting xanthene (**5**).

When the reactants were stirred at room temperature for 20 hr, unchanged xanthene was recovered quantitatively.

When equimolar quantities (0.01 mol each) of the reactants were heated under reflux in DME for 20 hr, the nmr spectrum of the total product (1.86 g), essentially completely distillable in the boiling range of **2**, showed the presence of 9-methylxanthene (**7**) [δ 1.40 (d, J = 7 Hz, CH_3) and 4.01 ppm (q, J = 7 Hz, CH)] in addition to **2** and **5**. From the peak integrations the composition of the mixture could be calculated as 54% **2**, 30% **7**, and 16% **5**. (In a second identical experiment the calculated composition was 55, 29, and 16%, respectively.)

Because 9-methylxanthene is unreported in the literature, further characterization was carried out. A 200-μg sample of the product mixture was subjected to high-pressure liquid chromatography in a Waters Associates Model ALC 202/401 instrument. A 4 ft × 0.125 in. column packed with C_{18}/Corasil was used with 40:60 CH_3CN–H_2O as solvent at a flow rate of 1.0 ml/min. Using ultraviolet (254 nm) detection, three well-resolved peaks were obtained, the first (18.6 min) and the third (30.6 min) corresponding to those observed for pure **5** and **2**, respectively. The eluate corresponding to the middle peak (23.6 min) was collected and the solute was analyzed in the high-resolution mass spectrometer: m/e of molecular ion, 196.0859 [calcd for $C_{14}H_{12}O$ (*i.e.*, **7**), 196.0888].

Reactions of Xanthene with *n*-BuLi and NaH in DME. Xanthene (0.01 mol) was heated under reflux in DME for 20 hr in the presence of these bases and worked up in the usual way. Product composition was determined by nmr. Results are summarized in Table I.

Reaction of Fluorene with $LiAlH_4$ in DME. Treatment of a 0.01-mol sample of fluorene with $LiAlH_4$ (0.02 mol) in hot DME for 23 hr gave an oily solid (93% recovery) whose nmr spectrum ($CDCl_3$) showed peaks for unreacted fluorene [δ 3.87 (CH_2)], 9-methylfluorene [δ 1.48 (d, CH_3, J = 7 Hz) and ~3.88–3.90 ppm (q, half obscured by fluorene peak, CH, J = 7 Hz)] [lit.[9] nmr ($CDCl_3$) δ 1.48 and 3.90 ppm (J = 7.5 Hz)] and 9,9-dimethylfluorene [δ 1.45 ppm (s, CH_3)] [lit.[1] nmr ($CDCl_3$) δ 1.45 ppm]. Despite the close proximity of the methyl peaks, the composition of the mixture could be estimated as 75% fluorene, 20% monomethylfluorene, and 5% dimethylfluorene. A sample of the mixture was submitted to high-resolution mass spectral analysis: m/e of molecular ions, 166.0773 [calcd for $C_{13}H_{10}$ (fluorene), 166.0782]; 180.0922 [calcd for $C_{14}H_{12}$ (methylfluorene), 180.0939]; 194.1094 [calcd for $C_{15}H_{14}$ (dimethylfluorene), 194.1096]. Peak heights of the molecular ions, respectively, were in the ratio 75:22:3, in essential agreement with the nmr analysis.

Registry No.—**1**, 50507-10-3; **2**, 19814-75-6; **3**, 50507-13-6; **4**, 50507-11-4; **4** dihydrochloride, 50507-12-5; **5**, 92-83-1; **6**, 50507-14-7; **7**, 38731-93-0; fluorene, 86-73-7; 9-methylfluorene, 2523-37-7; 9,9-dimethylfluorene, 4569-45-3.

References and Notes

(1) J. B. Chazan and G. Ourisson, *Bull. Soc. Chim. Fr.*, 1384 (1968).
(2) During the course of this work, Tomboulian and coworkers[3] reported some unexpected reactions resulting from the fragmentation of tetrahydrofuran in the presence of *n*-butyllithium and trityllithium.
(3) P. Tomboulian, D. Amick, S. Beare, K. Dumke, D. Hart, R. Hites, A. Metzger, and R. Nowak, *J. Org. Chem.*, **38**, 322 (1973).
(4) T. E. Hogen-Esch and J. Smid, *J. Amer. Chem. Soc.*, **88**, 307, 318 (1966); M. Szwarc, *Science*, **170** (3953), 23 (1970).
(5) The reactions of the present work are very likely related to those recently reported by Černý and Málek[6] in which diphenylmethane is alkylated by sodium bis(2-alkoxyethoxy)aluminohydrides at relatively high temperatures (140–170°) in aromatic solvents. Here the alkyl groups necessarily derive from the reducing agents rather than from the solvent. Also the more drastic conditions used led to more complex reaction mixtures (*i.e.*, appreciable amounts of a cyclopropane derivative were formed. Products of this type were not detectable in our crude reaction mixtures).
(6) M. Černý and J. Málek, *Tetrahedron Lett.*, 691 (1972).
(7) Melting and boiling points are uncorrected. Spectra were recorded on a Perkin-Elmer Model 521 ir spectrophotometer, a Varian T-60 nmr spectrometer, and an AEI Model MS902 mass spectrometer. We wish to thank Mr. W. Washburn for the ir spectra, Dr. R. Egan and Mr. M. Cirovic for the nmr spectra, Dr. M. Levenberg, Mrs. S. Mueller and Mr. P. Goodley for the mass spectra, Ms. J. Hood for the microanalyses, and Dr. R. Hasbrouck for the high pressure liquid chromatography.
(8) R. Baltzly, W. S. Ide, and E. Lorz, U. S. Patent 2,742,472 (1956); *Chem. Abstr.*, **51**, 1307*i* (1957).
(9) A. Mathieu, *Bull. Soc. Chim. Fr.*, 1526 (1971).

Photochemical Cycloaddition of Thiobenzophenone to Some Cyclic Polyolefins

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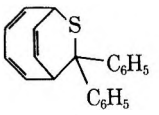
Received August 16, 1973

Thiobenzophenone has been found to undergo facile photochemical addition to diverse types of olefins to afford, in some cases, 1:1 adducts (thietanes) and in others 2:1 thione–olefin adducts (1,4-dithianes) depending on the exact structure of the olefinic substrate.[1,2] The factors governing the course of the reaction are both steric and electronic. In the case of 1,3-dienes a third type of reaction course, 1,4 addition of the thioketone to the diene system, is most often observed, with thietanes being found in some instances.[3]

The recent demonstration[4] that the 1:1 photoproduct from benzoquinone and cyclooctatetraene (COT) results from 1,4 rather than 1,2 addition to COT, as had been originally supposed,[5] prompts us to record our observations on the photochemical addition of thiobenzophenone to cyclooctatetraene, 6,6-diphenylfulvene, acenaphthylene, and norbornadiene.

Irradiation of thiobenzophenone (1) with light of ≥340 nm in excess COT gave a single product, the 1,4 adduct 2, in 58% yield. Its structure was assigned on the basis of spectral and analytical data. Of particular help in deciding between 2 and the isomeric structure 3 was information from the 220-MHz nmr spectrum of the adduct. At this frequency the bridgehead hydrogens appeared as two nonoverlapping apparent triplets of J = 4.2 and 3.6 Hz at τ 5.84 and 5.98, respectively. The lack of mutual coupling seen (and substantiated by appropriate decoupling experiments on 2 and on the corresponding sulfone, 4)[6] is in accord with structure 2, in which the two bridgehead hydrogens should both be strongly coupled to the two adjacent vinyl hydrogens, but not with structure 3, in which the bridgehead hydrogens are on adjacent carbons and have a dihedral angle near 0°, and should therefore be mutually coupled.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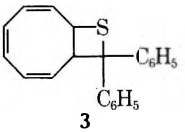
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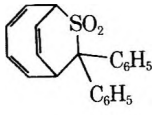
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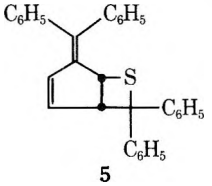
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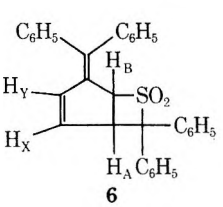
Irradiation of 1 with 6,6-diphenylfulvene gave a modest yield of 1:1 adduct, assigned structure 5 on the basis of its uv and nmr spectral properties. The uv absorption maximum (298 nm, ϵ 22,000) is reasonably similar to that exhibited by the parent 3-benzyhydrylidenecyclopentene,[7] but quite different from that expected for a 1,1-diphenylethylene chromophore which would be present in a 1,4-addition product. [For 1,1-diphenylethylene, λ_{max} is 251 nm (ϵ 10,500).] The nmr chemical shifts and splitting constants of the four hydrogens of 5 derived from the fulvene ring system (see Experimental Section) show a strong resemblance to the data reported for the [2 + 2] cycloadduct of dichloroketene and diphenylfulvene.[8] The orientation of 5 is assigned on the basis of the very close correspondence of the couplings between the four aliphatic hydrogens and those of the ketene adducts of diphenylfulvene described in ref 8. The complete parameters were elucidated by means of decoupling experiments on 5 and on the corresponding sulfone, 6. The orientation of 5 is that predicted by analogy with known reactions of fulvenes with radicals or radical-like reagents which proceed *via* initial attack at the 2 position of the fulvene ring.[9]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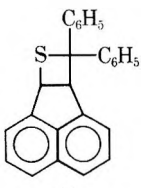
7

Addition of 1 to acenaphthylene gave a low yield of the expected 1:1 adduct, 7, identified on the basis of spectral and analytical data. The remainder of the starting compounds were converted to intractable material. No well-defined product could be isolated from irradiated solutions of 1 and norbornadiene.

No reaction was observed when cyclooctatetraene, diphenylfulvene, or acenaphthylene were treated in the dark with solutions of thiobenzophenone. Thus, the products described here are of photochemical, and not thermal, origin. In previous studies of the addition of free radicals and radical-like species to cyclooctatetraene, it has been found that 2-cyano-2-propyl radicals,[10a] N_2O_4,[9c] and N_2F_4[10b] all add in 1,4 fashion. Photoexcited thiobenzophenone can now be added to this list of reagents.

Experimental Section

Infrared spectra were run on a Perkin-Elmer Model 257 instrument and nmr spectra on either a Varian A-60 or HR-220 spectrometer. Mass spectra were obtained at 70 eV on a Consolidated Model 202-1.

Melting points are uncorrected. Irradiations were performed on argon-flushed solutions using light from a Hanovia 450-W medium-pressure mercury arc, filtered through uranium glass (transmits >330 nm).

Photochemical Reaction of Thiobenzophenone (1) with Cyclooctatetraene. A solution of thiobenzophenone (3.3 g, 16 mmol) in freshly distilled cyclooctatetraene (120 ml) was irradiated in the standard manner for 6 hr, during which time the color of the reaction mixture changed from blue-green to deep orange. Excess COT was removed by distillation at reduced pressure [bp 28–34° (8 mm)] and the residue was dissolved in benzene–hexane and cooled to −15°. During 2 days, a total of 2.6 g (58%) of adduct 2 precipitated as a tan solid. Recrystallization of this material from 3:1 hexane–benzene at 0°, keeping the solution under argon, gave pure 2 as off-white needles: mp 162–163.5°; ir (KBr) 1600 (w), 1448 (m), 1495 (m), 758 (s), 740 (s), 700 cm^{-1} (s); nmr ($CDCl_3$, 220 MHz) τ 2.5–2.9 (10 H, m), 4.05 (4 H, m), 4.42 (2 H, m), 5.90 (2 H, 2 t, J = 4.2 and 3.6 Hz); uv max (EtOH) 261 nm (ϵ 4300) and 300 (sh, 1200); mass spectrum m/e (rel intensity) 303 (P + 1, 20), 302 (P, 72), 205 (5), 198 (98), 167 (100), 165 (100), 121 (88), 104 (95), and 91 (82). *Anal.* Calcd for $C_{21}H_{18}S$: C, 83.47; H, 5.96. Found: C, 83.64; H, 5.87.

Oxidation of Sulfide 2 to Sulfone 4. A solution of 2 (0.30 g, 1.0 mmol) and *m*-chloroperbenzoic acid (0.20 g, 1.0 mmol) in methylene chloride (8 ml) was allowed to stand at room temperature for 20 hr. The solution was then washed three times with 10% sodium carbonate solution, followed by two washings with water. After drying of the solution and evaporation of the solvent, the residue was recrystallized from chloroform–hexane to give sulfone 4 as white needles: mp 203–204° (0.22 g, 65%); ir (KBr) 1290 and 1108 cm^{-1}; nmr ($CDCl_3$) τ 2.4–2.8 (10 H, m) 3.8–4.3 (6 H, m), 5.53 (1 H, t, J = 4.5 Hz), 5.99 (1 H, t, J = 3.8 Hz); mass spectrum m/e (rel intensity) 334 (P, 1), 270 (36), 193 (91), 192 (100), 191 (89), 179, (63), and 178 (160).

Photochemical Addition of 1 to 6,6-Diphenylfulvene. A solution of 1 (1.0 g, 5 mmol) and 6,6-diphenylfulvene (2.2 g, 9.5 mmol) in benzene (120 ml) was irradiated under the standard conditions for 5 hr. After evaporation of the solvent, the brownish residue was triturated with hexane–benzene and allowed to stand overnight. Filtration of the slurry gave 1.4 g of tan solid, mp 142–146°. Two recrystallizations of this material from 2:1 hexane–benzene at −5° gave adduct 5 as off-white rhombs: mp 147–148° (1.1 g); uv (EtOH) 298 nm (ϵ 22,100); nmr ($CDCl_3$) τ 2.6–3.0 (20 H, m), 3.54 (1 H, d of m, J = 5.6 Hz), 4.31 (1 H, 2 d, J = 5.6, J' = 3.0 Hz), 5.11 (1 H, m), and 5.55 (d, J = 5.6 Hz); mass spectrum m/e (rel intensity) 428 (P, 0.2), 230 (5), 186 (12), 185 (16), 91 (48), 78 (100). *Anal.* Calcd for $C_{31}H_{24}S$: C, 86.95; H, 5.60. Found: C, 86.90; H, 5.43.

Oxidation of Adduct 5 to Sulfone 6. To a solution of 5 (0.43 g, 1.0 mmol) in methylene chloride (10 ml) was added over 30 min a solution of *m*-chloroperbenzoic acid (85%, 0.40 g, 2 mmol). The reaction mixture was stirred at room temperature for 20 hr, then washed three times with 5% sodium bicarbonate and once with water and dried. Evaporation of the solvent and recrystallization of the residue from chloroform–hexane gave the sulfone 6 as colorless needles: mp 107–108; ir (KBr) 1298 and 1130 cm^{-1}; nmr ($CDCl_3$) τ 2.5–2.8 (20 H, m), 3.38 (1 H, H_Y, 2 d, J = 6.8, J' = 2.0 Hz), 4.03 (1 H, H_X, 2 d, J = 6.8, J' = 0.9 Hz), 4.56 (1 H, H_B, 2 d, J = 7.2, J' = 0.9 Hz), and 5.26 (1 H, H_A, 2 t, J = 7.2, J' = 2.3 Hz). Decoupling led to the following assignments: J_{XY} = 6.8, J_{AY} = −2.0, J_{AX} = 2.3, J_{BX} = 0.9, and J_{AB} = 7.2 Hz. *Anal.* Calcd for $C_{31}H_{24}SO_2$: C, 80.91; H, 5.21. Found: C, 80.60; H, 5.07.

Photochemical Reaction of 1 with Acenaphthylene. A solution of 1 (1.5 g) and acenaphthylene (3.0 g) in benzene (120 ml) was irradiated in the usual fashion for 5 hr. The residue remaining after evaporation of the solvent was chromatographed on a column of activity I alumina (2.0 × 25 cm). Elution with 25% benzene–hexane gave two fractions containing an off-white solid,

which after recrystallization from benzene–hexane gave adduct 7 as white prisms: mp 217–218° (0.18 g, 7%); nmr ($CDCl_3$) τ 2.4–2.9 (16 H, m), 5.5 and 5.7 (2 H, AB, $J \cong 7$ Hz); mass spectrum *m/e* (rel intensity) 350 (34, P), 317 (20), 239, (27), 198 (19), 152 (100), and 78 (55). *Anal.* Calcd for $C_{25}H_{18}S$: C, 85.74; H, 5.15. Found: C, 85.56; H, 5.31.

Acknowledgments. I am deeply grateful to the following individuals at the National Institutes of Health: Dr. Hermann Ziffer for 220-MHz nmr spectra; Dr. Herman Yeh for decoupling experiments; and Mr. Bill Landis for the mass spectra of the compounds reported.

Registry No.—1, 1450-31-3; 2, 49746-16-9; 4, 49746-17-0; 5, 49746-18-1; 6, 49746-19-2; 7, 49746-20-5; cyclooctatetraene, 629-20-9; 6,6-diphenylfulvene, 2175-90-8; acenaphthylene, 208-96-8.

References and Notes

(1) A. Ohno, Y. Ohnishi, and G. Tsuchihashi, *J. Amer. Chem. Soc.*, **91**, 5038 (1969), and references cited therein.
(2) (a) H. Gotthardt, *Tetrahedron Lett.*, 2345 (1971); (b) A. Ohno, T. Koizumi, Y. Ohnishi, and G. Tsuchihashi, *ibid.*, 2025 (1970).
(3) K. Yamada, M. Yoshioka, and N. Sugiyama, *J. Org. Chem.*, **33**, 1240 (1968).
(4) E. J. Gardner, R. H. Squire, R. C. Elder, and R. M. Wilson, *J. Amer. Chem. Soc.*, **95**, 1693 (1973).
(5) D. Bryce-Smith, A. Gilbert, and M. G. Johnson, *J. Chem. Soc. C*, 383 (1967).
(6) In these experiments irradiation of the entire vinyl multiplet of **2** and of **4** caused collapse of the two methine hydrogen signals to broadened singlets ($W_{1/2} < 2$ Hz) in each case.
(7) λ_{max} 290 nm (ε 20,000): J. L. Kice and F. M. Parham, *J. Amer. Chem. Soc.*, **80**, 3792 (1958).
(8) R. E. Harmon, W. D. Barta, S. K. Gupta, and G. Slomp, *Chem. Commun.*, 935 (1970).
(9) (a) J. L. Kice, *J. Amer. Chem. Soc.*, **80**, 348 (1958); (b) T. S. Cantrell, *J. Org. Chem.*, **32**, 911 (1967); (c) H. Shechter, J. J. Gardikes, T. S. Cantrell, and G. V. Tiers, *J. Amer. Chem. Soc.*, **89**, 3300 (1967).
(10) (a) J. L. Kice and T. S. Cantrell, *J. Amer. Chem. Soc.*, **85**, 2298 (1963); (b) T. S. Cantrell, *J. Org. Chem.*, **32**, 911 (1967).

Preparation of Benzoate Esters of Tertiary Alcohols by Transesterification[1]

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Received September 24, 1973

Standard procedures for esterification are usually not adequate for the synthesis of esters of tertiary alcohols.[2] Although several methods have been developed, they either suffer from lack of generality or present new disadvantages.[3] For example, procedures utilizing such intermediates as acid chlorides[4] or trialkyloxonium salts[5] require additional synthetic and purification steps, with consequent decreases in yield.

The finding that phenyl benzoate readily reacts with potassium 2-propoxide in liquid ammonia to give 2-propyl benzoate in high yield[6] prompted us to investigate the generality of the reaction. It offered promise as a method for the preparation of benzoate esters of tertiary alcohols. Accordingly we did a few experiments, now reported, which demonstrate the practicability of the method.

Operationally, the method involves two steps. First, phenol is converted to the desired benzoic ester through reaction with an appropiate benzoic acid in toluene, catalyzed by boric–sulfuric acid[7] (eq 1). This reaction gives good yields with all the acids so far studied (70–90%).

$$ArCO_2H + PhOH \longrightarrow ArCO_2Ph + H_2O \quad (1)$$

Second, the phenyl benzoate so obtained reacts with the potassium salt of the desired tertiary alcohol in liquid ammonia, giving an alkyl benzoate and potassium phenoxide (eq 2).

$$ArCO_2Ph + RO^- \longrightarrow ArCO_2R + PhO^- \quad (2)$$

Table I
Transesterification of Phenyl Benzoates by Alkoxide Ions in Liquid Ammonia

$ArCO_2Ph$		RO^-K^+		$ArCO_2R$ yield,
Ar	Mmol	R	Mmol	%
C_6H_5	41	*tert*-Butyl	42	91[a]
	35	Isopropyl	39	92[a]
	85	*tert*-Amyl	88	62[a]
	13	*tert*-Amyl	26	86[a]
	75	Isobutyl	90	89[a]
	5	*n*-Butyl[b]	9	90[c]
o-$CH_3OC_6H_4$	5	*tert*-Butyl	10	76[c]
	9	*tert*-Amyl	30	83[c]
3,5-$(NO_2)_2C_6H_3$	6	*tert*-Butyl	13	0[a]
m-ClC_6H_4	8.5	*tert*-Butyl	25	80[c]

[a] Determined by glpc. [b] Potassium *tert*-butoxide (9 mmol) also was present. No *tert*-butyl benzoate was found. [c] Isolated and weighed.

Potassium alkoxides are readily formed *in situ* by the iron-catalyzed reaction of potassium metal with tertiary alcohols in liquid ammonia.[8]

The second step is quite fast, and the conversion is complete in about 45 min. As expected, with primary alcohols the transesterification is even faster, as was demonstrated by an experiment in which equal amounts of primary and tertiary alkoxides were allowed to compete with phenyl benzoate. No tertiary ester was found, but *ca.* 90% of the primary ester was formed. In the cases we have examined the yields of the second step are 80–90%. Results obtained are summarized in Table I.

In the second step, two main factors cause the reaction to proceed in the desired direction. First, the phenoxide anion is a better leaving group (lower pK_a) that any aliphatic alkoxide. Second, potassium phenoxide appears to be less soluble in the reaction medium; we observed that at the end of the reaction a white precipitate is present, presumably potassium phenoxide.

Among others, this method has the advantage that the two operational steps are easy to perform, quickly, and since the solvent is ammonia the product is easily isolated from the reaction mixture. Small-scale preparations are feasible with this method because the reaction is very clean and the corresponding benzamide (2–10%) is the only contaminating product. This impurity is very easy to remove (see Experimental Section).

Substituents such as alkoxy and halogen in the aromatic moiety survive, as probably would also alkyl, aryl, and aryloxy groups. Also, alcohols sensitive to heat or acids would survive under our reaction conditions.

When an attempt was made to utilize phenyl 3,5-dinitrobenzoate in this synthesis, a deep red color was formed immediately after mixing the reagents, probably due to σ-complex formation,[9] and no transesterification product was found.

Experimental Section

Phenyl benzoates were prepared by the method of Lawrence.[7] The structures of the esters were established by melting point, nmr, ir, and agreement of physical constants with published data. Benzoic acids were all commercially available materials. Boiling and melting points are uncorrected. Infrared spectra were recorded on a Beckman IR-8 spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian T-60 spectrometer, using carbon tetrachloride as solvent and TMS as internal standard. Gas chromatographic analyses were performed on an F

& M Biomedical Gas Chromatograph Model 400, and yields were obtained using biphenyl as internal standard with appropiate corrections being made for relative response factors. A 4 ft × 3/16 in. column packed with 4% silicon rubber SE-30 on 60/80 Chromosorb P was used.

Transesterification of Phenyl Benzoates with Alkoxides. A procedure for transesterification of phenyl benzoate with potassium *tert*-butoxide is representative. Dried liquid ammonia from a commercial cylinder was condensed in a three-necked, round-bottomed flask (1 l.) fitted with a cold-finger condenser containing solid CO_2 in methyl alcohol and a magnetic stirrer and was constantly swept by a slow stream of dry N_2. Potassium metal (0.042 mol) was added, and the *tert*-butyl alcohol (0.042 mol) was added dropwise followed by the addition of a small amount (2–5 mg) of solid ferric chloride to catalyze the formation of potassium *tert*-butoxide. (*Caution:* very little catalyst should be used because the reaction can become violent.) Without ferric chloride the formation of potassium *tert*-butoxide is remarkably slow; 2–3 hr are necessary for completion. Solid phenyl benzoate (0.041 mol) was then added at once with stirring, and after 50 min the reaction solution was quenched by the addition of ammonium chloride. The ammonia was then allowed to evaporate. Water and ether were added and the two layers were separated. The aqueous phase was extracted with ether and the combined ether extracts were washed with 10% sodium hydroxide solution to remove phenol. This was further washed with water until neutral and dried over anhydrous sodium sulfate. A small portion of the ether extract was examined by glpc, and *tert*-butyl benzoate (91%) together with unreacted phenyl benzoate (3%) were identified. The ether was removed and the residue was distilled *in vacuo*, yielding 6.52 g (77%) of *tert*-butyl benzoate, bp 108–110° (20 mm), 97% pure by glpc, and the structure was confirmed by nmr and ir. The residue after distillation was washed with pentane, and the remaining white precipitate was identified as benzamide (3% yield) by its melting point (126–128°), nmr, and ir compared with those of an authentic sample. In small-scale preparations (5–8 mmol) the procedure was the same but the crude product was dissolved in pentane and the undissolved benzamide was removed before glpc analysis.

Properties of Alkyl Benzoic Esters. 2-propyl benzoate had bp 93–96° (19 mm), nmr δ 1.28 (d, J = 6.3 Hz, 6 H), 5.12 (septet, J = 6.3 Hz, 1 H), 7.2 (m, 3 H), and 7.9 (m, 2 H). *tert*-Butyl benzoate had bp 108–110° (20 mm), nmr δ 1.56 (s, 9 H), 7.4 (m, 3 H), and 8.0 (m, 2 H). *tert*-Amyl benzoate had bp 120–122° (20 mm), nmr δ 0.97 (t, J = 7 Hz, 3 H), 1.53 (s, 6 H), 1.91 (q, J = 7 Hz, 2 H), 7.4 (m, 3 H), and 8.0 (m, 2 H). Isobutyl benzoate had bp 114–117° (20 mm), nmr δ 0.97 (d, J = 6.7 Hz, 6 H), 2.02 (m, 1 H), 4.10 (d, J = 6.7 Hz, 2 H), 7.4 (m, 3 H), 8.0 (m, 2 H). *n*-Butyl benzoate had nmr δ 0.93 (m, 3 H), 1.2–1.8 (m, 4 H), 4.24 ("t", 2 H), 7.4 (m, 3 H), and 8.0 (m, 2 H). *tert*-Butyl 2-methoxybenzoate had nmr δ 1.90 (s, 9 H), 3.72 (s, 3 H), 6.8–7.8 (m, 4 H). *tert*-Amyl 2-methoxybenzoate had nmr 0.97 (t, J = 7 Hz, 3 H), 1.52 (s, 6 H), 1.89 (q, J = 7 Hz, 2 H), 3.74 (s, 3 H), 6.8–7.8 (m, 4 H). *tert*-Butyl *m*-chlorobenzoate had bp 123–125° (18 mm), nmr δ 1.58 (s, 9 H), 7.2–8.0 (m, 4 H).

Acknowledgment. We thank Professor Joseph F. Bunnett for helpful suggestions and critical reading of the manuscript. The gas chromatograph made available to us by Dr. R. Caputto is greatly appreciated.

Registry No.—2-Propyl benzoate, 939-48-0; *tert*-butyl benzoate, 774-65-2; *tert*-amyl benzoate, 3581-70-2; isobutyl benzoate, 120-50-3; *n*-butyl benzoate, 136-60-7; *tert*-butyl 2-methoxybenzoate, 16537-20-5; *tert*-amyl 2-methoxybenzoate, 50507-00-1; *tert*-butyl *m*-chlorobenzoate, 16537-17-0.

References and Notes

(1) Research supported in part by the Consejo Nacional de investigaciones Cientificas y Técnicas, Argentina.
(2) *Cf.* J. March, "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure," McGraw-Hill, New York, N. Y., 1968 p 320.
(3) R. C. Parish and L. M. Stock, *J. Org. Chem.*, **30**, 927 (1965); M. S. Newman, *J. Amer. Chem. Soc.*, **63**, 2431 (1941); S. B. Lippincott, U. S. Patent 2,476,052 (July 12, 1949); *Chem. Abstr.*, **43**, 7951e (1949).
(4) J. F. Norris and G. W. Rigby, *J. Amer. Chem. Soc.*, **54**, 2088 (1932); E. M. Kaiser and R. H. Woodruff, *J. Org. Chem.*, **35**, 1198 (1970).
(5) J. Raber and D. Gariano, *Tetrahedron Lett.*, 4741 (1971).
(6) R. A. Rossi and J. F. Bunnett, *J. Amer. Chem. Soc.*, submitted for publication.
(7) W. W. Lawrence, Jr., *Tetrahedron Lett.*, 3453 (1971).
(8) It is remarkable that formation of potassium alkoxides from the alcohol and potassium metal in liquid ammonia is very slow in the absence of catalyst, but it is achieved in a few minutes in the presence of small amounts of ferric chloride.
(9) M. Strauss, *Chem. Rev.*, **70**, 667 (1970).

Kinetics of Formation of Alkyl Grignard Reagents. Evidence for Rate-Determining Electron Transfer[1]

Summary: A technique for obtaining relative rates of reaction of organic halides with metallic magnesium has been developed, and rate data obtained using this technique have been interpreted to indicate that the rate-determining step for formation of alkyl Grignard reagents involves electron transfer from the metal to alkyl halide.

Sir: The mechanism of the reactions between alkyl halides and metallic magnesium in ethereal solvents has proved difficult to investigate, in part because in this, as in other surface processes, the influence of the structure of the organic reactant on the rate of the reaction is not easily characterized using absolute kinetics techniques.[2] Organic radicals have been implicated as intermediates in these reactions by stereochemical,[3] CIDNP,[4] and product[5] studies, but the relevance of these radicals to the principal reaction path leading to Grignard reagent, the strength of their interaction with the magnesium surface, and the nature of the rate-determining step for the overall reaction remain unsolved problems. Here we report that reliable relative rate data for these reactions may be obtained using competition techniques and present evidence suggesting that electron transfer from magnesium to the alkyl halide occurs in the rate-limiting step.

The principal difficulty in studying the kinetics of the reaction of an alkyl halide, RX, with magnesium is that of accounting for the unknown and variable effective surface area of the metal (S_{Mg}). We have hypothesized that an expression having the form of eq 1 might prove adequate to describe this reaction. If this hypothesis is correct, it should be possible to write precisely analogous expressions (eq 1 and 2) containing the same value of S_{Mg} for two

$$-d(R_1X)/dt = k_1(R_1X)^{\alpha}S_{Mg} \quad (1)$$

$$-d(R_2X)/dt = k_2(R_2X)^{\alpha}S_{Mg} \quad (2)$$

$$\ln[(R_1X)_t/(R_1X)_0] = (k_1/k_2)\ln[(R_2X)_t/(R_2X)_0] \quad (3)$$

structurally similar organic halides competing in the same reaction mixture for a common magnesium surface. Assuming that $\alpha = 1$, a simple expression (eq 3) containing no term in magnesium is obtained by dividing eq 1 by eq 2 and integrating. We find experimentally that plots of eq 3 are linear to >65% consumption of alkyl halide,[6,7] and that values of k_1/k_2 obtained from these plots are sensibly independent of the quanity and type of magnesium used, the starting concentration of alkyl halide, the presence of magnesium salts in the reacting solutions, and the presence of small quantities of water or oxygen intentionally added to the solutions; these values were reproducible within ±10%. Thus, eq 3 appears to describe adequately the kinetic behavior of a mixture of two alkyl halides competing for a single magnesium surface.

Comparison of the rate-structure profile produced by the kinetic data generated using this procedure (Figure 1) with profiles for reactions proceeding by SN2 and anionic mechanisms establishes that the rate of the Grignard reaction is much less sensitive to the structure of the organic moiety than are members of these classes of reactions[8] and confirms that the transition state for the formation of alkyl Grignard reagents is not similar to transition states typical of these classes. The exceptionally

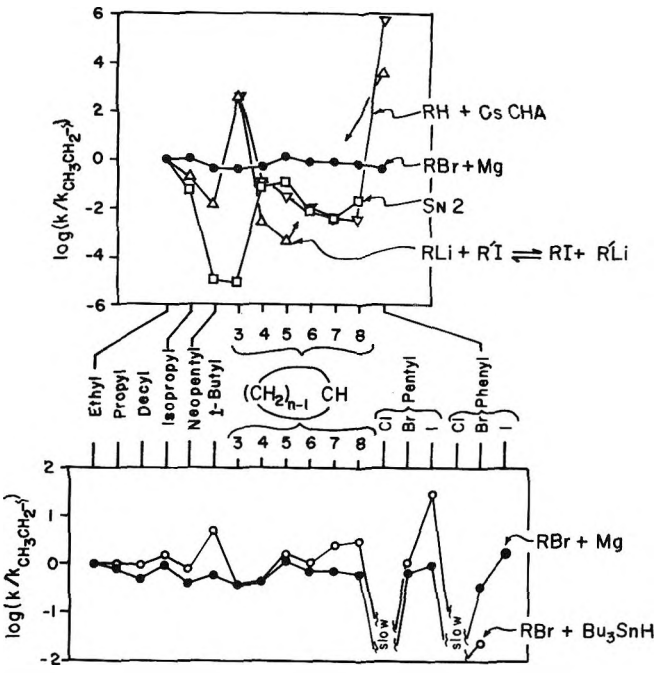
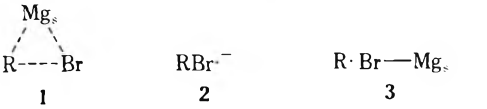


Figure 1. Rate-structure profiles for representative SN2 and anionic reactions, and for the reactions (diethyl ether, 0°) of organic halides, RX, with metallic magnesium and with tri-*n*-butyltin hydride ($h\nu$, AIBN). Unless indicated otherwise, X = Br.

small influence of the structure of the organic moiety on the rate of reaction is compatible with a diffusion-controlled reaction; however the absolute rates of the Grignard reactions are less than diffusion controlled.[6] Since these observations exclude heterolytic and diffusion-limited mechanisms for the reaction, and since the predominant loss of stereochemistry at carbon observed by others[3] on reaction of diasteriomeric alkyl halides with magnesium argues against concerted insertion of a surface magnesium atom (Mg_s) into a carbon–halogen bond (1), two basic types of transition states for the reaction remain to be considered. One (2) would resemble an alkyl halide radical anion, produced by one-electron reduction of the alkyl halide by the metal; a second (3) would approximate an alkyl radical, either free or surface-bound, and might be generated by abstraction of a halogen atom by the magnesium surface or by decomposition of 2.



1 2 3

Generalizable reaction-rate profiles for radical reactions are difficult to obtain, since many methods of generating radicals—including, in principle, the reaction considered here—impose polar character on their transition states.[9] We have used the reduction of alkyl halides with tri-*n*-butyltin hydride[10] to model 3 (Figures 1 and 2) and find that, although the rates of both the tin hydride and Grignard reactions are relatively insensitive to variations in structure, only a poor correlation exists between them: the latter are significantly *less* responsive to changes in structure than are the former, and, while the structure–rate profiles for the two reactions are similar in general form, they differ markedly at specific compounds. To estimate

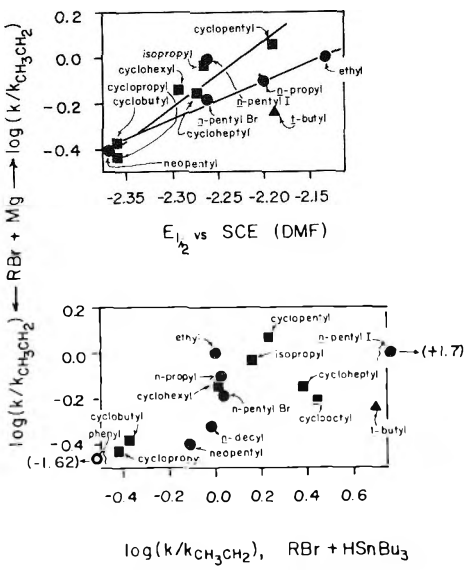


Figure 2. The relative rates of reactions of alkyl halides with magnesium correlate better with half-wave potentials for their reduction at a dropping mercury electrode than with their rates of reaction with tri-*n*-butyltin hydride. In this figure, primary halides are represented by ●, secondary by ■, the single tertiary halide by ▲, and phenyl, included on the plot for comparison, by ○.

the energy required to convert RX to RX·⁻ (2), we have used half-wave potentials, $E_{1/2}$, for reduction of alkyl halides.[11] For a reaction generating 2, the log of the rate of electron transfer to RX at constant potential should be approximately proportional to $E_{1/2}$, provided, as we observe, that the rate is not diffusion limited. The correlation between log (k_{RX}/k_{EtBr}) from the Grignard reactions and $E_{1/2}$ for the corresponding alkyl bromides is again not particularly close over the limited range of compounds for which consistent electrochemical data are available, but appears better than that characterizing the tri-*n*-butyltin hydride reductions.[12,13]

These rate studies indicate that the rate-determining transition state in the formation of an alkyl Grignard reagent does not involve a heterolytic fission of the C–X bond, nor is it diffusion limited. The superiority of the correlation of log $(k_{RX}/k_{EtBr})_{Mg}$ with $E_{1/2}$ to that with $\log(k_{RX}/k_{EtBr})_{triBuSnH}$ suggests, but does not prove, that 2 rather than 3 describes the transition state for the reaction. Evidence implicating 2 as an intermediate in the formation of Grignard reagents has been described by others,[3,4] but these data have not been sufficient to characterize the rate-determining step, or, in the instance of CIDNP experiments, to establish that the 2 lies along the principal reaction path leading to product.

Acknowledgment. Preliminary work in this problem was carried out by E. V. Merry and C. H. Breckheimer.

Supplementary Material Available. Experimental procedures used to obtain the data summarized in Figure 1, and a representative plot of experimental data according to eq 3, will appear following this article in the microfilm addition of this journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-857.

References and Notes

(1) Supported by the National Science Foundation, Grant GP-28586X.
(2) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Compounds," Prentice Hall, New York, N. Y., 1954.
(3) H. M. Walborsky and M. S. Aronoff, *J. Organometal. Chem.*, **51**, 31 (1973); H. L. Goering and F. H. McCarron, *J. Amer. Chem. Soc.*, **80**, 2287 (1958).
(4) H. W. H. J. Bodewitz, C. Blomberg, and F. Bickelhaupt, *Tetrahedron*, **29**, 719 (1973).
(5) W. C. Kossa, Jr., T. C. Rees, and H. G. Richey, Jr., *Tetrahedron Lett.*, 3455 (1971); C. Blomberg, *J. Organometal. Chem.*, **45**, 1 (1972); C. Rüchardt and H. Trautwein, *Ber.*, **95**, 1197 (1962).
(6) This observation and the fact that crude noncompetitive kinetics carried out using magnesium surfaces sufficiently large that their effective surface area does not change during the course of a kinetic run indicate that the assumption that $\alpha = 1$ is at least approximately justified: Y. Fujiwara, unpublished results.
(7) Supplementary material available. See paragraph at end of this communication.
(8) Data for these rate profiles were obtained from the following sources: A. Streitwieser, Jr., 'Solvolytic Displacement Reactions," McGraw-Hill, New York, N. Y., 1962; A. Streitwieser, Jr., and W. R. Young, *J. Amer. Chem. Soc.*, **91**, 529 (1969), and references cited therein; D. E. Applequist and P. F. O'Brien, *ibid.*, **85**, 743 (1963). Values for *SN2* reactions are Streitwieser's "average" values. The data for exchange of hydrocarbons with CsCHA have not been related to the rate of exchange of ethane. Since only the general forms of these profiles are important, the relative rate of exchange of cyclopropane has arbitrarily been given the same value as the equilibrium constant for metal–halogen exchange between ethyllithium and cyclopropyl iodide.
(9) C. Rüchardt, *Angew. Chem., Int. Ed. Engl.*, **9**, 830 (1970).
(10) H. G. Kuivila, *Accounts Chem. Res.*, **1**, 299 (1968).
(11) Details of the mechanism of electrochemical reduction of alkyl halides are still unclear; however, the bulk of the available evidence suggests one-electron transfer from the electrode to the alkyl halide as the potential-determining step; cf. C. K. Mann, J. L. Webb, and H. M. Walborsky, *J. Amer. Chem. Soc.*, **92**, 2042 (1970), and A. J. Fry and R. G. Reed, *ibid.*, **94**, 8475 (1972), for discussion of this point.
(12) All of the $E_{1/2}$ values included in Figure 2 are taken from a single source: F. L. Lambert and K. Kobayashi, *J. Amer. Chem. Soc.*, **82**, 5324 (1960). This study employed a dropping mercury electrode, DMF solvent, and $Bu_4N^+I^-$ as supporting electrolyte. Our efforts to obtain $E_{1/2}$ data in ethereal solvents have not been successful: C. L. Hill, unpublished work.
(13) The origin of the differences in the slopes of the lines correlating $E_{1/2}$ with log (k_{RX}/k_{EtBr}) for primary and secondary alkyl moieties is not obvious, but does not deserve speculation until it has been established that the difference persists in ethereal solvents.
(14) National Institutes of Health Predoctoral Fellow, 1966–1969.

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Received November 28, 1973

An Unusual Simmons–Smith Reaction Affording Noncyclopropyl Compounds. A New Route to 2-Methylenecycloalkanols from Silyl Alkenyl Ethers[1]

Summary: Reaction of silyl cycloalkenyl ethers under a certain Simmons–Smith reaction conditions gives silyl ethers of 2-methylenecycloalkanols, and these noncyclopropyl products have been shown to arise by the isomerization of initially produced silyl cyclopropyl ethers with zinc iodide which is formed during the course of Simmons–Smith reaction.

Sir: During the course of our study on the synthesis of cyclopropanols,[2] we found an interesting and unusual Simmons–Smith reaction which gave noncyclopropyl compounds.

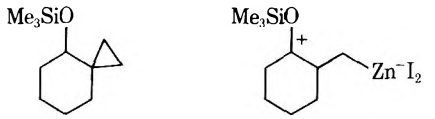
The reaction of trimethylsilyl cycloalkenyl ethers 1[3] (0.05 mol) with methylene iodide (0.08 mol) and zinc–copper couple[4] (0.16 mol) *in 110 ml of anhydrous ether* at 34° for 40 hr (procedure A) gave the silyl cyclopropyl ethers 2 as expected. A dramatical change of the product was observed by merely changing the amount of the solvent in this reaction (Scheme I). When the same reaction was carried out using *40 ml of anhydrous ether* as a solvent while keeping all other reaction variables unchanged (pro-

Table I
Normal and Unusual Simons–Smith Reactions

Compd	Procedure	Product	Yield, %[a]	Purity, %
1a	A	**2a**	76	>97[b]
1a	B	**3a**	71	100
1b	A	**2b**	71	>92[b]
1b	B	**3b**	68	100

[a] Isolated by distillation. [b] Impurities included were the starting olefin **1** and the isomeric product **3**, which could be easily removed.

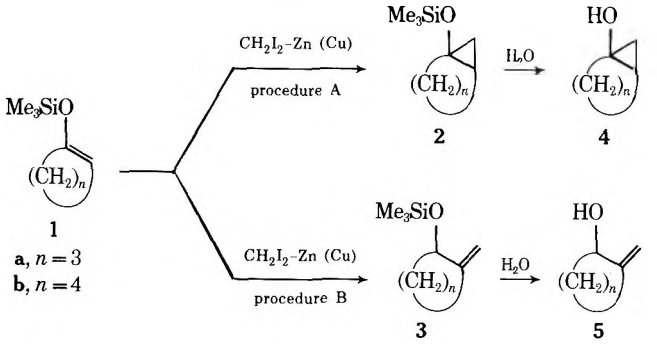
cedure B), the products obtained were trimethylsilyl ethers of 2-methylenecycloalkan-1-ols **3**: **3a**, bp 60–61° (18 mm), ir (direct) 1666 cm^{-1}, nmr (CCl_4) δ 4.26 (1 H, CH) and 4.85 (2 H, $=CH_2$); **3b**, bp 60–65° (10 mm), ir (direct) 1660 cm^{-1}, nmr (CCl_4) δ 3.90 (1 H, CH) and 4.62 and 4.75 (2 H, $=CH_2$). The results are summarized in Table I. Both procedures A and B gave reproducible results and worked well on larger (fourfold) and smaller (one fifth) reaction scales. Under the reaction conditions of procedure B, **1b** gave no trace of a spiro compound **6** which would result from further cyclopropanation of **3b**. However, **6** was obtained in 42% yield in addition to **3b** (14%)



6 **7**

under more forcing reaction condition, *i.e.*, when additional methylene iodide (0.13 mol), zinc–copper couple (0.26 mol), and ether (15 ml) were added at 40 hr and the reaction was continued for another 24 hr.

Scheme I



To clarify the nature of the unusual Simmons–Smith reaction, the product distribution was followed as a function of time by glc. This revealed that the reaction of **1b** using procedure B did afford cyclopropyl ether **2b** as the initial product. Its concentration increased with the decrease in that of **1b**; it reached maximum concentration after about 5 hr and then decreased with concomitant increase in the concentration of **3b**. This clearly demonstrates that **3b** is obtained by *in situ* isomerization of the initial product **2b**. This isomerization has been shown to be caused by zinc iodide which is produced during the course of the Simmons–Smith reaction. In a control experiment, cyclopropyl ether **2b** (0.01 mol) was treated with zinc iodide (0.01 mol) in 7 ml of ether at 34° for 40 hr to give a mixture containing **2b** (12%) and **3b** (88%). On the other hand, when 35 ml of the same solvent was used **3b** was not formed; **2b** was recovered unchanged.

Just as **2** have been converted to cyclopropanols **4**,[2] so the silyl ethers **3** can be hydrolyzed to 2-methylenecycloalkan-1-ols[5] (**5**) in quantitative yields by treating **3** (0.01 mol) with a mixture of 30 ml of CH_3OH and 3 ml of 1 *N* NaOH at room temperature for 3 hr. Thus, the above-described unusual Simmons–Smith reaction provides a new convenient synthetic route to 2-methylenecycloalkan-1-ols[6] whose synthesis is otherwise somewhat troublesome.[5,7]

By procedure B 2-methylene compounds similar to **3** were also obtained from 4-methyl and 4-*tert*-butyl derivatives of **1b**, but no unusual product was detected in the case of 1-trimethylsiloxycyclohept-1-ene and 1-trimethylsiloxy-5,6-benzocyclohex-1-ene.[8] The product obtained from 1-trimethylsiloxy-6-methylcyclohex-1-ene contained both the cyclopropanated and the allylic compounds.

It is tentatively assumed that the isomerization of **2** with zinc iodide proceeds *via* an intermediate **7**.[9] Internal strain of **2** and stabilization of the positive charge in **7** by the siloxy group would account for the ease of the isomerization. The reasons why procedure A and B give different results is not clear at this time. It could be attributed to the difference of coordination pattern around the zinc atom or merely to the function of reaction rate (*i.e.*, concentration of the reactants).

There has been no report,[10] to our knowledge, on the formation of noncyclopropyl compound by the reaction of an olefin under Simmons–Smith reaction conditions. The present results suggest that one should be very careful to identify products of the Simmons–Smith reaction, at least in the case of enol ethers. Indeed, preliminary result in this laboratory shows that 1-ethoxycyclohex-1-ene also gives 1-ethoxy-2-methylenecyclohexane. Further study of the scope and limitation, as well as mechanism, of this unusual Simmons–Smith reaction is in progress.

Acknowledgment. We wish to express our thanks to Professor Henry G. Kuivila for his helpful comments on the manuscript. We are grateful to Shin-Etsu Chemical Industry Co., Ltd., for providing the trimethylsilyl chloride.

References and Notes

(1) Synthesis *via* Silyl Alkenyl Ethers. V. For Part IV, see ref 2.
(2) S. Murai, T. Aya, and N. Sonoda, *J. Org. Chem.*, **38**, 1354 (1973).
(3) H. O. House, L. J. C. Czuba, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, **34**, 2324 (1969).
(4) R. J. Rawson and I. T. Harrison, *J. Org. Chem.*, **35**, 2057 (1970).
(5) T. Tsuji, I. Moritani, and S. Nishida, *Bull. Chem. Soc. Jap.*, **40**, 2338 (1967). We wish to thank these authors for providing us with the ir and nmr spectra of **5**.
(6) Many naturally occurring compounds having this structural unit are known. For examples, see the following: A. S. Gupta and S. Dev, *Tetrahedron*, **27**, 635 (1971); A. I. Scott and A. D. Wrixon, *ibid.*, **27**, 4787 (1971).
(7) W. C. Still, Jr., A. J. Lewis, and D. Goldsmith, *Tetrahedron Lett.*, 1421 (1971); V. S. Joshi, N. P. Damodaran, and S. Dev, *Tetrahedron*, **27**, 475 (1971).
(8) The reasons why isomerized products are not obtained from these latter two compounds are not clear at present time. The H (C-4) and H (C-5) in the former or perihydrogen in the latter could possibly cause steric compression with trimethylsilyl group.
(9) Alternatively the formation of **7** and the following hydrogen migration could take place in a concerted manner.
(10) The formation and the partial isomerization of 1,1,2,2-tetramethoxycyclopropane by the reaction of bis(iodomethyl)zinc with tetramethoxyethylene have been reported by Hoffman and his coworkers.[11] Recent reports on the reaction of the Simmons–Smith reagent with **1a**[12] and **1b**[12,13] contain no mention of the formation of noncyclopropyl compound.
(11) R. W. Hoffman, U. Bressel, and G. Mühl, *Chem. Ber.*, **105**, 2104 (1972).
(12) J. M. Conia and C. Girard, *Tetrahedron Lett.*, 2769 (1973).
(13) G. M. Rubottom and M. I. Lopez, *J. Org. Chem.*, **38**, 2097 (1973).

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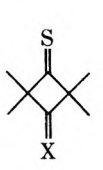
Received January 22, 1974

The Effect of Solvent on the Regioselectivity of Cycloaddition of Diazomethane to the Thione Group in Adamantanethione

Summary: The Δ^2-1,2,3-thiadiazoline to Δ^3-1,3,4-thiadiazoline product ratio for the cycloaddition of diazomethane to the thione group in adamantanethione is highly dependent on the reaction solvent.

Sir: The cycloaddition of diazomethane to each of the C=S groups in **1** (X = S, ethereal solution) proceeds regiospecifically to yield *cis*- and *trans*-bis-Δ^3-1,3,4-thiadiazolines **2**.[1] Treatment of **1** (X = O, ether solution) with an ethereal solution of diazomethane also leads to the regiospecific cycloadduct **3**.[2] On the other hand, cycloaddition of diazomethane to the C=S group in adamantanethione (**4**) in ether occurs in a regioselective manner. The Δ^3-1,3,4-thiadiazoline **5** to Δ^2-1,2,3-thiadiazoline **6** product ratio was found to be ~3 when the reaction was carried out in ether.[1]



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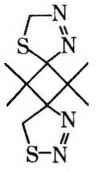

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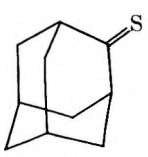

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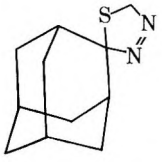

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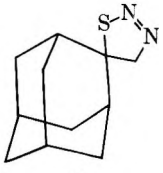


6

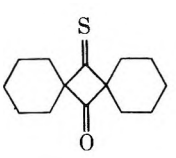
We now wish to report that the **5** to **6** product distribution found in the cycloaddition of diazomethane to the C=S group in **4** is highly dependent on the solvent which is used in the reaction. The results of this study are tabulated in Table I.

Table I
Diazomethane Cycloadditions to the C=S Group of 4 in Various Solvents

Solvent[a]	% Δ^3 (**5**)[b]	% Δ^2 (**6**)	E_T[c]
Petroleum ether	87	13	
Ether	80	20	34.6
Benzene	76	24	34.5
Methylene chloride	58	42	41.1
Ethanol[d]	41	59	51.9
Methylene chloride[e]	40	60	41.1
Acetonitrile[f]	32	68	46.0
Methanol[g]	30	70	55.5
Methanol[h]	22	78	55.5

[a] Solutions of **4** (0.12 *M*) were cooled to 0°. An alcohol-free ethereal solution of diazomethane was prepared from Diazald. The cold diazomethane solution was added dropwise to the orange thione solutions. The reaction appeared to be instantaneous. The solvent was removed under reduced pressure with cooling. The residue was dissolved in $CDCl_3$ and the pmr recorded. [b] Thiadiazolines **5** and **6** exhibit singlets at δ 5.8 and δ 5.0, respectively. The percentages are based on area integrations of these singlets. [c] Solvent polarity parameter; see C. Reichardt, *Angew. Chem., Int. Ed. Engl.*, **4**, 29 (1965). [d] A 0.03 *M* solution of **4** at 22° was treated with a cold, ethereal solution of diazomethane. [e] A 0.12 *M* solution of **4** was treated with a methylene chloride solution of diazomethane. [f] A 0.03 *M* solution of **4** at 0°. The reaction was also performed at room temperature and the same product ratio was found. [g] A 0.04 *M* solution of **4** at 0°. [h] A 0.03 *M* solution of **4** (0°) was treated with a methylene chloride solution of diazomethane.

Treatment of dithione **1** (X = S) in a methanol solution (0°) with an ethereal solution of diazomethane leads to the same isomeric mixture of thiadiazolines **2** as is obtained when the reaction is performed in ether as solvent. Similarly, treatment of the thione ketone **7** in ether or methanol as solvent (0°) leads only to the Δ^3-1,3,4-thiadiazoline **8**. No evidence for the other regioisomers could be found in the pmr spectra of the products from either of these compounds.



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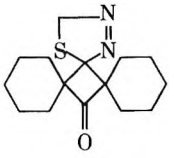

8

The mechanistic aspects of 1,3-dipolar cycloadditions have been the subject of much debate[3,4] and theoretical treatment.[5]

As a dipolarophile the C=S bond exhibits high reactivity.[1-3] Other cycloadditions to substrates with C=S bonds such as aliphatic thiones,[6] thiobenzophenone,[7] thion esters,[6,8] dithio esters,[6,9] and phenyl isothiocyanate[10] have been reported.

The exclusive formation of Δ^3-1,3,4-thiadiazolines from **1** (X = S), **1** (X = O), and **7** (independent of solvent polarity) is perhaps due to steric control of approach of the diazomethane to the thione group.[1,3c] However, in **4** models seem to indicate a somewhat more accessible thione group. Either directional approach of the diazomethane is possible. The dominance of the Δ^2 isomer in polar solvents might be due to the fact that the alignment of dipoles for the transition state leading to this isomer has a greater overall moment than the alternative transition state.[11]

It is not clear to us whether the regiospecificity found in **1** (X = S), **1** (X = O), and **7** or the varying regioselectivity found in **4** as a function of the solvent could have been predicted *via* the HOMO–LUMO model recently proposed by Houk and coworkers.[5] The question must be asked as to whether other dipolar cycloadditions might show regioisomeric product variations which depend on solvent.[5c]

Acknowledgment. The authors are indebted to the Humphrey Chemical Co., North Haven, Conn., 06473, for a Fellowship (M.P.S).

References and Notes

(1) A. P. Krapcho, D. R. Rao, M. P. Silvon, and B. Abegaz, *J. Org. Chem.*, **36**, 3885 (1971). Similar results were obtained in cycloadditions of diazomethane to several dispiro analogs of **1** (X = S).
(2) C. E. Diebert, *J. Org. Chem.*, **35**, 1501 (1970).
(3) (a) R. Huisgen, *Angew. Chem., Int. Ed., Engl.* **2**, 565 (1963); (b) R. Huisgen, *ibid.*, **2**, 633 (1963); (c) R. Huisgen, *J. Org. Chem.*, **33**, 2291 (1968); (d) R. Huisgen, R. Grashey, and J. Sauer, in "The Chemistry of Alkenes," S. Patai, Ed., Interscience, London, 1964, p 739.
(4) (a) R. A. Firestone, *J. Org. Chem.*, **37**, 2181 (1972); (b) R. A. Firestone, *ibid.*, **33**, 2285 (1968).
(5) (a) R. Sustmann, *Tetrahedron Lett.*, 2717, 2721 (1971); (b) J. Bastide, N. El Ghandour, and O. Henri-Rousseau, *ibid.*, 4225 (1972); (c) K. N. Houk, *J. Amer. Chem. Soc.*, **94**, 8953 (1972); (d) J. Sims and K. N. Houk, *ibid.*, **95**, 5798 (1973); (e) K. N. Houk, J. Sims, R. E. Duke, Jr., R. W. Strozier, and J. K. George, *ibid.*, **95**, 7287 (1973); (f) K. N. Houk, J. Sims, C. R. Watts, and L. J. Luskus, *ibid.*, **95**, 7301 (1973), and other pertinent references cited therein. The 1,3-dipole and dipolarophile frontier orbital energies and coefficients are used to rationalize regioselectivity in cycloadditions.
(6) (a) J. M. Beiner, D. Lecadet, D. Paquer, A. Thuillier, and J. Vialle, *Bull. Soc. Chim. Fr.*, 1979 (1973); (b) J. M. Beiner, D. Lecadet, D. Paquer, and A. Thuillier, *ibid.*, 1983 (1973).
(7) (a) R. Huisgen and W. Mack, *Chem. Ber.*, **105**, 2815 (1972); (b) R. Huisgen, R. Grashey, M. Seidel, H. Knupfer, and R. Schmidt, *Justus Liebigs Ann. Chem.*, **658**, 169 (1962).
(8) U. Schmidt, E. Heymann, and K. Kabitzke, *Chem. Ber.*, **96**, 1478 (1963).

(9) (a) K. Bunge, R. Huisgen, R. Raab, and H. J. Sturm, *Chem. Ber.*, **105**, 1307 (1972); (b) K. Bunge, R. Huisgen, R. Raab, and H. Stangl, *ibid.*, **105**, 1279 (1972).
(10) J. C. Sheehan and P. T. Izzo, *J. Amer. Chem. Soc.*, **71**, 4059 (1949).
(11) J. A. Berson, Z. Hamlet, and W. A. Mueller, *J. Amer. Chem. Soc.*, **84**, 297 (1962). The [4 + 2] cycloaddition of cyclopentadiene to methyl acrylate in various solvents has been studied and the endo/exo product ratio used as a measure of solvent polarity.

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Received December 20, 1973

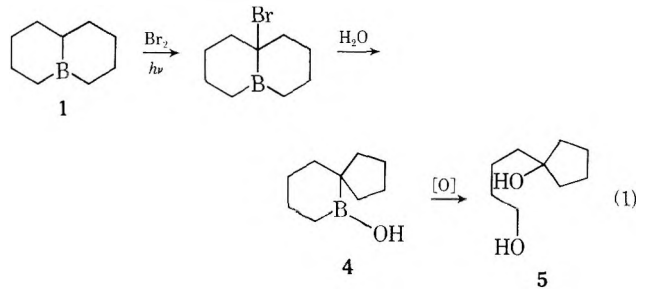
Synthetic Approach to New Organoborane Structures *via* the α-Bromination of Borapolycyclanes

Summary: The light-induced reaction of bromine with borapolycyclanes (**1**, **2**, **3**) in the presence of water provides an entry into polycyclic organoborane intermediates with interesting new structures and to the organic derivatives into which they may be converted.

Sir: A simple six-membered boracyclane can undergo ring contraction to produce a five-membered carbocyclic boron intermediate by photochemical reaction with bromine in the presence of water.[1] The reaction proceeds through a rapid, selective α-bromination, followed by a facile migration of the B–C bond from boron to carbon.[2] This development makes possible the synthesis of carbocyclic structures from the corresponding straight-chain dienes.

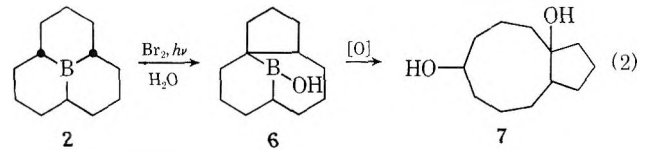
We now wish to report that the reaction is applicable to much more complex systems. Thus, its application to representative borapolycyclanes (**1**, **2**, **3**)[3] proceeds satisfactorily and provides an entry to interesting new organoborane structures (**4**, **6**, **8**) and to the organic derivatives into which such boron compounds can be converted (**5**, **7**, **9**).

For example, treatment of 9-boradecalin (**1**) with bromine in the presence of light and water provides 6-hydroxy-6-boraspiro[4.5]decane (**4**). The structure of **4** was confirmed by oxidation with alkaline hydrogen peroxide to 1-(4-hydroxybutyl)cyclopentanol[4] (eq 1), in an overall yield of 50%. It is evident that the α-bromination occurs selectively at the α tertiary hydrogen atom, rather than at the α secondary position.



1 4 5 (1)

Similarly, the α-bromination of *cis,cis,trans*-perhydro-9b-boraphenylene (**2**) proceeds selectively at the tertiary

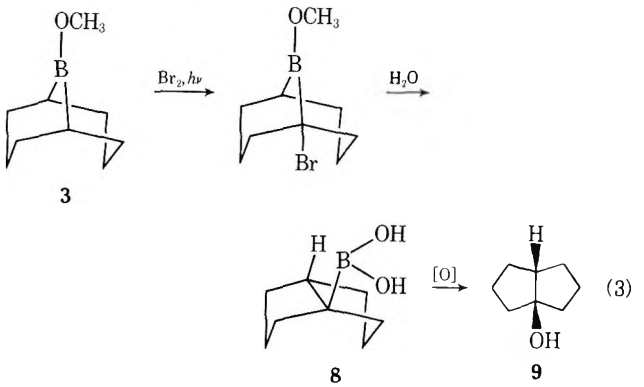


2 6 7 (2)

position. Hydrolysis-oxidation in the usual manner provides bicyclo[7.3.0]dodecane-1,5-diol[4] in 70% yield *via* the polycyclic borane intermediate, 13-hydroxy-13-boratricyclo[7.3.1.0^{1,5}]tridecane (**6**) (eq 2).

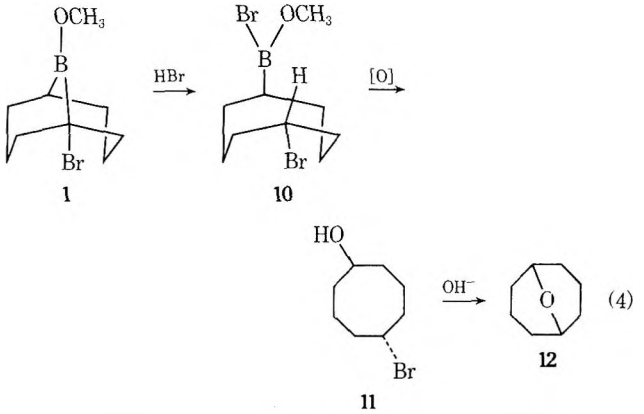
The case of 9-methoxy-9-borabicyclo[3.3.1]nonane (**3**) is of special interest. It was recently established that the α-bromination of *B*-isopropyl-9-borabicyclo[3.3.1]nonane occurs almost exclusively at the α position of the isopropyl group.[5] No significant attack occurs at the α bridgehead positions. Consequently, it was uncertain whether α-bromination in **3** would be feasible.

In fact the bromination, albeit somewhat more sluggish than the other cases, proceeds satisfactorily, producing the *cis*-bicyclo[3.3.0]octane-1-boronic acid (**8**), readily oxidized to *cis*-bicyclo[3.3.0]octan-1-ol[6] (**9**) in a yield of 65% (eq 3). Although the bromo intermediate was not isolated, it is evident that bridgehead substitution must have taken place in view of the structures of the products (**8**, **9**).



3 8 9 (3)

The reaction is accompanied by the formation of cyclooctane 1,5-epoxide[7] (**12**) in 22% yield. This product may arise from a competing attack of hydrogen bromide on the bromination intermediate to form **10** (eq 4). Pmr examination of the reaction mixture reveals the presence of a methine proton (4.05–4.50 ppm in CCl_4) assigned to **10**. The integral area ratio of the spectrum reveals that the reaction proceeds 70% through path 3 and 30% through path 4.

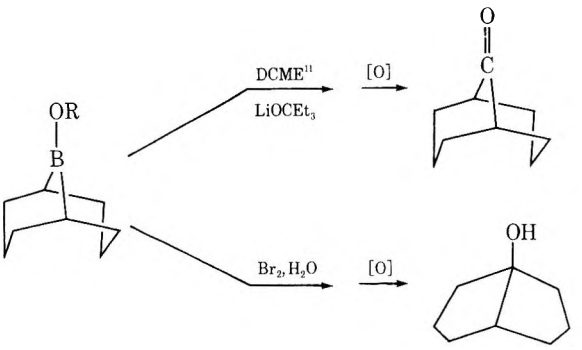


1 10 11 12 (4)

The following procedure for the preparation of *cis*-bicyclo[3.3.0]octan-1-ol is representative. A dry 300-ml flask, equipped with a septum inlet, thermometer well, pressure-equalizing dropping funnel, reflux condenser, and magnetic stirrer, was flushed with dry nitrogen and maintained under a positive nitrogen pressure. The flask was cooled to 0–5° and charged with 4.56 g (30 mmol) of pure 9-methoxy-9-borabicyclo[3.3.1]nonane,[8] 40 ml of methylene chloride, and 30 ml of water. Bromine (1.65 ml, 30 mmol) in 20 ml of methylene chloride was slowly added at 0–5° over 1.5 hr. After the bromine color disappeared, sodium hydroxide solution (6 *N*, 15 ml), ethanol (60 ml), and aqueous hydrogen peroxide (30%, 10 ml) were added at 0–5°. The mixture was then refluxed for 1 hr. The or-

ganic layer was separated and dried over anhydrous potassium carbonate. Glpc analysis revealed a 65% yield of *cis*-bicyclo[3.3.0]octan-1-ol and a 22% yield of cyclooctane 1,5-epoxide. Distillation gave 2.07 g (55%) of *cis*-bicyclo[3.3.0]octan-1-ol: bp 82–83° (15 mm), *p*-nitrobenzoate mp 123.5–124.5° (lit.[6] 124–124.8°).

The carbonylation[9] and dichloromethyl methyl ether (DCME) reactions[10] convert such polycyclic organoboranes to other structures. The difference in these alternative synthetic routes is indicated by eq 5. Consequently, it



(5)

is now possible to proceed from the same intermediate to different boron derivatives and to the organic structures to which they can be converted.

References and Notes

(1) Y. Yamamoto and H. C. Brown, *J. Chem. Soc. Chem. Commun.*, 801 (1973).
(2) C. F. Lane and H. C. Brown, *J. Amer. Chem. Soc.*, **93**, 1025 (1971); H. C. Brown and Y. Yamamoto, *ibid.*, **93**, 2796 (1971). For a survey of the α-bromination reaction with references, see H. C. Brown, "Boranes in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1972.
(3) For preparation of **1**, see R. Köster, W. Larbig, and G. W. Rotermund, *Justus Liebigs Ann. Chem.*, **682**, 21 (1965); H. C. Brown and E. Negishi, *J. Amer. Chem. Soc.*, **91**, 1224 (1969). For preparation of **2**, see G. W. Rotermund and R. Köster, *Justus Liebigs Ann. Chem.*, **686**, 153 (1965); H. C. Brown and W. C. Dickason, *J. Amer. Chem. Soc.*, **91**, 1226 (1969). For preparation of **3**, see E. F. Knights and H. C. Brown, *ibid.*, **90**, 5280 (1968).
(4) Satisfactory elemental analyses and spectral data were obtained for all new compounds.
(5) H. C. Brown and N. R. De Lue, *J. Amer. Chem. Soc.*, **96**, 311 (1974).
(6) R. C. Fort, Jr., R. E. Hornish, and G. A. Liang, *J. Amer. Chem. Soc.*, **92**, 7558 (1970).
(7) A. C. Cope and A. Fournier, Jr., *J. Amer. Chem. Soc.*, **79**, 3896 (1957).
(8) Readily prepared from commercial 9-borabicyclo[3.3.1]nonane (Aldrich Chemical Company) by treatment with methanol, followed by distillation (nitrogen protection): bp 30–33° (0.08 mm).
(9) H. C. Brown, *Accounts Chem. Res.*, **2**, 65 (1969).
(10) H. C. Brown and B. A. Carlson, *J. Org. Chem.*, **38**, 2422 (1973).
(11) B. A. Carlson and H. C. Brown, *Synthesis*, 776 (1973).
(12) Postdoctorate research associate on Grant GP-27742X supported by the National Science Foundation.

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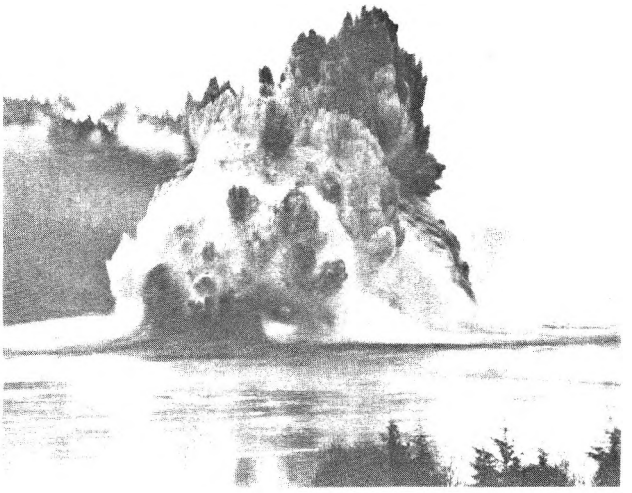

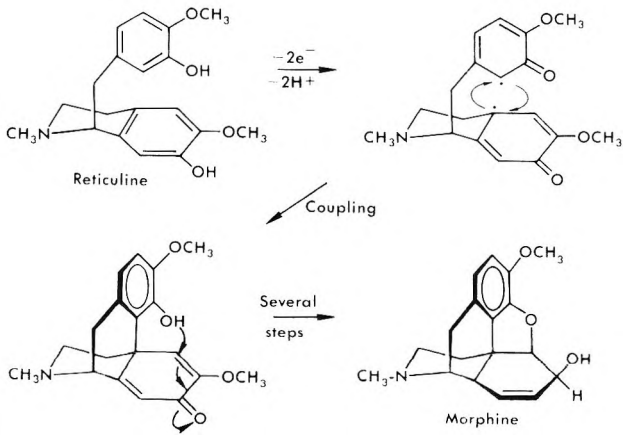

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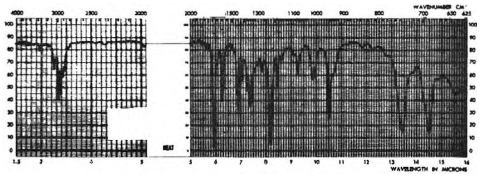

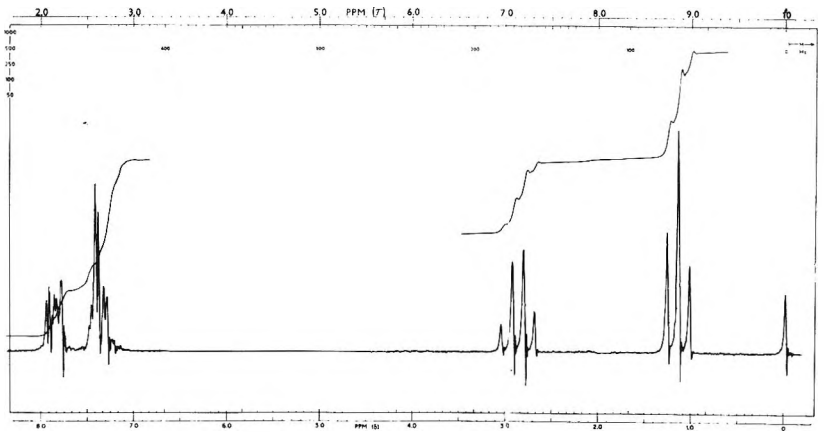

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